Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Statistical analysis plan.
1.0 Title Page

Clinical Study Protocol M13-098

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)

Abbott Investigational Product: ABT-450/Ritonavir/ABT-267, ABT-333
Date: 21 August 2012
Development Phase: 3
Study Design: This is a randomized, double-blind combination drug study
EudraCT Number: 2012-002035-29
Investigator: Multicenter. Investigator information is on file at Abbott.
Sponsor: Abbott Laboratories (Abbott)*
Sponsor/Emergency Contact: Thomas Podsadecki, MD

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 Abbott 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 Abbott is permitted without prior written authorization from Abbott.
1.1 Synopsis

<table>
<thead>
<tr>
<th>Abbott Laboratories</th>
<th>Protocol Number: M13-098</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Study Drug:</td>
<td>Phase of Development: 3</td>
</tr>
<tr>
<td>ABT-450, ritonavir, ABT-267, ABT-333</td>
<td>Date of Protocol Synopsis: 21 August 2012</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td></td>
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<tr>
<td>ABT-450: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{{[5-methylpyrazin-2-yl]carbonyl}amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocycloprop[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</td>
<td></td>
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<tr>
<td>ritonavir: [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester</td>
<td></td>
</tr>
<tr>
<td>ABT-267: Dimethyl {[(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diy]bis{benzene-4,1-diy carbamoyl(2S)pyrrolidine-2,1-diy}(2S)-3-methyl-1-oxobutane-1,2-diy]}biscarbamate hydrate</td>
<td></td>
</tr>
<tr>
<td>ABT-333: (sodium N-6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl]methanesulfonamide hydrate</td>
<td></td>
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<tr>
<td>Protocol Title:</td>
<td></td>
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<tr>
<td>A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)</td>
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<tr>
<td>Objectives:</td>
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<td>The primary objectives of this study are to assess the efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR12 (HCV ribonucleic acid (RNA) &lt; lower limit of quantification (LLOQ) 12 weeks following treatment) and safety of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks in HCV genotype 1-infected adults. The secondary objectives of this study are to assess the rapid virologic response rate (RVR) (the percentage of subjects with HCV RNA &lt; LLOQ at Week 4), the end of treatment response (EOTR) rate (the percentage of subjects with HCV RNA &lt; LLOQ at Week 12), and the percentage of subjects with ALT normalization (ALT ≤ ULN at the end of treatment for subjects with ALT &gt; ULN at Baseline).</td>
<td></td>
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<tr>
<td><strong>Investigators:</strong></td>
<td>Multicenter, investigator information on file at Abbott</td>
</tr>
<tr>
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<td>------------------------------------------------------</td>
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<tr>
<td><strong>Study Sites:</strong></td>
<td>Approximately 90</td>
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<tr>
<td><strong>Study Population:</strong></td>
<td>Non-cirrhotic, HCV genotype 1-infected adults that are null-responders, partial responders or relapsers to prior pegylated-interferon alfa-2a or 2b with RBV (pegIFN/RBV) treatment, aged 18 – 70 years of age inclusive</td>
</tr>
<tr>
<td><strong>Number of Subjects to be Enrolled:</strong></td>
<td>Approximately 400 subjects</td>
</tr>
<tr>
<td><strong>Methodology:</strong></td>
<td>This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 co-administered with RBV in pegIFN/RBV treatment experienced non-cirrhotic HCV genotype 1-infected adults. Approximately 400 HCV genotype 1-infected, treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind Treatment Period. Arm A: ABT-450/r /ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) weight-based RBV BID for 12 weeks. Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + Placebo for ABT-333 250 mg BID with weight-based Placebo for RBV BID for 12 weeks followed by ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID with weight-based RBV BID for 12 weeks. Randomization will be stratified by type of response to previous pegIFN/RBV treatment type (prior null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). The number of relapsers to previous pegIFN/RBV treatment will be limited to ≤ 120 subjects and the total number of partial responders plus relapsers to previous pegIFN/RBV treatment will be limited to ≤ 300 subjects to ensure adequate representation in the presumed harder to treat null-responder population. This study will consist of three Periods: Double-blind (DB) Treatment Period, an Open-label (OL) Treatment Period for Previous Placebo Subjects, and a Post-Treatment (PT) Period for all subjects who received active drugs. DB Treatment Period The Sponsor, investigators and subjects will be blinded to drug assignment. Virologic results will be reviewed and virologic failure criteria will be applied to those subjects randomized to active drug by an unblinded independent reviewer. Upon reaching Week 12 or premature discontinuation of study drug, subjects, investigators and the Sponsor will be unblinded. Subjects randomized to active drug will enter the Post-Treatment Period; subjects randomized to placebo will enter the OL Treatment Period. Subjects randomized to placebo who prematurely discontinue placebo during the DB Treatment Period will be eligible for open-label DAA and RBV treatment at the scheduled DB Week 12 Visit and not at the time of discontinuation of placebo.</td>
</tr>
</tbody>
</table>
Methodology (Continued):

OL Treatment Period

After being unblinded at the Week 12 Visit, subjects initially randomized to placebo will receive 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV. Study drug, virologic results, and safety laboratory results will not be blinded during this Period. Virologic failure criteria will be evaluated and applied by the investigator. Upon completing the Open-label Treatment Period (OL Week 12) or premature discontinuation of study drug, subjects will enter the PT Period.

PT Period

All subjects initially randomized to active drug who complete or prematurely discontinue study drug in the DB Treatment Period and all subjects initially randomized to placebo who complete the OL Treatment Period or prematurely discontinue study drug in the OL Treatment Period, will be followed for 48 weeks in the PT Period, to monitor safety, HCV RNA and the emergence and persistence of resistant viral variants and assessments of PROs.

The following criteria will be considered evidence of virologic failure. Subjects receiving active study drug in the DB or OL Treatment Periods demonstrating any of the following will be discontinued from direct-acting antiviral agent (DAA) therapy:

- 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,
- Failure to achieve HCV RNA < LLOQ by Week 6; or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ at any point during treatment after HCV RNA < LLOQ.

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met for subjects on DAA therapy, the subject will discontinue study treatment.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female and age is between 18 and 70 years, inclusive, at time of screening.
2. Subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:
   - Null-responder: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 log_{10} IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or received less than 12 weeks of pegIFN/RBV for the treatment of HCV and achieved a <1 log_{10} IU/mL reduction in HCV RNA at Week 4 (≥ 25 days); or
   - Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 log_{10} IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
   - Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 24 weeks of treatment follow-up

PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.
Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

3. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCVAb at the time of Screening; or
   - Positive for anti-HCV Ab and HCV RNA 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).

4. Screening laboratory result indicating HCV genotype 1-infection.

5. Per local standard practice, documented results of one of the following:
   - 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
   - A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
   - A screening FibroScan result of < 9.6 kPa.
   Subjects with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.

6. Subject has plasma HCV RNA level > 10,000 IU/mL at Screening.

Main Exclusion:

1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.

2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).

3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5%, at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.

4. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir Score of >3 or Ishak score of > 4.
### Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

#### Main Exclusion (Continued):

5. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) > 5 × ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
   - Albumin < Lower limit of normal (LLN)
   - Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the Abbott Study Designated Physician
   - Hemoglobin < LLN
   - Platelets < 120,000 cells per mm³
   - Absolute neutrophil count (ANC) < 1500 cells/μL
   - Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

#### Investigational Products:

<table>
<thead>
<tr>
<th>Investigational Products</th>
<th>Doses:</th>
<th>Mode of Administration:</th>
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<tr>
<td>ABT-450/ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet</td>
<td>ABT-450/ritonavir/ABT-267 150 mg/100 mg/25 mg QD</td>
<td>Oral</td>
</tr>
<tr>
<td>ABT-333 250 mg tablet</td>
<td>ABT-333 250 mg BID</td>
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<tr>
<td>Ribavirin 200 mg tablet</td>
<td>RBV weight-based dosing 1000 to 1200 mg divided twice daily</td>
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<tr>
<td>Ribavirin 200 mg capsule</td>
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#### Reference Therapy:

<table>
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<th>Reference Therapy</th>
<th>Dose:</th>
<th>Mode of Administration:</th>
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<tbody>
<tr>
<td>Placebo for ABT-450/ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet</td>
<td>Placebo for ABT-333 250 mg tablet</td>
<td>Oral</td>
</tr>
<tr>
<td>Placebo for ABT-333 250 mg tablet</td>
<td>Placebo for Ribavirin 200 mg capsule</td>
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<tr>
<td>Placebo for Ribavirin 200 mg capsule</td>
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#### Duration of Treatment:

In the DB Treatment Period, subjects will receive ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with RBV or matching placebos for 12 weeks. Subjects randomized to placebo in the DB Treatment Period will receive ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with RBV for 12 weeks in the OL Treatment Period.
Criteria for Evaluation:

Efficacy:
HCV RNA in IU/mL will be assessed at all Treatment Period Visits and at all post-treatment visits.

Patient Reported Outcomes (PROs):
The change in disease-specific function and wellbeing will be assessed using the HCV Patient Reported Outcomes (HCVPRO) instrument. Health State Utility will be assessed using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L). General Health Related Quality of Life (HRQoL) will be assessed using the short form 36, version 2 (SF-36V2) non-disease specific HRQoL instrument.

Resistance:
The following resistance information will be tabulated and summarized for subjects receiving active drugs who experience virologic failure: the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline and prototypic reference sequences.

Pharmacokinetic:
Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be tabulated and summarized for subjects treated with the active regimen in the DB Treatment Period and the OL Treatment Period.

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

Statistical Methods:

Efficacy:
The primary endpoint is the percentage of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in subjects who were randomized to and received DB active study drug. The secondary endpoints are the percentage of subjects with RVR (HCV RNA < LLOQ at Week 4), percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12), and percentage of subjects with ALT normalization at the end of treatment. For endpoints of SVR, RVR, and EOTR, the simple percentage of subjects achieving the response out of all subjects initially randomized to and treated with active study drug will be calculated and 2-sided 95% confidence interval of the percentage will be computed using normal approximation to the binomial. The active regimen will be considered successful if the lower confidence bound of the 95% confidence interval for SVR12 is > 51%. A fixed-sequence testing procedure will be used, in which the analysis will proceed to the secondary endpoint of RVR only if a lower confidence bound > 51% is achieved for the primary endpoint of SVR12 and will proceed from RVR to EOTR only if a lower confidence bound > 51% is achieved for RVR. The third secondary endpoint (ALT normalization) will be calculated for all randomized and treated subjects comparing the percentage of subjects with ALT normalization at the Final Treatment Visit in the DB Treatment Period in the active or placebo arms using Fisher's exact test.
**Statistical Methods (Continued):**

**PROs:**
Exploratory analyses of the change in non-disease-specific HRQoL, HCV-specific function and wellbeing and Health State Utility will be measured using the SF-36V2, HCVPRO and EQ-5D-5L instruments, respectively. SF-36V2 and HCVPRO will be analyzed by their total/component scores, as appropriate. The EQ-5D-5L will be analyzed by utility score and by visual analogue scale (VAS) response. Changes from baseline in the patient reported outcome (PRO) summary measures will be summarized and compared between treatment arms using ANCOVA models with a treatment group factor and the baseline score as a covariate. The number and percentage of subjects with decrease that is less than the minimally clinically important difference (MCID) for HCVPRO total score and EQ-5D-5L health index score will be calculated for all subjects in each treatment group. MCID for HCVPRO total score is based on Receiver Operating Characteristic (ROC) curve anchored by SF-36 MCS and SF-36 PCS decrease of 5 points.

**Resistance:**
The following resistance information will be analyzed for subjects receiving active drugs who experience virologic failure: the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline and prototypic reference sequences. The most prevalent amino acid variants found by population sequencing and amino acid variants that emerge or become enriched in isolates from at least 2 subjects will be summarized.

**Pharmacokinetic:**
Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be tabulated and summarized for subjects treated with the active regimen in the DB Treatment Period and the OL Treatment Period.

**Safety:**
The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment arm; comparisons will be performed between the active regimen and placebo during the DB Treatment Period using Fisher's Exact test. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA term) in each treatment group is additionally categorized by rating (mild, moderate, or severe) and relationship to study drugs. Change from baseline in laboratory tests and vital sign measurements to each timepoint of collection during the DB Treatment Period will be summarized by treatment group and compared between the active and placebo groups in the DB Treatment Period using contrasts within an ANOVA model with treatment group as the factor. Laboratory and vital sign values that are potentially clinically significant (PCS), according to predefined criteria, will be identified, and the percentage of subjects with potentially clinically significant values during the DB Treatment Period will be compared between groups using Fisher's exact tests.
## 1.2 List of Abbreviations and Definition of Terms

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ABT-450/r</td>
<td>ABT-450 administered with ritonavir</td>
</tr>
<tr>
<td>ABT-450/r/ABT-267</td>
<td>ABT-450 co-formulated with ritonavir and ABT-267</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>APRI</td>
<td>Aspartate aminotransferase-to-Platelet Ratio Index</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>AARDEX</td>
<td>Advanced Analytical Research on Drug Exposure</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BID</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index BUN</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CYP2C8</td>
<td>Cytochrome P450 2C8</td>
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<tr>
<td>CYP3A</td>
<td>Cytochrome P450 3A</td>
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<tr>
<td>DAA</td>
<td>Direct-acting antiviral agent</td>
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<tr>
<td>DB</td>
<td>Double-blind</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
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<tr>
<td>EDC</td>
<td>Electronic data capture</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EOT</td>
<td>End of treatment</td>
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<tr>
<td>EOTR</td>
<td>End of treatment response</td>
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<tr>
<td>EQ-5D-5L</td>
<td>EuroQol 5 Dimensions 5 Levels Health State Instrument</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>GAM</td>
<td>Generalized additive method</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GCSF</td>
<td>granulocyte colony stimulating factor</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
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<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>hCG</td>
<td>Human Chorionic Gonadotropin</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HCV Ab</td>
<td>Hepatitis C virus antibody</td>
</tr>
<tr>
<td>HCVPRO</td>
<td>Hepatitis C Virus Patient Reported Outcomes Instrument</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td>HIV Ab</td>
<td>Human immunodeficiency virus antibody</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<td>IL28B</td>
<td>Interleukin 28B</td>
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<td>IMP</td>
<td>Investigational Medical Product</td>
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<tr>
<td>INR</td>
<td>International normalized ratio</td>
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<td>IP-10</td>
<td>Interferon gamma-induced protein 10</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IRT</td>
<td>Interactive Response Technology</td>
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<tr>
<td>ITT</td>
<td>Intent to Treat</td>
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<tr>
<td>IU</td>
<td>International units IUD</td>
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<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
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<tr>
<td>LLN</td>
<td>Lower limit of normal</td>
</tr>
<tr>
<td>LLOD</td>
<td>Lower limit of detection</td>
</tr>
<tr>
<td>LLOQ</td>
<td>Lower limit of quantification</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimal clinically important difference</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger RNA</td>
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<tr>
<td>NS3A</td>
<td>Nonstructural viral protein 3A</td>
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<td>NS4A</td>
<td>Nonstructural viral protein 4A</td>
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<td>NS5A</td>
<td>Nonstructural viral protein 5A</td>
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<td>NS5B</td>
<td>Nonstructural viral protein 5B</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OATP1B1</td>
<td>Organic anion transporting polypeptide 1B1</td>
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<tr>
<td>OL</td>
<td>Open-label</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PCS</td>
<td>Potentially clinically significant or Physical component Summary</td>
</tr>
<tr>
<td>PegIFN</td>
<td>Pegylated-interferon alfa-2a or 2b</td>
</tr>
<tr>
<td>PG</td>
<td>Pharmacogenetic</td>
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<td>Reverse transcriptase PCR</td>
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<td>RVR</td>
<td>Rapid virologic response</td>
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<td>SAE</td>
<td>Serious adverse event</td>
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<td>Statistical Analysis System</td>
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<td>Short-Form 36 Version 2 health status survey</td>
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<tr>
<td>SGOT</td>
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<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>SVR</td>
<td>Sustained virologic response</td>
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<td>SVR$_{24}$</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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<td>Baseline/DB Day 1 through last dose of active drugs (DB through OL Treatment Periods)</td>
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3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals chronically infected worldwide.\(^1\) While therapy for this condition has improved considerably with approval of the protease inhibitors telaprevir and boceprevir, these direct-acting antiviral agents (DAA) must be used in combination with pegylated-interferon (pegIFN) and ribavirin (RBV) for up to 48 weeks.\(^2,3\) Treatment with pegIFN and RBV may be associated with considerable, often treatment-limiting toxicities. Thus, the currently available treatment regimens are not optimal and there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment and/or decrease the need for pegIFN and RBV as components of HCV therapy.

Combinations of multiple DAAs with pegIFN and RBV may further improve sustained virologic response (SVR) rates or shorten duration of therapy. Ultimately, it is anticipated that regimens combining multiple DAAs may be curative without the need for combination pegIFN and RBV. Exploratory studies with such pegIFN and RBV sparing combination regimens in humans have been initiated, and promising short-term antiviral efficacy has been reported from IFN-free combinations (either with or without RBV) of an HCV protease inhibitor with a nucleoside polymerase inhibitor,\(^4\) a nonnucleoside polymerase inhibitor,\(^5\) and a nonstructural viral protein 5A (NS5A) inhibitor.\(^6\) Additionally, studies evaluating the combination of a nonstructural protein 5B (NS5B) nucleotide polymerase inhibitor and RBV have been initiated.\(^7\) Sustained virologic response 12 weeks post-doing (SVR\(_{12}\)) in rates as high as 90% (9/10 subjects) have been observed in genotype 1b infection with an NS5A plus protease inhibitor combination\(^8\) and 100% (10/10 subjects) in genotype 2 or 3 infection with a nucleotide polymerase inhibitor plus RBV.\(^7\)

Abbott currently has a number of DAA compounds in clinical development: ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor, ABT-267 is an NS5A inhibitor, and ABT-333 is a NS5B non-nucleoside polymerase inhibitor. These agents have the potential for co-administration in the treatment of HCV...
infection. This double-blind, placebo-controlled study is intended to examine the safety and antiviral activity of 12 weeks treatment with ABT-450/r/ABT-267 with ABT-333 co-administered with RBV in treatment-naïve adults with chronic HCV genotype 1 infection.

**ABT-450**

ABT-450, (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-\{[(5-methylpyrazin-2-yl)carbonyl]amino\}-5,16-dioxo-2-(phenanthridin-6-yl)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocycloprop[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate, is a NS3 protease inhibitor with nanomolar potency against genotype 1 HCV in vitro. ABT-450 is metabolized primarily by cytochrome P450 3A4 (CYP3A) and thus is dosed with ritonavir, (the combination is denoted as ABT-450/r) a potent CYP3A inhibitor, in order to enhance exposures.

ABT-450/r has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown potent antiviral activity at doses of 50/100 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-450.9

**ABT-267**

ABT-267, dimethyl \([(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diy][bis\{benzene4,1-diylcarbamoyl(2S)prrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]]\}biscarbamate hydrate, is a novel NS5A inhibitor, with inhibitory concentrations in the picomolar range against genotypes 1a and 1b in subgenomic replicon systems.

ABT-267 has a favorable safety, tolerability, and pharmacokinetic profile at all doses administered to date, and has shown substantial antiviral activity during 3 days of monotherapy in HCV genotype 1-infected subjects. Additional detailed information
about preclinical toxicology, metabolism, pharmacology, and clinical data can be found in the Investigator's Brochure for ABT-267.10

The ABT-267 formulation used in the Phase 2b study M11-652 is a HME tablet. The formulation to be used in this study is a HME co-formulation of ABT-450 and ritonavir with ABT-267. Exposures to ABT-267 from the co-formulation is comparable to that from the HME formulation used in Study M11-652.

**ABT-333**

ABT-333, (sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide), is a non-nucleoside NS5B polymerase inhibitor with inhibitory concentrations in the nanomolar range against genotypes 1a and 1b NS5B in subgenomic replicon systems. ABT-333 has been well tolerated in single and multiple dose studies in healthy volunteers, and when administered to HCV-infected subjects at doses up to 800 mg BID for up to 12 weeks. The mean $t_{1/2}$ ranged from approximately 5 to 8 hours.

ABT-333 has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown antiviral activity in HCV genotype 1-infected subjects at doses greater than 100 mg BID. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-333.11

The ABT-333 formulation used in the Phase 2b Study M11-652 is a 400 mg tablet. The formulation to be used in this study is a 250 mg optimized formulation of ABT-333. Exposures of the 250 mg ABT-333 dose from the optimized formulation is expected to be comparable to that from 400 mg dose of the formulation used in Study M11-652.

**Combination Dosing in HCV-Infected Subjects**

In the M12-267 study open-label ABT-450/r 150/100 mg QD was administered for 12 weeks to 11 HCV genotype 1-infected treatment-naïve subjects with host interleukin
28B (IL28B) rs12979860 CC genotype, in combination with weight-based RBV and a non-nucleoside polymerase inhibitor, ABT-072, which has antiviral activity comparable to that of ABT-333. The combination was safe and well tolerated and was associated with rapid and durable virologic suppression, with all 11 subjects achieving HCV RNA levels below the limit of quantitation by Week 4. To date, 10 of 11 subjects have achieved sustained virologic response 24 weeks post-dosing (SVR24) with one subject subsequently experiencing a late relapse at post-treatment Week 36.12

In a separate Study M12-746 open-label ABT-450/r QD and ABT-333 400 mg BID were administered for 12 weeks in combination with weight-based RBV to 33 treatment-naive and 17 treatment-experienced (pegIFN/RBV non-responders and null-responders) HCV genotype 1-infected adults. ABT-450/r in this study was given at doses of 150/100 mg or 250/100 mg QD. Thirty-one of 33 treatment-naive subjects have completed 12 weeks of dosing; rapid virologic suppression was seen in all 31 subjects and all 31 (94%) achieved SVR12. No relapses have been identified to date among these subjects with durations of follow-up as long as 48 weeks. Among the 17 treatment-experienced subjects, 6 experienced breakthrough during treatment and to date 3 have experienced post-treatment relapse. The remaining 8 subjects have achieved SVR24 resulting in an overall SVR24 rate of 47% (8/17) in this treatment-experienced population.13,14

Preliminary safety results in Study M12-746 show that the regimen was generally well tolerated. There have been no serious adverse events with the majority of adverse events being reported as mild, including fatigue, pruritus, and headache. One subject in the ABT-450/r 250/100 mg and ABT-333 400 mg BID treatment arm experienced a Grade 3 ALT elevation at Week 2 and discontinued study drug dosing as a result. The subject was asymptomatic, did not have concomitant total bilirubin increases, and the ALT decreased promptly after discontinuing study drug. There were no Grade 3 or greater elevations of ALT at ABT-450/r doses less than 250/100 mg QD. A second subject in the ABT-450/r 250/100 mg and ABT-333 400 mg BID treatment arm experienced an asymptomatic Grade 3 total bilirubin elevation of 6.2 mg/dL at Week 2, which remained at Grade 2 throughout most of the remainder 12 weeks of dosing and
normalized after treatment was discontinued. The elevation was predominately due to increases in indirect bilirubin and was not associated with symptoms referable to the hepatobiliary system, or with elevated levels of transaminases or alkaline phosphatase.

**StudyM11-652**

Study M11-652 is an ongoing multicenter, open-label Phase 2b study evaluating the antiviral activity, safety and pharmacokinetics of multiple ABT-450/r-based DAA combination regimens in HCV genotype 1-infected adults who are either treatment-naïve or are previous null responders to pegIFN and RBV. This study consists of 14 arms: 9 arms with planned enrollment of 440 treatment-naïve subjects and 5 arms with planned enrollment of 120 null responders. The primary and secondary efficacy endpoints compare the percentage of treatment-naïve subjects achieving SVR24 across the various regimens.

Preliminary efficacy data suggest that all regimens demonstrate rapid suppression of HCV-1 RNA levels. The majority of subjects in all 8- and 12-week treatment arms have completed study treatment and are in post-treatment follow-up. In the null responders to previous pegIFN/RBV 12-week treatment arms, the 4 drug regimen using the higher ABT-450 dose (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID with RBV) demonstrates numerically higher SVR4 rates (SVR4 95%) than either the 3 drug regimen (ABT-450/r 200 mg QD + ABT-267 25 mg QD with RBV, SVR4 90%) or the 4 drug regimen using the lower ABT-450 dose (ABT-450/r 100/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID with RBV, SVR4 90%). Thus, the 4 drug regimen using the higher ABT-450 dose for 12 weeks will be used in the current study.

Preliminary resistance testing in Study M11-652 suggests that in the majority of subjects who experienced virologic failure, viral mutations were selected in the target regions corresponding to the DAAs each subject was receiving with the exception of those treated for 8 weeks, among whom most had populations at the time of relapse that were identical to their baseline sample.
Preliminary safety analysis showed that all study drug regimens were well tolerated for up to 24 weeks in treatment-naive and prior null responder subjects. Approximately 1.2% discontinued study drug treatment due to adverse events. The majority of adverse events reported have been mild or moderate in severity, the most frequent including nausea, headache, fatigue, insomnia and diarrhea. Laboratory abnormalities included decreases in hemoglobin, most likely related to RBV, since mean decreases in hemoglobin from baseline to the end of treatment were greater in arms with RBV than in the arm without RBV (2.0 – 2.8 g/dL versus 0.7 g/dL). Grade 3 (or higher) elevations of ALT occurred in 5 subjects (all without bilirubin elevation) all of whom were asymptomatic. In all 5 cases ALT normalized without intervention or study drug modification or interruption. Four of these subjects were receiving ABT-450/r at a dosage of 200/100 mg which is greater than the planned ABT-450/r dose in the current study. The highest ALT level in Study M11-652 was 408 U/L. To date, the majority of subjects randomized to 24 weeks of treatment in Study M11-652 are still receiving study treatment. However, preliminary assessment of safety and efficacy suggest that these treatment regimens are comparable to the corresponding 12-week treatment regimens.

The current double-blind, placebo-controlled study is intended to examine the safety and antiviral activity of 12 weeks treatment with ABT-450/r/ABT-267 with ABT-333 co-administered with RBV in pegIFN/RBV treatment-experienced adults with chronic HCV genotype 1-infection. Additional discussion and justification of study design may be found in Section 5.6.

3.1 Differences Statement

The differences between this study and the previous DAA combination studies are as follows:

- This is a Phase 3 DAA combination study in all types of pegIFN/RBV treatment experienced subjects: null responders, partial responders, and relapsers. Prior Phase 2b studies have assessed only prior null responders to pegIFN/RBV.
• Differences in study design: This is a Phase 3 study. Prior DAA combination studies have been conducted in an open-label fashion. This study is a double-blind, placebo-controlled study to confirm the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 co-administered with ribavirin for 12 weeks in approximately 400 treatment-experienced subjects.

• This study will expose significantly more subjects to ABT-450/r/ABT-267 and ABT-333 co-administered with RBV to allow for a more robust assessment of safety and efficacy.

• The DAA formulations used in this study also differ from those used in Study M11-652.

3.2 Benefits and Risks

Study M13-098 consists of two arms in which three DAAs and RBV are administered together in one arm with placebo for the DAAs and RBV in the other arm. All subjects randomized to placebo will be eligible to received active drugs after completing 12 weeks on study. Promising clinical data on interferon free regimens have been reported using combination DAA regimens; the Sponsor is currently conducting two trials, Study M11-652 and Study M12-998 which include arms evaluating interferon and ribavirin free regimens for 12-week durations.

Based on data from Study M11-652, the SVR₄ rate of 12 weeks of ABT-450/r, ABT-333, ABT-267 co-administered with RBV in a null responder population is 90% and 95% with the lower dose of ABT-450/r (100/100 mg) and the higher dose of ABT-450/r (150/100 mg), respectively. Previous analyses have reported that SVR₄ has a 91% positive predictive value for SVR₂₄, suggesting SVR₄ results provide clinically meaningful assessment of long term response.¹⁵ Partial responders and relapsers have had higher SVR rates than null responders in multiple regimens by other sponsors.

In Study M11-652, the regimen has been generally well-tolerated. Details about the safety of the DAAs, including data from Study M11-652 are provided in the Investigator's Brochures for the individual DAAs.
Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the ICF 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 co-administered with RBV, including the risks of toxicity and virologic failure, appear limited and manageable based on the results of ongoing trials. Given the potential high rate of cure in this population of HCV-infected subjects, the risk-benefit comparison is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to assess the efficacy (the percentage of subjects achieving SVR12, HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) and safety of ABT-450/r/ABT-267, and ABT-333 co-administered with RBV for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults.

4.2 Secondary Objective

The secondary objectives of this study are to assess the rapid virologic response (RVR) rate (the percentage of subjects with HCV RNA < LLOQ at Week 4), end of treatment response (EOTR) rate (the percentage of subjects with HCV RNA < LLOQ at Week 12), and the percentage of subjects with ALT normalization at the Final Treatment Visit among the subjects with ALT > upper limit normal (ULN) at Baseline.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT 450/r/ABT-267 and ABT-333 co-administered with RBV in pegIFN/RBV treatment experienced non-cirrhotic HCV genotype 1-infected adults.
Approximately 400 HCV genotype 1-infected, pegIFN/RBV treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind (DB) Treatment Period at approximately 90 sites.

- **Arm A:** ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks;
- **Arm B:** Placebos for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + Placebo for ABT-333 250 mg BID + Placebo for RBV for 12 weeks followed by active study drug (ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV) for 12 weeks

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

The duration of the study will be up to 72 weeks long (not including a screening period of up to 35 days) consisting of three periods: The DB Treatment Period, the Open-Label (OL) Treatment Period (for subjects randomized to placebo/Arm B), and the Post-Treatment (PT) Period (for all subjects that received active study drugs).

In the DB Treatment Period, randomization will be stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). Subjects on placebo will be administered open-label active study drugs for 12 weeks following completion of the DB Treatment Period. All subjects administered active study drugs will be followed for 48 weeks post-treatment to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants and assessment of PROs. (Figure 1).
The primary analysis will occur after subjects who were initially randomized to active drug have completed through PT Week 12 or prematurely discontinued the study and subjects who were initially randomized to placebo have completed 12-weeks of open-label active treatment or prematurely discontinued study drug.

Safety evaluations will occur throughout the study by a Data Monitoring Committee (DMC). See Section 5.5.2.2. Efficacy evaluations will occur throughout the DB and OL Treatment Periods and if virologic failure criteria as detailed in Section 5.4.1.1 are met, the findings will be discussed with the investigator and reviewed by the Sponsor.

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 Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 associated with the Screening Visit. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through DB 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 35 days following the Screening Visit to enroll into the study.
Screening is required prior to entering the DB Treatment Period only. Subjects randomized to placebo will not be required to re-screen prior to entering the OL Treatment Period.

Subjects should otherwise meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

The study is designed to enroll 400 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

5.1.1.1 Rescreening

Subjects may be rescreened only once as follows:

- Subjects who meet all eligibility criteria with the exception of one exclusionary laboratory parameter may rescreen once without prior Abbott approval with the exception of exclusionary genotype, a positive drug screen (without prescription for the positive drug), or a positive HIV, HBV or pregnancy test. Subjects who test positive at Screening for any of these parameters are not eligible to rescreen.

- Subjects who have multiple exclusionary laboratory results require approval from the Abbott Study Designated Physician prior to rescreening the subject.

Subjects being rescreened because of an exclusionary laboratory parameter must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt (with the exception of HCV genotype, IL28B genotype, FibroTest, FibroScan or liver biopsy which do not need to be repeated).

Eligible subjects who fail to enroll within 35 days of screening, regardless of the reason for falling outside the 35-day screening window, may be allowed to rescreen only once.
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 EDC systems.

5.1.2 Treatment Period

5.1.2.1 Double-Blind (DB) Treatment Period

Subjects with HCV genotype 1 who meet the eligibility criteria will be randomized via IRT in a 3:1 ratio to either active drug (ABT-450/r/ABT-267 and ABT-333 co-administered with RBV) or matching placebos on DB Day 1. The DB Treatment Period of the study consists of 12 weeks of double-blind treatment. The Sponsor, investigators and subjects will be blinded to drug assignment and virologic results for the duration of the DB Treatment Period. Virologic results will be reviewed and virologic failure criteria will be applied to those subjects randomized to active drugs by an unblinded independent reviewer. See Section 5.4.1.1 for further details. Certain safety laboratory results which, if available, could potentially be unblinding (such as hemoglobin, hematocrit, AST, ALT, total and indirect bilirubin) will also be blinded to the Sponsor, investigators and subjects. For each of the blinded laboratory tests if a prespecified toxicity threshold is exceeded then the relevant unblinded laboratory data will be provided to the investigator and Sponsor. See Section 6.7 for further details. In addition, a subject's study drug assignment may be unblinded as directed by the toxicity management guidelines or at the investigator's discretion, if deemed necessary for subject safety.

Sites should ensure that subjects adhere to the study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drugs prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

At the Week 12 Visit of the DB Period, the study drug assignment will be unblinded and subjects randomized to placebo who complete the 12-week DB Treatment Period may enter the OL Treatment Period, consisting of 12 weeks of active therapy. Following completion or discontinuation of active therapy (either in the DB or OL Treatment
Period), all subjects will enter the PT Period consisting of 48 weeks of post-treatment follow-up.

Subjects who prematurely discontinue from the DB Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as defined in Table 3 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 drug and prior to the initiation of any other anti-HCV therapy. At the Treatment Discontinuation Visit, subjects will be unblinded to study drug assignment. Subjects who were randomized to active study drug will immediately start the PT Period and be monitored for virologic failure and resistance as detailed in Section 5.1.4. Subjects who prematurely discontinue study drugs during the DB Treatment Period and who are found to be on placebo at unblinding must continue study visits through DB Week 12 in order to be enrolled into the OL Treatment Period.

5.1.2.2 Open-Label (OL) Treatment Period

After completing the DB Treatment Period, subjects initially randomized to placebo (Arm B) will receive 12 weeks of active treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV. Subjects will be dispensed drugs at the DB Week 12 Visit for administration starting the next day, which will become Day 1 of the OL Treatment Period. The same type of blister cards as were used for placebo will be used for active study drugs ABT-450/r/ABT-267 + ABT-333 and will be dispensed during the OL Treatment Period; open-label RBV tablets will be dispensed during the OL Treatment Period.

Sites must call subjects the next day to verify the first day of open-label, study drug administration and record this date on the eCRF and in the source documents. Study drugs, virologic results and safety laboratory results will not be blinded during the OL Treatment Period. Virologic failure criteria and toxicity management will be evaluated and applied by the investigator (Section 5.4.1.1 and Section 6.7).
Subjects who prematurely discontinue from the OL Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as defined in Table 4 and as described in Section 5.4.1. Ideally, this should occur on the day of 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. Subjects who complete or discontinue the OL Treatment Period will be monitored in the PT Period for virologic resistance as detailed in Section 5.1.3.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of active drugs will be monitored for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of PROs for an additional 48 weeks following the last dose of active study drugs. Subjects will return to the study site as outlined in Table 5 for the PT Period. The PT Period will begin the day after the last dose of active study drugs (in either the DB Treatment Period for subjects who were randomized to Arm A or the OL Treatment Period for subjects who were randomized to Arm B). Subjects who prematurely discontinue the PT Period should return to the site for a PT Discontinuation Visit as outlined in Table 5.

All subjects who receive at least one dose of active DAA may be offered participation in an Abbott-sponsored observational study to evaluate the durability of virologic response for subjects who achieve SVR or to study the emergence and persistence of resistant variants in subjects who fail treatment.

All subjects who receive at least one dose of active DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered another Abbott-sponsored treatment study including ABT-450/r + ABT-267 + pegIFN/RBV. Subjects may also be offered another non-Abbott treatment as determined appropriate by the investigator.
5.1.4 Treatment Failure Extension

During the DB Treatment Period, if greater than or equal to 50% of subjects completing 12 weeks of treatment with active study drug who were null or partial responders to previous pegIFN/RBV treatment experience virologic relapse post-treatment, then the treatment will extend to 24 weeks for all ongoing subjects randomized to active regimen in the DB Treatment Period and all subjects subsequently randomized to the active regimen in the DB Treatment Period (see Appendix C for 24-week Study Activities table). Subjects ongoing in the OL treatment period will have OL active treatment extended to 24 weeks. Subjects subsequently randomized to the placebo group in the DB Treatment Period will still be administered 12 weeks of placebo, but 24 weeks of the active regimen will follow in the OL Treatment Period. This treatment extension assessment will be applied starting when the first 10 null or partial responder subjects who complete 12 weeks of treatment relapse or reach PT Week 12, and weekly thereafter until all subjects have enrolled. The subjects who were relapsers to previous pegIFN/RBV treatment will not be included in these assessments as their response to anti-HCV treatment is presumed to be more like subjects who are naïve to treatment. Treatment may be extended for some strata (e.g., type of response to previous pegIFN/RBV treatment or HCV subgenotype) and not for others based on the strata of the subjects experiencing relapse at a high rate.

5.2 Selection of Study Population

HCV genotype 1-infected adult subjects who are either null-responders, partial responders, or relapsers to prior pegIFN/RBV treatment, and 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 and age is between 18 and 70 years, inclusive, at time of screening.
2. If female, subject is:

- 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
- of childbearing potential:
  - and currently using one of the following methods of birth control at the time of screening and throughout the screening period:
    - total abstinence from sexual intercourse (minimum 1 complete menstrual cycle); or
    - vasectomized partner(s); or
    - intrauterine device (IUD); or
    - condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or creams, or hormonal contraceptives including, oral, injected and implantable forms.
  - and willing to use two effective forms of birth control (as described above) while receiving study drugs. Oral contraceptives or contraceptives containing ethinyl estradiol are not considered effective during study drug treatment. Subject must also be abstinent from sexual intercourse or be willing to use two effective forms of birth control for 7 months (or per local ribavirin label) after stopping study drugs.

3. Females must have negative results for pregnancy tests performed:

- at Screening by serum specimen within 35 days prior to initial study drug administration, and
- at Baseline (prior to dosing) by urine specimen.
4. Males must be abstinent from sexual intercourse, surgically sterile or agree to practice two effective forms of birth control from those listed below, throughout the course of the study, starting with DB Day 1 and for 7 months after the last dose of study drugs (or per local RBV label):
   - Partner(s) using an IUD,
   - Partner(s) using oral, injected, or implanted methods of hormonal contraceptives,
   - Subject and/or partner(s) using condoms, contraceptive sponge or diaphragm with spermicidal jellies or creams.

5. Subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:
   - Null-responder: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a $2 \log_{10} \text{IU/mL}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16); or received less than 12 weeks of pegIFN/RBV for the treatment of HCV and achieved a $< 1 \log_{10} \text{IU/mL}$ reduction in HCV RNA at Week 4 ($\geq 25$ days); or
   - Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10} \text{IU/mL}$ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
   - Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 24 weeks of treatment follow-up.

PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.

6. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.
7. Body Mass Index (BMI) is from \( \geq 18 \) to \( < 38 \) kg/m\(^2\) at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).

8. Must voluntarily sign and date an informed consent form, approved by an IRB/IEC, prior to the initiation of any screening or study specific procedures.

9. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:
   
   ● Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   
   ● Positive for anti-HCV Ab and HCV RNA 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).

10. Screening laboratory result indicating HCV genotype 1-infection.

11. Per local standard practice, documented results of one of the following:
   
   ● 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
   
   ● A screening FibroTest score of \( \leq 0.72 \) and Aspartate Aminotransferase to Platelet Ratio Index (APRI) \( \leq 2 \); or
   
   ● A screening FibroScan result of \( < 9.6 \) kPa.

   Subjects with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy preformed within 24 months prior to or during screening.

12. Subject has plasma HCV RNA level \( > 10,000 \) IU/mL at Screening.
**Rationale for Inclusion Criteria**

(1, 5, 9, 10 – 12) To select the appropriate subject population with sufficient disease severity for evaluation.

(7) For the safety of study subjects.

(2 – 4) RBV has known teratogenic effects.

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

**5.2.2 Exclusion Criteria**

1. History of severe, life-threatening or other significant sensitivity to any drug.

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

3. Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.

4. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.

5. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human immunodeficiency virus antibody (HIV Ab).

6. HCV genotype performed during screening indicates co-infection with any other genotype.
7. Use of any medications listed below as well as those that are contraindicated for ritonavir and ribavirin within 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer, including but not limited to:

Table 1. Medications Contraindicated for Use with the Study Regimen

<table>
<thead>
<tr>
<th>Alfuzosin</th>
<th>Lovastatin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Midazolam (oral)</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Mifepristone</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Modafinil</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Montelukast</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Nefazodone</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Phenobarbital</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Phenytoin</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Pimozide</td>
<td>Triazolam</td>
</tr>
<tr>
<td>Eleptriptan</td>
<td>Pioglitazone</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Propafenone</td>
<td>Troglitazone</td>
</tr>
<tr>
<td>Ergot Derivatives</td>
<td>Quercetin</td>
<td>Troleandomycin</td>
</tr>
<tr>
<td>Fusidic Acid</td>
<td>Quinidine</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
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</tr>
</tbody>
</table>

Or
Table 2. Medications Contraindicated Because Dose Adjustments Cannot Be Readily Made Prior to or During the Blinded Placebo-Controlled Phase of the Study

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Lidocaine (use for local anesthesia is permitted)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Perphenadine</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Risperadone</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Tacrolimus (use topically is permitted)</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Tadalafil</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Thioridazine</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Vardenafil</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
</tr>
</tbody>
</table>

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.

8. Use of known inhibitors or inducers of cytochrome P450 3A (CYP3A), inhibitors of cytochrome P450 2C8 (CYP2C8) within 2 weeks or 10 half-lives (if known) of the respective medication/supplement, prior to study drug administration.

9. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result (including methadone) associated with documented short-term use or chronic stable use of a prescribed medication in that class.
10. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator.

11. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.

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

13. Any cause of liver disease other than chronic HCV infection, including but not limited to the following:
   - Hemochromatosis
   - Alpha-1 antitrypsin deficiency
   - Wilson's disease
   - Autoimmune hepatitis
   - Alcoholic liver disease
   - Nonalcoholic steatohepatitis
   - Drug-related liver disease

14. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - ALT > 5 × Upper limit of normal (ULN)
   - AST > 5 × ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
- Albumin < Lower limit of normal (LLN)
- Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the Abbott Study Designated Physician
- Hemoglobin < LLN
- Platelets < 120,000 cells per mm³
- Absolute neutrophil count (ANC) < 1500 cells/μL
- Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

15. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or DB Day 1 (prior to dosing).

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

17. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir or RBV.

18. Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than pegIFN/RBV) including previous exposure to telaprevir, boceprevir, ABT-450, ABT-267, ABT-333. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled with the approval of the Abbott Study Designated Physician if they can produce documentation that they received only placebo. Concurrent participation in a non-interventional, epidemiologic or registry trial may be permitted with approval by the Abbott Study Designated Physician.
19. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period.

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

**Rationale for Exclusion Criteria**

(1, 3, 8 – 12, 14, 15, 17, 20) To ensure safety of the subjects throughout the study.

(2, 4, 6, 7, 16, 18, 19) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.

(5, 13) To exclude subjects with liver diseases other than HCV.

**5.2.3 Prior and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of signing the consent through the DB and OL (if applicable) Treatment Periods of the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

All medication use will be recorded until 30 days following the last dose of study drugs. Only medications associated with HCV treatment or a serious adverse event (SAE) will be collected thereafter.

The Abbott study-designated physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).
5.2.3.1 Prior HCV Therapy

All study subjects must have previously received pegIFN and RBV and failed treatment (either on treatment or via relapse post-treatment). These subjects should have documentation of pegIFN and RBV treatment history, including start and stop dates and HCV RNA levels to document the type of non-response in the source.

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

Prior or current use of any other investigational or commercially available anti-HCV agents other than pegIFN/RBV, including telaprevir, boceprevir, 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 or herbal supplements within 2 weeks or within 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to initial study drug administration and up to 2 weeks following discontinuation of study drug dosing. Subjects must be consented prior to discontinuing any prohibited medications or herbals supplements for the purpose of meeting study inclusion criteria.

Investigator should confirm that concomitant medication can be administered with DAAs (including ritonavir) and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. The investigator can also review the label(s) for the concomitant medication(s) for additional information.

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

In addition to the medications listed above in Table 1 and Table 2; use of known inhibitors or inducers of CYP3A, or inhibitors of CYP2C8 is prohibited within 2 weeks or 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to the initial dose of study drug and for the first two weeks after the subject has completed active study drugs.

Alprazolam, diazepam, clonazepam, clorazepate, estazolam and flurazepam, may be contraindicated depending on the anticipated duration, dose and frequency of use. Individuals on these medications must contact the Abbott Study Designated Physician to verify if the use of these medications is exclusionary.

Anti-HCV medications other than those specified in the protocol will not be allowed during either the DB or OL Treatment Periods of the study.

Use of hematopoietic growth factors is not permitted during this study without the approval of the Abbott Study Designated Physician. Management of hematologic growth factor therapy is the responsibility of the investigator; growth factors will not be provided by the Sponsor, and the Sponsor will not reimburse for the expense of growth factors or their use.

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

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in Table 3, Table 4, and Table 5.
<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C from DB Treatment&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
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<td>Informed Consent</td>
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<td>Provide RBV Medication Guide and Partner Risk Fact Sheet&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Vital Signs, Weight, Height&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>ECG&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
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<tr>
<td>Pregnancy Test [serum (s) urine (u)]&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X (s)</td>
<td>X (u, s)</td>
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<td>FSH (all females)</td>
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<td></td>
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</tr>
<tr>
<td>HBsAg, Anti-HCV Ab, Anti HIV Ab</td>
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<tr>
<td>Drug/Alcohol Screen</td>
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<td>HgbA1c</td>
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<tr>
<td>HCV Genotype and Subtype</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Liver Biopsy or FibroTest or FibroScan&lt;sup&gt;h&lt;/sup&gt;</td>
<td>X</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pharmacogenetic Sample (optional)&lt;sup&gt;i&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>DB Day 1: Day of Randomization, <sup>b</sup>DB Wk 12 (EOT): End of Treatment, <sup>c</sup>Premature D/C from DB Treatment: Premature Discontinuation of Double-blind Treatment, <sup>d</sup>Risk Fact Sheet: Document to inform participants about potential risks associated with the study, <sup>e</sup>Vital Signs: Measurement of body temperature, blood pressure, and heart rate, <sup>f</sup>ECG: Electrocardiography, <sup>g</sup>Pregnancy Test: Test for pregnancy, <sup>h</sup>Liver Biopsy: Biopsy of liver tissue, <sup>i</sup>IL28B Sample: Sample for IL28B gene analysis.
Table 3. Study Activities – Double-blind (DB) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C from DB Treatment&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messenger RNA (mRNA) Sample (optional)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total Insulin</td>
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<td></td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Adverse Event Assessment</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Patient Reported Outcomes Instruments (PROs)&lt;sup&gt;j&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td></td>
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<td>X</td>
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</tr>
<tr>
<td>Study Drugs Dispensed</td>
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<td>X</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medication Event Monitoring System (MEMS) cap dispensed</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drugs Collected, MEMs Cap Downloaded and Compliance Reviewed</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;l&lt;/sup&gt;</td>
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<td>Unblinding</td>
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<td></td>
<td>X</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
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</tr>
<tr>
<td>HCV RNA Samples</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV Resistance Sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Table 3. Study Activities – Double-blind (DB) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C from DB Treatment&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon gamma-induced protein 10 (IP-10) Sample</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Albumin&lt;sup&gt;n&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

- a. All procedures will be performed prior to first dose.
- b. Subjects randomized to Arm B and beginning the OL Treatment Period should have all procedures completed prior to dosing OL Day 1.
- c. Subjects randomized to Arm A should begin the PT Period after the subject completes or prematurely discontinues study drugs treatment in this period.
- d. Where applicable/locally available.
- e. Height will be measured at the Screening Visit only.
- f. Evaluate DB day 1 ECG prior to dosing to determine eligibility.
- g. Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal.
- h. For subjects who have not had a qualifying liver biopsy within the previous 24 months.
- i. If the optional Pharmacogenetic sample is not collected at DB Day 1, it may be collected at any other visit during the study.
- j. SF-36V2, EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), and Hepatitis C Virus Patient Reported Outcomes Instrument (HCVPRO) should be administered before any study procedures including unblinding and in the order listed.
- k. Subjects randomized to Arm B will have study drugs and a MEMS cap dispensed for open-label RBV at the DB Week 12 Visit.
- l. MEMS cap will be collected at the DB Week 12 or Premature D/C visit (if applicable).
- m. Subjects randomized to active study drugs will proceed to the PT Period (Table 5). Subjects randomized to Arm B will begin the OL Treatment Period (Table 4) after completing DB Week 12 with active study drugs dispensed to begin dosing the next day (OL Day 1).
Table 3. **Study Activities – Double-blind (DB) Treatment Period (Continued)**

n. May also be done as part of toxicity management (Section 6.7.5).

* In the event that the treatment failure extension parameters are met (Section 5.4.1.1) subjects will attend visits as outlined in Table 3 and then upon unblinding will be extended to the 24-week active treatment duration as outlined in Appendix C.
# Table 4. Study Activities – Open-label (OL) Treatment Period

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8</th>
<th>OL Wk 10</th>
<th>OL Wk 12 (EOT)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Premature D/C from OL Treatment&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject takes first doses of active study drugs and site calls subject to confirm start date</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical Exam</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs, Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology/Chemistry/Urina lysis/Coagulation Panel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Pregnancy Test [urine (u)]&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
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<td>X (u)</td>
<td>X (u)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Study Drugs Dispensed</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drugs Collected, MEMs Cap Downloaded and Compliance Reviewed</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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<td>HCV RNA Samples</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>HCV Resistance Sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Archive Plasma Sample</td>
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</table>
Table 4. Study Activities – Open-label (OL) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8</th>
<th>OL Wk 10</th>
<th>OL Wk 12 (EOT)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Premature D/C from OL Treatment&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
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<td></td>
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<td>X</td>
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</tr>
<tr>
<td>mRNA Sample (optional)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Total Insulin</td>
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<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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

a. Take first doses of all study drugs the day after the last day of the DB Treatment Period. The site will call the subject and record the study drug start dates in the electronic data capture (EDC) system and source notes. The study drug end date of all drugs will be recorded in EDC and the source at OL Week 12 or Premature D/C.

b. Subjects will begin the PT Period after completing study drug treatment or prematurely discontinuing the OL Treatment Period.

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

d. MEMs cap will be collected at the OL Week 12 or Premature D/C visit.
### Table 5. Study Activities – Post-Treatment (PT) Period

<table>
<thead>
<tr>
<th>Activity</th>
<th>PT Wk 2</th>
<th>PT Wk 4</th>
<th>PT Wk 8</th>
<th>PT Wk 12</th>
<th>PT Wk 24</th>
<th>PT Wk 36</th>
<th>PT Wk 48 or PT D/C</th>
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<tr>
<td>Vital Signs and Weight</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Monthly Pregnancy Test (females)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Weeks 12, 16, 20, 24, 28)</td>
</tr>
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<td>PRO Instruments&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>X</td>
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<td>X</td>
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<td>Concomitant Medication Assessment&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Assessment&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>HCV RNA Samples</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV Resistance Sample</td>
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<td>Archive Plasma Sample</td>
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<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>mRNA Sample (Optional)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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

- a. Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or who are confirmed post-menopausal. At PT Weeks 16, 20, and 28, subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

- b. SF-36V2, EQ-5D-5L, and HCVPRO should be administered before any study procedures and in the order listed. Subjects who were randomized to placebo and completed the OL Treatment Period do not need to complete PRO instruments during the PT Period.

- c. Only medications related to the treatment of HCV and medications prescribed in association with an SAE will be collected after 30 days post-dosing.

- d. Only SAEs will be collected after 30 days post-dosing.

**Note:** Day 1 of the PT Period will be defined as the day after the last dose of active study drug treatment (in either the DB Treatment Period, for subjects randomized to active drug or the OL Treatment Period for subjects randomized to Arm B and treated with open-label active drug).
5.3.1.1 Study Procedures

The study procedures outlined in Table 3 through Table 5 are discussed in detail in this section, with the exception of the assessment of concomitant medications (Section 5.2.3.2), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), the monitoring of treatment compliance (Section 5.5.6) and the collection of adverse event information (Section 6.4).

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. All subjects will be given the RBV Medication Guide (where applicable/locally available). Male subjects will be given an additional copy of the RBV Medication Guide (where applicable/locally available) and a RBV Partner Risk Fact Sheet to share with their female partner(s). 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, alcohol and injection drug use, will be taken from each subject during the Screening Visit. The subject's medical history will be updated at the DB Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Table 3 and Table 4 (if applicable), or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on DB Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.
**Vital Signs, Weight, Height**

Body temperature (oral), blood pressure, pulse and body weight will be measured at the visits specified in Table 3 and Table 4 (if applicable) and Table 5. The vital signs performed on DB Day 1 will serve as the baseline for clinical assessment. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

**12-lead Electrocardiogram**

A 12-lead resting ECG will be obtained at the visits specified in Table 3 and Table 4 (if applicable), or upon subject discontinuation (or as clinically needed). The Part 1 Day 1 reading will serve as the baseline assessment.

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

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

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

The original ECG tracing will be retained in the subject's records at the study site.
Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 6 at the visits specified in Table 3 and Table 4 (if applicable) and Table 5.

Blood samples for serum chemistry tests should ideally be collected following a minimum 8-hour fast (with the exception of the Screening Visit, which may be 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. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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

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

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

For sites in Canada, Mexico, Puerto Rico, USA:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA
For sites in Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Russia, Spain, Turkey, United Kingdom:

Covance
7 rue Marcinhes
1217 Geneva
Meyrin Switzerland

For sites in Australia:

Covance (Asia) Pte Ltd
1 International Business Park
#01-01 The Synergy
Singapore 609917
# Table 6. Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Urinalysis</th>
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<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Specific gravity</td>
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<tr>
<td>Hemoglobin</td>
<td>Creatinine</td>
<td>Ketones</td>
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<tr>
<td>Red Blood Cell (RBC) count</td>
<td>Total bilirubin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>pH</td>
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<tr>
<td>White Blood Cell (WBC) count</td>
<td>Direct and indirect bilirubin</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Blood</td>
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<tr>
<td>Bands</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Glucose</td>
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<tr>
<td>Lymphocytes</td>
<td>Alkaline phosphatase</td>
<td>Urobilinogen</td>
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<tr>
<td>Monocytes</td>
<td>Sodium</td>
<td>Bilirubin</td>
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<tr>
<td>Basophils</td>
<td>Potassium</td>
<td>Leukocyte esterase</td>
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<tr>
<td>Eosinophils</td>
<td>Calcium</td>
<td>Microscopic (reflex)</td>
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<tr>
<td>Platelet count (estimate not acceptable)</td>
<td>Inorganic phosphorus</td>
<td>Albumin&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>ANC</td>
<td>Uric acid</td>
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<tr>
<td>Prothrombin Time/INR</td>
<td>Cholesterol</td>
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<td>Activated partial thromboplastin time (aPTT)</td>
<td>Total protein</td>
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<tr>
<td>Reticulocyte count</td>
<td>Glucose</td>
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<td>Triglycerides</td>
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<td>Albumin</td>
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<td>Bicarbonate</td>
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<td>Magnesium</td>
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<td></td>
<td>Gamma-glutamyl transferase (GGT)&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>Creatinine clearance</td>
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<td></td>
<td>(Cockcroft-Gault calculation)</td>
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<td></td>
<td>Estimated glomerular filtration rate (calculation)</td>
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<td>Modification of Diet in Renal Disease (MDRD) (calculation)</td>
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<tr>
<td></td>
<td>Alpha2-macroglobulin&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>Haptoglobin&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>Apolipoprotein A1&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>IL28B&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>HCV genotype and subtype&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Pharmacogenetic sample</td>
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<td>HCV RNA</td>
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<td>Hemoglobin A1C&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Anti-HCV Ab&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>Anti-HIV Ab&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>FSH (females)&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>Opiates&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Barbiturates&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Amphetamines&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>Cocaine&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Benzodiazepines&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Alcohol&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Phencyclidine&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Propoxyphene&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td>Methadone&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Urine and Serum Human</td>
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<tr>
<td></td>
<td>Chorionic Gonadotropin (hCG) (females)&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td>Total insulin</td>
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<td>HCV RNA</td>
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<td>Hemoglobin A1C&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Pharmacogenetic sample</td>
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<td></td>
<td>mRNA sample (optional)</td>
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<sup>a</sup> Component of FibroTest.

<sup>b</sup> Performed only during Screening Period for FibroTest, if needed.

<sup>c</sup> Collected if Creatinine Clearance level < 50 mL/minute. See Section 6.7.5 Creatinine Clearance for details.

<sup>d</sup> Performed only at Screening.

<sup>e</sup> Urine pregnancy testing is not required after DB Day 1 for female subjects who are confirmed to be post-menopausal or who have a documented history of prior bilateral tubal ligation, bilateral oophorectomy or hysterectomy.
For any laboratory test value outside the reference range that the investigator considers clinically significant:

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

The management of laboratory abnormalities that may occur during the study, including procedures for blinded laboratory measurements, are described in Section 6.7.

**Pregnancy Test**

A urine pregnancy test will be performed for all female subjects at all the visits specified in Table 3 and Table 4 (if applicable) and Table 5. In addition, a serum pregnancy test will be performed at Screening and DB Day 1 and analyzed by the central laboratory. All urine pregnancy tests will be performed on-site during the study visit if there is a scheduled visit, as specified in Table 3, Table 4 (if applicable) and monthly for a minimum of 7 months after the discontinuation of RBV, or according to the local RBV label and/or consistent with local treatment guidelines for RBV. Urine pregnancy tests are not required after DB Day 1 for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of postmenopausal status measured by FSH will be obtained at the Screening Visit only.

During the PT Period where there is not a scheduled study visit, female subjects of childbearing potential 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; site personnel should contact these female study subjects to capture the results of any
study-related pregnancy tests performed at home. The pregnancy test results will only be recorded in the subject's source records.

If the subject elects to return to the study site for an unscheduled visit for pregnancy testing, the results of the urine pregnancy test will be recorded in the subject's source records. If a serum pregnancy test is collected, the sample will be analyzed by the central lab and reported in the database.

If urine pregnancy result is positive a confirmatory hCG serum test should be collected and sent to Central Lab.

**Concomitant Medication Assessment**

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) from 2 weeks prior to study drug administration through 30 days after last dose of study drug will be recorded in the eCRF at each study visit indicated in Table 3, Table 4 and Table 5. Only medications associated with HCV treatment or a serious adverse event (SAE) will be collected more than 30 days after the last dose of study drugs.

**Hepatitis and HIV Screen**

HBsAg, anti-HCV Ab and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary. The anti-HIV Ab results will not be reported by the central laboratory to the clinical database.

**Urine Screens for Drugs of Abuse**

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed in Table 6. A positive screen is exclusionary, with the exception of a positive screen (including methadone) associated with documented short-term use or chronic stable use of a prescribed medication in that class.
These analyses will be performed by the certified central laboratory chosen for the study.

**HCV Genotype and Subtype**

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

**Liver Diagnostic Testing**

Subjects who have not had a qualifying liver biopsy within the previous 24 months but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo liver biopsy or non-invasive testing (FibroTest/APRI or FibroScan) prior to enrollment. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice. Subjects with a FibroScan result is ≥ 9.6 kPa, a FibroTest result that is ≥ 0.73 or an APRI > 2 must have a liver biopsy showing no evidence of cirrhosis within 24 months of screening, or in the absence of an available biopsy result within 24 months of Screening, may undergo a liver biopsy to rule out cirrhosis. Subjects with an exclusionary non-invasive test may be enrolled only if the biopsy performed within the previous 24 months or during the Screening period shows no evidence of cirrhosis.

**Pharmacogenetic Blood Samples**

**IL28B Sample**

One required whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected from each subject at Screening for Interleukin 28B (IL28B) analysis. This sample will not be used for any testing other than IL28B genotypes.

**Optional Pharmacogenetic Sample**

A separate optional whole blood sample will be collected on DB 1 from those subjects who choose to participate and consent to additional pharmacogenetic analysis. If this
sample is not collected at DB Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent for this optional sample is discussed in Section 9.3.

Optional Blood Samples for Messenger (mRNA) Analysis

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

Subjects who consent to participate in the mRNA substudy will have blood samples taken as indicated in Table 3, Table 4 (if applicable) and Table 5.

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

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

The optional blood samples for mRNA must be collected at the visits specified in Table 3, Table 4 (if applicable) and Table 5.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-450, ABT-267, ABT-333 or drugs of these classes continues but no longer than 20 years.

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 3 and Table 5. Subjects will be instructed to follow the instructions provided with each instrument and to provide the
best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all visits and will ensure that a response is entered for all items.

In this study, PRO instruments should be consistently presented so that subjects complete the SF-36V2 instrument first, the EQ-5D-5L, and finally the HCVPRO. PRO instruments should be completed prior to drug administration and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

As previously noted, subjects who were randomized to placebo during the DB Treatment Period and completed the OL Treatment Period do not need to complete PRO instruments during the OL or PT Periods.

**ShortForm36–Version2HealthStatusSurvey**

The SF-36V2 is a general 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 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Scoring is totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36V2 scores indicate a better state of health. Completion of the SF-36V2 should require approximately 10 minutes.

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

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

**HCV Patient Report Outcomes (HCVPRO) Instrument**

The HCVPRO has been developed specifically to capture the function and wellbeing impact of HCV conditions and treatment. The HCVPRO contains 16 items important to HCV patients; items are totaled to a summary score. Higher HCVPRO score indicates a better state of health. Completion of the HCVPRO should require approximately 5 minutes.

**Randomization and Assignment of Subject Numbers**

All screening activities must be completed and reviewed prior to randomization. Screening numbers will be unique 6-digit numbers and will begin with 100301, with the first three digits representing the investigative site and the last three digits representing the subjects at that site. Subjects who meet the eligibility criteria may proceed to randomization via the IRT system at the DB Day 1 Visit.

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

**MEMS Caps**

At the DB Day 1 Visit subjects will be assigned 1 MEMS cap for the RBV bottle. To ensure that a dosing event is recorded for the first dose of study drug at the site on DB Day 1, the site should place the MEMS cap on the RBV bottle before dispensing the first dose. Additionally, at each visit, site personnel should download the MEMS dosing history data from the MEMS cap, review, and counsel the patient as appropriate regarding
compliance. Additional information regarding Treatment Compliance and MEMS can be found in Section 5.5.7.

**HCVRNASamples**

Plasma samples for HCV RNA levels will be collected as indicated in Table 3, Table 4 (if applicable) and Table 5. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. The lower limit of detection (LLOD) is 15 IU/mL and results below LLOD are reported as "HCV RNA not detected"; the LLOQ for this assay is 25 IU/mL and results below LLOQ but detectable are reported as "< 25 IU/mL HCV RNA detected."

**HCVResistanceTestingSample**

A plasma sample for HCV resistance testing will be collected at the study visits, indicated in Table 3, Table 4 (if applicable) and Table 5.

**ArchivePlasmaandSerumSample**

Archive plasma and serum samples will be collected at the study visits, indicated in Table 3, Table 4 (if applicable) and Table 5. Archive plasma and serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

**InterferonGamma-InducedProtein10(IP-10)Levels**

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 3, Table 4 (if applicable) and Table 5. The IP-10 testing is exploratory and may not be provided to the investigator.
5.3.1.2 **Meals and Dietary Requirements**

All study drugs should be administered with food.

5.3.2 **Drug Concentration Measurements**

5.3.2.1 **Collection of Samples for Analysis**

Blood samples for assay of ABT-267, possible ABT-267, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, as well as ritonavir and RBV (if applicable) will be collected by venipuncture at each study visit specified in Section 5.3.1 (irrespective of study drug dosing time).

The time that each blood sample is collected will be recorded to the nearest minute.

5.3.2.2 **Handling/Processing of Samples**

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and RBV will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 **Disposition of Samples**

The frozen plasma samples for the pharmacokinetic assays of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and RBV will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory. An inventory of the samples included will accompany the package.

Covance CLS will then ship the ABT-267, ABT-333, ABT-450, ritonavir, and RBV samples to:
An inventory of the included samples will accompany the package and an electronic copy of the Manifests (including subject number, study day, the time of sample collection and barcode) will be sent to the contact person at sample.receiving@abbott.com.

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, and RBV will be determined using validated assay methods under the supervision of the Sponsor's Drug Analysis Department. Plasma concentrations of metabolites of ABT-450 and ABT-267, and other metabolites of ABT-333 may also be determined using non-validated methods.

5.3.3 Efficacy Variables

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

5.3.3.1 Primary Variable

The primary endpoint is the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of active study drugs).
5.3.3.2 **Secondary Variables**

The secondary endpoints are:

- The percentage of subjects with RVR (HCV RNA < LLOQ at Week 4);
- The percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12);
- The percentage of subjects with ALT normalization (ALT ≤ ULN at Final Treatment Visit for subjects with ALT > ULN at Baseline).

5.3.4 **Resistance Variables**

The following resistance information will be analyzed for subjects receiving active drug who experience virologic failure: the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline and prototypic reference sequences.

5.3.5 **Safety Variables**

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

5.3.6 **Pharmacokinetic Variables**

Individual plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, ribavirin and possible metabolites of ABT-450, ABT-267 and ABT-333 (other than ABT-333 M1) will be tabulated and summarized.

5.3.7 **Pharmacogenetic Variables**

IL28B genotypes are associated with response to pegIFN and RBV and to some pegIFN-free regimens. IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B genotype results may be analyzed as part of a multi-study assessment of IL28B and response to
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 results of additional pharmacogenetic analyses may not be reported with the clinical study report.

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be analyzed for genetic factors contributing to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to HCV therapy; no other analyses will be performed.

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

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.
If, during the course of study drug administration, the subject prematurely discontinues during the DB or OL Treatment Periods, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 3 and Table 4. It is recommended that this Visit occur on the day of study drug discontinuation, however, this Visit should occur within 2 days following their final dose of study drugs and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drugs, the subject will be treated in accordance with the investigator's best clinical judgment. The dosing end dates and reason for discontinuation will be recorded in the eCRF. If the subject received any active study drugs, the subject should then begin the PT Period where the subject will be monitored for 48 weeks for the development and persistence of resistance to the DAAs.

Subjects prematurely discontinuing from the DB period and who on unblinding are found to have been randomized to placebo will be required to continue with study procedures in the DB Treatment Period and upon reaching the DB Week 12 Visit, may enter the OL Treatment Period and receive active treatment.

If a subject discontinues from the PT Period the subject should return for PT discontinuation procedures as defined in Table 5. The reason for discontinuation from the PT Period will also be recorded in the Study Discontinuation eCRF.

If a subject is discontinued with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved (Section 6.7).

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drugs (including RBV) to that subject must be discontinued immediately. Specific instructions regarding
subject pregnancy can be found in Section 6.6. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

### 5.4.1.1 Virologic Failure Criteria

During the DB Treatment Period of the study, the virologic results will be reviewed and virologic failure criteria will be applied to those subjects randomized to active drugs by an unblinded independent reviewer who will provide information to the investigators to assist with managing these subjects according to the criteria below. No virologic failure criteria will be applied to subjects randomized to placebo during the DB Treatment Period. During the OL Treatment Period, investigators will be unblinded to virologic data and will manage subjects according to the criteria below.

The following criteria will be considered evidence of virologic failure while the subject is on active drugs and in PT Period:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements > 1 log_{10} IU/mL above nadir) at any time point during treatment;
- Failure to achieve HCV RNA < LLOQ by Week 6;
- Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

When confirmatory testing is required it should be completed as soon as possible. Also, when confirmation is required subjects should remain on study treatment until the virologic failure has been confirmed.

If any of the above criteria are met, the subject will discontinue study treatment (Section 5.4.1).
During the DB Treatment Period, if greater than or equal to 50% of subjects completing 12 weeks of treatment with active study drug who were null or partial responders to previous pegIFN/RBV treatment experience virologic relapse post-treatment, then the treatment will extend to 24 weeks for all ongoing subjects randomized to active regimen in the DB Treatment Period and all subjects subsequently randomized to the active regimen in the DB Treatment Period (see Appendix C for 24 week Study Activities table). Subjects ongoing in the OL treatment period will have OL active treatment extended to 24 weeks. Subjects subsequently randomized to the placebo group in the DB Treatment Period will still be administered 12 weeks of placebo, but 24 weeks of the active regimen will follow in the OL Treatment Period. This treatment extension assessment will be applied starting when the first 10 null or partial responder subjects who complete 12 weeks of treatment relapse or reach PT Week 12, and weekly thereafter until all subjects have enrolled. The subjects who were relapsers to previous pegIFN/RBV treatment will not be included in the assessment as their response to other anti-HCV treatment is presumed to be more like subjects who are naïve to treatment. Treatment may be extended for some strata (e.g., type of non-response to previous pegIFN/RBV treatment or by HCV subtype) and not for others based on the strata of the subjects experiencing relapse at a high rate.

5.4.2 Discontinuation of Entire Study

The Sponsor 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 the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If terminates the study for safety reasons, the Sponsor will notify the investigator and subsequently provide written instructions for study termination.
5.5 Treatments

5.5.1 Treatments Administered

Each dose of blinded and open-label DAA study drugs (ABT-450/r/ABT-267 and ABT-333) or placebo for DAAs and open-label RBV will be dispensed in the form of tablets. Each dose of double-blind RBV or matching placebo for RBV will be dispensed as capsules. Study drugs will be dispensed at the visits listed in Table 3 and Table 4 (if applicable).

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 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

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 capsules during the DB Treatment Period and will be provided as tablets during the OL Treatment Period. Ribavirin has weight-based dosing 1000 to 1200 mg divided twice daily per local label. (For example, for subjects weighing < 75 kg, RBV may be taken orally as 2 tablets [or capsules] in the morning and 3 tablets [or capsules] in the evening which corresponds to a 1000 mg total daily dose. For subjects weighing ≥ 75 kg RBV may be taken orally as 3 tablets [or capsules] in the morning and 3 tablets [or capsules] in the evening which corresponds to a 1200 mg total daily dose.)

Subjects will be instructed to take study medication at the same time(s) every day. All study drugs should be taken with food.

Following enrollment, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Table 3 and Table 4 (if applicable). Study drugs must not be dispensed without contacting the IRT system, and only for
subjects enrolled in the study through the IRT system. At the end of the DB and OL Treatment Period or at the Premature Discontinuation Visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit (Section 5.3.1.1).

At DB Day 1 subjects will be administered study drugs by the study site personnel and receive instructions for self administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period. Subjects will be administered study drugs on DB Day 1 and the date and time of administration of each drug will be recorded. Subjects entering the OL Treatment Period will be given drugs at the DB Week 12 Visit, along with instructions to begin dosing the next day. The site will call the subject on OL Day 1 and record the first date of dose.

All subjects who receive at least one dose of active DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered another Abbott-sponsored treatment study including ABT-450/r + ABT-267 + pegIFN/RBV. Subjects may also be offered another non-Abbott treatment as determined appropriate by the investigator.

5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 7.
Table 7. Identity of Investigational Products

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Manufacturer</th>
<th>Mode of Administration</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/ Ritonavir/ ABT-267</td>
<td>Abbott Laboratories</td>
<td>Oral</td>
<td>Tablet</td>
<td>75 mg/ 50 mg/ 12.5 mg</td>
</tr>
<tr>
<td>ABT-450/ Ritonavir/ ABT-267 placebo</td>
<td>Abbott Laboratories</td>
<td>Oral</td>
<td>Tablet</td>
<td>0 mg</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott Laboratories</td>
<td>Oral</td>
<td>Tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>ABT-333 placebo</td>
<td>Abbott Laboratories</td>
<td>Oral</td>
<td>Tablet</td>
<td>0 mg</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Roche or Generic Manufacturer</td>
<td>Oral</td>
<td>Tablet</td>
<td>200 mg</td>
</tr>
<tr>
<td>Ribavirin capsules</td>
<td>Table: Roche or Generic Manufacturer Capsule: Abbott Laboratories or Fisher Clinical Services for Abbott Laboratories</td>
<td>Oral</td>
<td>Hard Gelatin Capsule</td>
<td>200 mg</td>
</tr>
<tr>
<td>Placebo for Ribavirin tablets</td>
<td>Abbott Laboratories</td>
<td>Oral</td>
<td>Hard Gelatin Capsule</td>
<td>0 mg</td>
</tr>
</tbody>
</table>

5.5.2.1 Packaging and Labeling

Blinded 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 (or matching placebo) and 16 ABT-450/r/ABT-267 75 mg/50 mg/12.5 mg tablets (or matching placebo) for a total of 32 tablets per blinded 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 1 ABT-333 tablet) with a picture of a sun and which should be take in the evening (1 ABT-333 tablet) with a picture of a moon.

Blinded RBV capsules will be supplied to the site in bottles containing 96 capsules each to be used during the DB Treatment Period.
RBV (open-label) tablets will be supplied to the site in bottles containing 168 tablets each to be used during the OL Treatment Period.

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

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

### 5.5.2.2 Storage and Disposition of Study Drugs

#### Table 8. Storage and Disposition of Study Drug

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/r/ABT-267 and ABT-333 or placebo blister cards</td>
<td>15° to 25°C (59° to 77°F) Australia: Store below 25°C</td>
</tr>
<tr>
<td>Open label Ribavirin bottles</td>
<td>15° to 25°C (59° to 77°F) Australia: Store below 25°C</td>
</tr>
<tr>
<td>Ribavirin or placebo bottles</td>
<td>15° to 25°C (59° to 77°F) Australia: Store below 25°C</td>
</tr>
</tbody>
</table>

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 system and identify the subject as a screen failure.

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

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

5.5.4 Selection and Timing of Dose for Each Subject

Study drug dosing will be initiated at the DB Day 1 Visit. ABT-450/r/ABT-267 will be dosed QD; ABT-333 and RBV will be dosed BID. Thus with normal dosing, 2 ABT-450/r/ABT-267 tablets, 1 ABT-333 tablet, should be taken in the morning, and 1 ABT-333 tablet should be taken in the evening.

RBV should be dosed BID, e.g., 2 to 3 tablets (or capsules) taken in the morning, and 3 RBV tablets (or capsules) should be taken in the evening.

All study drugs should be taken with food.

5.5.5 Blinding

Treatment assignment during the DB Treatment Period will remain blinded to the investigator, subject and Sponsor during the 12-week treatment period. ABT-450/r/ABT-267 and ABT-333 or matching placebos will be provided as tablets, and RBV or matching placebo will be provided as capsules.

During the DB Treatment Period, measures to prevent implicit unblinding by laboratory results will be used. Specifically, the results of HCV RNA, hemoglobin, hematocrit, ALT, AST, bilirubin (indirect and total), will be blinded to the investigator, subject and Sponsor until the DB Week 12 or Premature D/C Visit, unless criteria for virologic failure or relevant predefined toxicity are met, in which case the relevant laboratory data will be unblinded to the investigator, subject and Sponsor, see Section 5.5.5.3.
A subject's study drug assignment may be unblinded as part of toxicity management, at the investigator's discretion, if deemed necessary for subject safety or at premature discontinuation.

In the setting of premature discontinuation of double-blind study drug for toxicity management or virologic failure (for those subjects on active drug), the investigator, subject and Sponsor will be unblinded to study drug assignment via IRT. Subjects prematurely discontinuing and who on unblinding are found to have been randomized to placebo will be required to continue with study procedures in the DB Treatment Period while off study drugs and upon reaching the DB Week 12 Visit, may enter the OL Treatment Period and receive active treatment. During the OL Treatment Period, open-label ribavirin tablets and ABT-450/r/ABT-267 and ABT-333 blister cards will be supplied. Subjects prematurely discontinuing and who on unblinding are found to have been randomized to active study drugs will enter the PT Period. During the blinded period, an unblinded independent reviewer will review HCV RNA data and provide guidance related to virologic failure (Section 5.4.1.1).

The Sponsor or the unblinded independent reviewer must be notified before the blind is broken unless identification of the study drugs is required for medical emergency, i.e., a situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). In which case, the Sponsor or the unblinded independent reviewer must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF.

5.5.5.1 Blinding of Investigational Product

During the DB Treatment Period, ABT-450/r/ABT-267 and ABT-333 or matching placebos will be provided as tablets and blinded study medication will be identical in appearance. RBV and matching placebos will be provided as capsules and will be identical in appearance. During the OL Treatment Period open-label RBV will be supplied as tablets with the ABT-450/r/ABT-267 and ABT-333 tablets.
The IRT system will dispense the appropriate treatment during the DB and OL Treatment Periods.

### 5.5.5.2 Data Monitoring Committee (DMC)

An independent DMC will review safety data from this study and provide recommendations to the Sponsor as per the DMC charter. The charter also describes DMC membership, which will include individuals with experience in the management of patients with chronic HCV infection, and member responsibilities. The DMC will receive interim summaries of safety data according to a schedule and format specified in the charter. After each review, the DMC will communicate its recommendations to the Sponsor. The Sponsor will retain sole responsibility for study management, communication with study sites and regulatory authorities.

### 5.5.5.3 Blinding of Other Study Data

DAA therapy exerts a normalizing effect on the levels of hepatic transaminases, ABT-450 may cause a transient asymptomatic elevation of indirect bilirubin and RBV exposure may reduce hemoglobin/hematocrit levels in a characteristic manner. Consequently, provision of transaminases, bilirubin and/or hemoglobin and hematocrit values during the DB Treatment Period might implicitly unblind a subject's study assignment. In order to preserve the blinded nature of the DB Treatment Period, there will be blinding of the HCV RNA levels, transaminases, bilirubin (indirect and total), hemoglobin and hematocrit. Unblinding of any of these laboratory data may occur for the investigator, subject and sponsor as required for toxicity management (Section 6.7) or in the setting of protocol defined virologic failure.

### 5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drugs only to subjects enrolled in the study in accordance with the protocol. The study drugs must not be used for reasons other than that 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 regards to virologic response and potential development of resistance. Subjects will be administered study drugs at the site at the DB Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

Subjects will be instructed to return all blister cards of ABT-450/r/ABT-267 and ABT-333, and all bottles of RBV (full, partial, or empty) to the study site at each visit indicated in Table 3 and Table 4 (if applicable). Study site personnel will inspect the contents of the blister cards and bottles 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 capsules of RBV and the date of reconciliation in the IRT system. Reconciliation should occur when the card or bottle is returned to the site at every visit during the DB Treatment Period in Table 3. During the OL Treatment Period, the blister cards should be returned for destruction at the dispensation visits in Table 4 and reconciliation performed; however, open-label RBV for subjects in Arm B may be re-dispensed so study drug compliance should occur when drugs are returned for final destruction. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

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

5.5.7 MEMS Caps

All subjects will utilize a MEMS monitor (cap), manufactured by AARDEX on the bottles for RBV. The MEMS cap will be used to obtain daily dosing histories for RBV for all subjects. In addition, MEMS data will be provided to the investigator to guide treatment
compliance discussions and will be the primary data used to assess PK time relative to dose.

The MEMS cap is a threaded cap containing an internal electronic clock, with an integrated electronically erasable programmable read-only memory, a special micro-switch and battery. Once fastened onto the medication bottle, the MEMS cap silently records the date and time of all dosing events (event = opening + closing). This electronic monitor provides a means of objectively measuring a subject's adherence with the study medication.

At the DB Day 1, subjects will be assigned one MEMs cap that will be placed on the RBV bottles in place of the original cap. The original cap should be saved so it can be placed back on the bottle upon return by the subject in order to store returned study drug.

The MEMS cap must only be used by the subject to whom it was assigned. Each MEMS cap has a unique serial number that must be recorded in the subject's source documentation. It is suggested that the subject's subject number be written on his or her MEMS cap in permanent ink.

The subjects will be instructed to open the bottle when it is time to take the medicine, to remove the proper amount of medication and promptly close the bottle, then ingest the prescribed dose. The subject should be instructed to transfer the MEMS cap to the next full bottle of study drug at the same time that they take their last dose from the current in-use bottle.

The MEMS cap will be collected from the subject at the completion of study drugs as applicable. If MEMS caps cannot be imported into a participating study country or if other issues preclude the use of MEMS cap at a site(s), dosing histories will not be obtained using the MEMS caps for subjects enrolled at that site(s). Additional instructions for the subject on how to use the MEMS cap will be provided by the Sponsor.
5.5.8 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drugs will be kept by the investigator and will include lot number, POR number, number of tablets/capsules dispensed, subject number, initials of person who dispensed study drugs and date dispensed for each subject. An overall accountability of the study drugs will be performed and verified by the Sponsor monitor throughout the DB and OL Treatment Periods. Final accountability will be performed by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug blister card or bottle, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the blister cards/bottles are damaged, the subject will be requested to return the remaining study drugs to the site. Replacement study drugs may only be dispensed to the subject by contacting the IRT system. Study drug replacement and an explanation of the reason for the misplaced or damaged study drug will be documented within the IRT system. Study drug start/end dates will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each blister card/bottle, number of tablets/capsules remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original blister cards and 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 or capsules of each type of study drug returned in each blister card and each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.
5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The 3 DAA regimen of ABT-450/r/ABT-267 + ABT-333 with RBV is being evaluated in the current study based on data from Phase 2 Study M12-746 and Study M11-652 in treatment experienced subjects treated for 12 weeks. Available data from Study M11-652 indicate that, when dosed for 12 weeks, the 3 DAA arm of 150/100 mg QD ABT-450/r + 25 mg QD ABT-267 + 400 mg BID ABT-333 + RBV shows higher SVR₄ results (18 of 19 subjects, 95%) as compared to the 2 DAA arm of 150/100 mg QD ABT-450/r + 25 mg QD ABT-267 + RBV (35 of 39 subjects, 90%). The 2 DAA arm of 150/100 mg QD ABT-450/r + 400 mg BID ABT-333 + RBV had a much lower SVR₄ rate (8 of 17 subjects, 47%) as compared to the 3 DAA + RBV arm. Thus, the 3 DAA + RBV regimen dosed for 12 weeks provides the highest possibility of achieving SVR in treatment-experienced genotype 1 subjects.

The 3 DAA combination of ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + ABT-267 25 mg QD + RBV BID is being evaluated at 2 different durations – 12- and 24-week in treatment experienced subjects in the Phase 2b study. Available data indicate that the SVR₄ rates for the 12-week arm are very high (18 of 19 subjects, 95%) and none of the 18 subjects who were suppressed at end-of-treatment relapsed by 4-weeks post-treatment suggesting that 12 weeks of treatment will be sufficient for the 3 DAA + RBV combination in treatment experienced subjects. Additionally, modeling and simulations predict minimal effect in SVR rates for durations longer than 12 weeks with the 3 DAA + RBV regimen in treatment experienced subjects. While shorter durations have not been studied in treatment experienced subjects, data from treatment naïve subjects indicate that due to the high relapse rates following 8-week of dosing with 3 DAAs + RBV, durations lower than 12-week will not be adequate in treatment experienced subjects. Thus, 12 weeks of dosing with the 3 DAA + RBV is considered to be the optimal duration of treatment in HCV treatment experienced subjects.
A placebo-controlled study in treatment-experienced subjects is justified based on the following:

Infeasibility of enrolling a study with an active comparator arm: Despite the improvement in SVR rate with the addition of telaprevir and boceprevir to pegIFN/RBV over a regimen of pegIFN/RBV alone, many physicians recommend to delay treatment, and many patients are deferring treatment because of the toxicity associated with the currently approved protease inhibitor/pegIFN/RBV regimens. Experts have confirmed that studies which include a pegIFN containing comparator would be difficult to enroll or to retain adequate numbers of subjects in the IFN-containing arm.

Active comparator which contains pegIFN cannot be effectively blinded. Because of the high rate of adverse events associated with administration of the protease inhibitors (rash, anorectal symptoms, and anemia with telaprevir and anemia and neutropenia with boceprevir), and pegIFN (influenza like illness, injection site reactions, myalgias and pancytopenia), the ability to effectively blind a protease inhibitor/pegIFN/RBV comparator arm is limited. Even within a double dummy design where subjects randomized to receive the pegIFN-free DAA combination with RBV are given sham injections and placebo protease inhibitor and subjects randomized to receive protease inhibitor/pegIFN/RBV are given placebo DAA combination, the characteristic side effect profile of the protease inhibitor/pegIFN/RBV regimen will make the treatment randomization obvious to both subjects and investigators. As patients will likely be attracted to the trial because of the possibility that they will receive a pegIFN-free regimen, effective unblinding may disincentivize patients randomized to the active comparator arm from continuing to participate in the study. In addition, poor adherence to a protease inhibitor/pegIFN/RBV regimen because of its perceived inferiority may result in development of protease inhibitor resistance mutations that could limit future treatment options. Premature discontinuations in the protease inhibitor/pegIFN/RBV arm of the study due to dissatisfaction with the assigned regimen would necessarily be counted as failures, thus the SVR rate for the active comparator will likely be inaccurately low. Early discontinuation of a large portion of the comparator arm may also give an
inaccurate safety profile with which to compare the pegIFN-free DAA regimen. Thus, high rates of discontinuation of the active comparator arm may affect the quality and validity of comparison of safety and efficacy, and bias the study in favor of the investigational combination DAA regimen.

Antiviral activity in the placebo group is expected to be negligible. Because of the bias likely to arise with a pegIFN-based active comparator, as described above, and because the primary efficacy endpoint (SVR12) is objective, comparison of the pegIFN-free DAA regimen results to efficacy and safety results in the package inserts of approved regimens is more likely to provide a meaningful assessment of the Phase 3 study results compared to the current standard of care.

Comparison of active drug to placebo in a blinded fashion provides a highly effective method to assess safety and tolerability of the DAA + RBV regimen in the population for whom the treatment will ultimately be utilized. Given the potential for patients chronically infected with HCV to report symptoms or adverse events unrelated to DAA therapy, the placebo control group allows characterization of adverse events in an untreated, chronically HCV-infected population. The open-label period allows the subjects initially randomized to placebo access to active DAA therapy.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Clonal sequencing and population sequencing methods are experimental. SF-36V2 and EQ-5D-5L PRO instruments are standards in the literature and thoroughly validated; the HCVPRO is preliminarily validated.

5.6.3 Suitability of Subject Population

The selection of subjects infected with HCV genotype 1 virus will allow for the assessment of safety, pharmacokinetics and antiviral activity of ABT-450/r, ABT-267,
ABT-333 and RBV dosed in combination. HCV-infected subjects with transaminase levels up to 5 times the ULN will be allowed to enroll, as many with chronic HCV infection who are otherwise healthy have stable elevations of AST and ALT levels (≤ 5 × ULN) and are considered representative of the population who will receive ABT-450/r, ABT-267, and ABT-333. The age range selected for this study, 18 through 70 years, is also intended to be representative of the target population. Similarly, a substantial portion of the HCV-infected population has a relatively high BMI. Because of the acceptable safety and pharmacokinetic profiles of ABT-450/r, ABT-267 and ABT-333 demonstrated across Phase 1 and Phase 2 studies which enrolled subjects with a similar BMI range, this protocol will enroll subjects with a BMI up to 38 kg/m². Patients chronically (rather than acutely) infected with HCV comprise the target population for DAA-based regimens. This study will enroll subjects who are prior non-responders to treatment with pegIFN/RBV, but are considered eligible for treatment currently. Subjects who are naïve to treatment, those with more advance liver disease, such as cirrhosis, and those co-infected with HIV-1 are also in the target population. These groups may respond differently to pegIFN-free DAA regimens and are being evaluated in separate studies.

5.6.4 Selection of Doses in the Study

Doses of the three DAAs to be used in this study have shown significant antiviral activity and have been shown to be generally safe and well tolerated both as monotherapy, in combination with pegIFN + RBV, and in combination with each other and RBV. Of note, coadministration of ABT-450/r, ABT-267 and ABT-333 at the doses planned for use in this study do not clinically significantly impact plasma exposures compared to administration as single agents thus dose adjustments based on drug interactions are not required.

**ABT-450**

The ABT-450/r doses of 100/100 and 150/100 mg evaluated in the Phase 2 studies using the ABT-450 SDD tablet provided high SVR₄ rates in treatment-naïve (100% and 98%, respectively) and treatment-experienced (90% and 95%, respectively) subjects when
dosed with ABT-333 and ABT-267 + RBV. The higher ABT-450 dose of 150 mg, administered with 100 mg ritonavir has been selected to advance into Phase 3 studies as it provides an optimal balance between safety and suppression of resistant variants.

In combination with other DAAs ± RBV, the highly fit, moderately resistant R155K viral variant was observed in a lower fraction of patients who had virologic failure at the 150/100 and 200/100 mg ABT-450/r dose (SDD tablet of ABT-450) as compared to the 100/100 mg ABT-450/r dose. This finding is consistent with monotherapy data for ABT-450/r where the higher 200/100 mg dose of ABT-450/r selected fewer resistant variants including R155K as compared to the lower 50/100 and 100/100 mg doses of ABT-450/r. Higher ABT-450 doses were also associated with higher SVR24 rates when combined with pegIFN and RBV. Thus based on resistance profile and SVR24 data with pegIFN + RBV, higher doses provide better efficacy. However, ABT-450 doses of 200/100 and 250/100 mg (SDD tablet) were associated with a greater incidence of asymptomatic grade 3+ ALT elevations (~4% at doses ≥ 200/100 versus < 0.5% at lower doses) suggesting that doses < 200/100 mg SDD tablet might have a more favorable safety profile.

The ABT-450 150 mg dose from the ABT-450/r/ABT-267 co-formulation planned for this study has a ~60% higher exposure as compared to the 150/100 mg SDD formulation but the exposure is ~50% lower than that from the 200/100 mg SDD formulation. The 150 mg ABT-450 dose from the coformulation will hence minimize the incidence of asymptomatic, transient Grade 3 ALT elevations while maximizing virologic suppression and minimizing the appearance of resistant variants.

**ABT-333**

An ABT-333 dose of 250 mg BID using the optimized tablet formulation that is expected to provide exposures comparable to the 400 mg BID dose used in Phase 2 studies and has been selected to advance into Phase 3 studies. This is based on comparable efficacy and better safety profile compared to exposures at higher ABT-333 doses.
Comparable viral load decline following monotherapy (approximately 1 log$_{10}$ IU/mL) was observed at exposures greater than that achieved with the 400 mg BID dose evaluated in Phase 2 studies. Additionally, the 400 and 800 mg BID doses resulted in identical SVR rates (63%) when combined with pegIFN and RBV for 12 weeks followed by 36 weeks of pegIFN + RBV, indicating that increasing ABT-333 dose > 400 mg BID did not improve efficacy. Additionally, available data from the Phase 2b study indicates that when ABT-333 400 mg BID dose is combined with ABT-450 and ABT-267 ± RBV for 12 weeks, very high SVR$_4$ rates were observed in treatment-naïve and treatment-experienced subjects (> 90%).

While both the 400 mg BID and 800 mg BID doses of ABT-333 in combination with pegIFN and RBV were well tolerated by HCV-infected subjects for 12 weeks, the 800 mg BID dose was associated with a greater mean hemoglobin reduction compared to the 400 mg BID dose and compared to placebo plus pegIFN and RBV.

The optimized formulation used in the current study has a higher bioavailability and is expected to provide comparable exposures to the 400 mg tablet formulation used in Phase 2 studies. Hence, the ABT-333 dose in the current study is the 250 mg optimized formulation dosed BID as it provides exposures that maximizes efficacy and a superior safety profile compared to higher ABT-333 doses.

**ABT-267**

An ABT-267 dose of 25 mg has been selected to advance into Phase 3 studies. Compared to higher doses, the 25 mg QD dose provided comparable viral load decline following monotherapy and lower potential to decrease ABT-450 exposures.

Following 2 to 3 days of ABT-267 monotherapy at doses of 1.5 mg to 200 mg QD, the 25 mg dose of ABT-267 showed viral load decline comparable to higher doses with none of the rebound between doses seen at lower doses. Preliminary resistance analysis following monotherapy suggests that doses significantly greater than 25 mg would be needed to improve the resistance profile as a variety of NS5A resistant mutants were
observed following monotherapy with doses of 5 to 200 mg. In addition, higher ABT-267 doses have been associated with decreases in ABT-450 exposures; the ABT-267 200 mg dose resulted in ~80% lower ABT-450 exposures when ABT-450 250 mg was dosed with 100 mg ritonavir. Hence doses > 25 mg could decrease the exposures of the "anchor" molecule ABT-450, without providing significant benefit in terms of improved efficacy. Additionally, available data from the Phase 2b study indicates that when ABT-267 25 mg QD dose of ABT-267 is combined with ABT-450 and ABT-333 ± RBV for 12 weeks, very high SVR4 rates were observed in treatment-naïve and treatment-experienced subjects (> 90%).

The co-formulated ABT-450/r/ABT-267 formulation used in the current study has ABT-267 bioavailability comparable to the ABT-267 25 mg tablet used in Phase 2 studies. Hence, the ABT-267 dose in the current study is the 25 mg dose, as it provides exposures that maximizes efficacy without compromising ABT-450 exposures.

**RBV**

The daily dose of RBV in this study is 1000 to 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 is selected for this study because its safety profile has been well characterized when administered with pegIFN, including the incidence of hemolytic anemia, and there are well-defined dose reduction criteria in the event of RBV-induced anemia. In addition, this dose was studied in the absence of pegIFN in approximately 61 subjects with chronic hepatitis C infection in Study M12-267 and Study M12-746, and was found to be generally safe and well tolerated and resulted in high SVR rates.

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. 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 associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

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

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

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

### 6.1.2 Serious Adverse Events

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

<table>
<thead>
<tr>
<th><strong>Death of Subject</strong></th>
<th>An event that results in the death of a subject.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Life-Threatening</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Hospitalization or Prolongation of Hospitalization</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Congenital Anomaly</strong></td>
<td>An anomaly detected at or after birth, or any anomaly that results in fetal loss.</td>
</tr>
<tr>
<td><strong>Persistent or Significant Disability/Incapacity</strong></td>
<td>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).</td>
</tr>
</tbody>
</table>
Important Medical Event
Requiring Medical or
Surgical Intervention to
Prevent Serious Outcome

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

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

6.2 Adverse Event Severity

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

**Mild**

The adverse event is transient and easily tolerated by the subject.

**Moderate**

The adverse event causes the subject discomfort and interrupts the subject's usual activities.

**Severe**

The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.
6.3  Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug. Assessment of relatedness will be made with respect to the DAAs (ABT-450/r/ABT-267 and ABT-333) and with respect to RBV:

**Reasonable Possibility**
An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated."

In addition, when the investigator has not reported a causality or deemed it not assessable, the Sponsor will consider the event associated.

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

6.4  Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

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

<table>
<thead>
<tr>
<th>Consent Signed</th>
<th>Study Drug Start</th>
<th>Study Drug</th>
<th>30 Days After Study Drug Stopped</th>
<th>End of Study</th>
</tr>
</thead>
</table>

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify the Antiviral Safety Management Team within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the EDC system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be faxed to the Antiviral Safety Management Team within 24 hours of being made aware of the serious adverse event.

FAX to: [XXXXXXXX]

For serious adverse event concerns, contact the Antiviral Safety Team at:

Antiviral Safety Team  
Dept. R477, Bldg. AP30-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6146  

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

Primary Study-Designated Physician:
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 documents used for SUSAR reporting in the EU countries will be the most current versions of the Investigator's Brochures or Labels.

6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with the DB Day 1 Visit and 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 Sponsor within 1 working day of the site becoming aware of the pregnancy. Subjects who report a positive pregnancy test during the DB or OL Treatment Period must be notified to stop all study medication (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.
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 D. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 and Section 6.7.2.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or the Sponsor as having a "reasonable possibility" of being related to the study drugs (Section 6.3). 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.

Study drugs should not be interrupted for toxicity management for more than 7 consecutive days. If study drugs needs to be interrupted for more than 7 consecutive days, consideration should be given to discontinue the subject and the Abbott Study Designated Physician should be contacted.

During the study, timeliness of EDC data entry to reflect blinded or unblinded study drug interruptions and/or blinded or unblinded RBV dose modifications and consequent required adverse events ensures that the Abbott Safety Team (medical monitor, safety monitor) and the DMC have the data necessary for signal detection at safety data review and DMC meetings. The investigator should ensure that any study drug interruptions or RBV dose modifications and consequent required adverse events are entered into the appropriate eCRFs.
Safety surveillance, via regular review of safety labs will be performed in a blinded manner by the Sponsor personnel and/or its designee. If during these reviews, an issue is identified which warrants discontinuation of study drug by a subject, the investigator will be notified.

The toxicity management guidelines below should be followed. In the DB Period, unblinding of study drug assignment may occur as directed by the toxicity management guidelines. In addition, a subject's study drug assignment may be unblinded at the investigator's discretion, if deemed necessary for subject safety. Subjects who are unblinded may remain on study drug except as described below.

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

Subjects who develop a study drug-related (reasonable possibility) mild or moderate adverse event or Grade 1 or 2 laboratory abnormality (other than those discussed separately in Toxicity Management Sections for hemoglobin parameters [Section 6.7.3], total bilirubin and hepatic transaminase parameters [Section 6.7.4] and creatinine clearance parameters [Section 6.7.5]) may continue study drugs with follow-up per study protocol. In the DB Period unblinding of study drug assignment does not need to occur. If the adverse event or laboratory parameter does not improve or normalize within 2 scheduled study visits and an etiology other than study drug has not been determined, then the Abbott Study Designated Physician can be contacted to further discuss subject management. Subjects may continue study drugs; study drug interruption is not required.

6.7.2 Grades 3 or 4 Laboratory Abnormalities and Severe or Serious Adverse Events

Grade 3–4 Laboratory Abnormalities

With the exception of Grade 3 or higher elevations in uric acid, total cholesterol or triglycerides, if a subject experiences a Grade 3 or greater laboratory parameter during the study (other than those discussed in the toxicity management Sections 6.7.3 through 6.7.5
below), the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the study drugs should be interrupted and the laboratory parameter followed until it reaches Grade 1. In the DB Period for a confirmed Grade 3 laboratory abnormality as above, unblinding of study drug assignment is not required by protocol. The study drugs can be restarted if the laboratory parameter reaches Grade 1 within 7 days of study drug interruption. If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued. If the abnormality does not improve to Grade 1 or less within 7 days of interruption, the study drugs should be permanently discontinued.

If the investigator believes that the confirmed Grade 3 laboratory abnormality can be managed medically without interruption, then the Abbott Study Designated Physician should be contacted to discuss continued study drug administration with medical management. If the laboratory abnormality does not improve with medical management within 2 scheduled study visits, then study drugs should be interrupted and the laboratory abnormality followed. The study drugs can be restarted if the laboratory parameter reaches Grade 1 within 7 days of study drug interruption. If the laboratory abnormality recurs upon restart, then study drugs should be permanently discontinued. If the laboratory abnormality does not improve within 7 days, then study drugs should be permanently discontinued.

**Severe Adverse Event**

If a subject experiences a severe drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed in Sections 6.7.3 through 6.7.5 below) during the study, the study drugs should be interrupted. In the DB Treatment Period for a drug-related severe adverse event, unblinding of study drug assignment is not required by protocol. Study drugs may be restarted if the adverse event improves or resolves within 7 days of the interruption. If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued. If the adverse event does not improve or resolve within 7 days of the interruption the study drugs should be permanently discontinued.
If the investigator believes that the severe drug-related (reasonable possibility) adverse event can be managed medically without interruption, then the Abbott Study Designated Physician should be contacted to discuss continued study drug administration with medical management. If the severe adverse event does not improve with medical management within 2 scheduled study visits, then study drugs should be interrupted. If the severe adverse event improves within 7 days of the interruption, then study drugs may be restarted. If the severe adverse event recurs upon restart, then study drugs should be permanently discontinued. If the severe adverse event does not improve within 7 days of the interruption, then study drugs should be permanently discontinued.

For a drug-related (reasonable possibility) severe adverse event, unblinding is not required by protocol.

If a subject experiences a non drug-related (no reasonable possibility) severe adverse event study drugs may be continued; unblinding is not needed.

A severe adverse event and any associated dose interruptions (or discontinuations) should be entered into the appropriate eCRFs.

**Serious Adverse Event**

If a subject experiences a serious drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed in Sections 6.7.3 through 6.7.5 below) during the study, study drugs should be permanently discontinued, and in the DB Period unblinding should occur. If the investigator believes that the serious drug-related (reasonable possibility) adverse event can be managed medically without permanent discontinuation of study drug, then the Abbott Study Designated Physician should be contacted to discuss continued study drug administration and medical management. If study drug requires interruption longer than 7 days, the subject should have study drug permanently discontinued.

If a subject experiences a serious adverse event considered unrelated (no reasonable possibility) to study drugs, study drugs may be continued. If the study drugs are
interrupted because it is deemed necessary for clinical management the interruption should not exceed 7 days.

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

6.7.3 Management of Decreases in Hemoglobin

Reductions in hemoglobin are a well characterized side effect of ribavirin exposure. Therefore in order to avoid implicit unblinding during the DB Treatment Period of the study the results of hemoglobin testing will be blinded unless confirmed hemoglobin values meet or exceed predefined toxicity thresholds (Table 10), in which case current and preceding hemoglobin and hematocrit values will be unblinded to the investigator and Sponsor as will all subsequent values.

If a subject experiences a hemoglobin decrease (as outlined in Table 9 and Table 10), an alert will be provided to the investigator which will require the test to be repeated. If confirmed, the RBV dose should be adjusted per local label. Alternative management of the RBV dose in the setting of reduced renal function will require approval of the Abbott Study Designated Physician. If the hemoglobin decrease is confirmed, an alert will be provided to the investigator and Sponsor which will include the abnormal hemoglobin result along with all preceding hemoglobin and hematocrit results.

Hemoglobin abnormalities (and relevant unblinding in the DB Treatment Period) should be managed according to Table 10. Management will be different for subjects with or without a history of known cardiac disease.

Use of hematologic growth factors such as erythropoietin or filgrastim or blood transfusions is not recommended; and is permitted only with approval of the Abbott Study
Designated Physician. If these agents are to be used in the DB Treatment period, study drug treatment should be unblinded for appropriate management. Management of hematologic growth factor therapy is the responsibility of the investigator, and growth factors will not be provided or reimbursed by the Sponsor.

Alternative management of hemoglobin decreases including unblinding of study drugs or of hemoglobin data in the DB Period outside of these criteria requires approval of the Abbott Study Designated Physician.

**Table 9. Indications for Unblinding of Hemoglobin and Hematocrit Levels During the DB Period and the Nature of Data Unblinded**

<table>
<thead>
<tr>
<th>Hemoglobin (Hb) Level (Confirmed)</th>
<th>Hb Unblinding Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level &lt; 10g/dL confirmed</td>
<td>• Unblind subject's current and prior Hb data to Investigator and Sponsor.</td>
</tr>
<tr>
<td>Hb levels ≥ 10 g/dL with either of the following:</td>
<td>• All subsequent Hb data will also be unblinded.</td>
</tr>
<tr>
<td>• a ≥ 2 gm/dL decline over a 4-week period</td>
<td></td>
</tr>
<tr>
<td>• a ≥ 4 gm/dL decline between study visits</td>
<td></td>
</tr>
</tbody>
</table>

When Hb/hematocrit results are blinded it can be assumed that Hb levels are ≥ 10g/dL and without either of markers of decline described above.
<table>
<thead>
<tr>
<th>Hemoglobin in Patients with No Cardiac Disease</th>
<th>Study drugs may be continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce RBV dose and continue to monitor hemoglobin per protocol</td>
<td></td>
</tr>
<tr>
<td>If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose</td>
<td></td>
</tr>
<tr>
<td>If Hb decreases to &lt; 8.5 g/dL see appropriate row below</td>
<td></td>
</tr>
<tr>
<td>In the DB Treatment Period, unblinding of study drugs will occur</td>
<td></td>
</tr>
<tr>
<td>Permanently discontinue all study drugs and in the DB Treatment Period unblinding of the study drugs will occur</td>
<td></td>
</tr>
<tr>
<td>Manage the subject as medically appropriate</td>
<td></td>
</tr>
<tr>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event</td>
<td></td>
</tr>
<tr>
<td>Manage the subject as medically appropriate</td>
<td></td>
</tr>
<tr>
<td>Study drugs may be continued</td>
<td></td>
</tr>
<tr>
<td>In the DB Treatment Period unblinding of study drug will occur</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin in Patients with History of Stable Cardiac Disease</th>
<th>Study drug may be continued and in the DB Treatment Period unblinding of study drugs will occur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce RBV dose</td>
<td></td>
</tr>
<tr>
<td>Continue to monitor hemoglobin levels per protocol</td>
<td></td>
</tr>
<tr>
<td>If hemoglobin increases to a level that is less than a 2 g/dL decrease from Baseline, may increase RBV; with gradual dose increases in 200 mg increments towards original dose</td>
<td></td>
</tr>
<tr>
<td>If hemoglobin does not increase; investigator may manage the subject as medically appropriate. If hemoglobin decreases to &lt; 10 g/dL see appropriate row below</td>
<td></td>
</tr>
<tr>
<td>If the subject has symptoms consistent with their cardiac disease; manage subject as medically appropriate; Abbott Study Designated Physician may be contacted</td>
<td></td>
</tr>
<tr>
<td>Study drugs may be continued but in the DB Treatment Period unblinding of study drugs will occur. If upon unblinding, the subject is determined to be on RBV, then consider management as for those without cardiac signs and symptoms in the rows above</td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Management of Hemoglobin Decreases (Continued)

<table>
<thead>
<tr>
<th>Hemoglobin in Patients with History of Stable Cardiac Disease (Continued)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decrease ≥ 4g/dL between study visits but hemoglobin ≥ 10 g/dL</td>
<td>Investigator should manage subject as medically appropriate, but study drugs may be continued. In the DB Treatment Period unblinding of study drugs will occur</td>
</tr>
<tr>
<td>8.5 g/dL ≤ Hemoglobin &lt; 10.0 g/dL</td>
<td>Study drugs may be continued but in the DB period unblinding of study drugs will occur</td>
</tr>
<tr>
<td>Reduce RBV dose and continue to monitor hemoglobin per protocol</td>
<td></td>
</tr>
<tr>
<td>If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200mg increments towards original dose</td>
<td></td>
</tr>
<tr>
<td>If hemoglobin &lt; 10g/dL despite 4 weeks at the reduced RBV dose, permanently discontinue all study drugs; manage as medically appropriate. Enter the discontinuation into appropriate eCRFs and create corresponding adverse event</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>Permanently discontinue all study drugs; manage subject as medically appropriate</td>
</tr>
<tr>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event</td>
<td></td>
</tr>
<tr>
<td>In the DB Treatment Period unblinding of study drugs will occur</td>
<td></td>
</tr>
</tbody>
</table>

6.7.4 Management of Transaminase Elevations

As discussed in Section 3.0, ABT-450/r is associated with transient asymptomatic increases in total and indirect bilirubin. Furthermore, treatment with direct acting anti-HCV agents may have a normalizing effect on ALT levels. Therefore in order to avoid implicit unblinding during the DB Treatment Period the results of hepatic transaminases, ALT and AST, and total and indirect bilirubin will be blinded unless confirmed ALT values meet or exceed predefined toxicity thresholds (Table 12) in which case current and preceding ALT, AST, and bilirubin values will be unblinded to the investigator and Sponsor as will all subsequent values (Table 11).

If a subject experiences an ALT level ≥ 5 × ULN and ≥ 2 × baseline, an alert will be provided to the investigator which will require the test to be repeated. If the ALT is confirmed ≥ 5 × ULN and ≥ 2 × baseline, an alert will be provided to the investigator and
Sponsor which will include the abnormal ALT along with all preceding ALTs and other pertinent liver laboratory parameters.

Management guidelines for elevations in ALT are provided in Table 12.

For subjects presenting with clinical jaundice the investigator may contact the Study designated physician to initiate unblinding of ALT, AST, bilirubin (total and indirect) and hemoglobin. Alternative management of transaminase elevations or other liver chemistry abnormality outside of these criteria including unblinding of study drugs or unblinding of liver chemistries requires approval of the Abbott Study Designated Physician.

**Table 11. Indications for Unblinding of ALT levels during the DB Period and the Nature of Data Unblinded**

<table>
<thead>
<tr>
<th>ALT Level (Confirmed)</th>
<th>ALT, (ALT Bilirubin) Unblinding Activities</th>
</tr>
</thead>
</table>
| ALT ≥ 5 × ULN and ≥ 2 × Baseline | • Unblind subject's current and prior ALT, AST and bilirubin*(total and indirect) data to investigator and Sponsor.  
• All subsequent ALT, AST and bilirubin data will also be unblinded |

When ALT results are blinded it can be assumed that ALT levels are < 5 × ULN or ≥ 5 × ULN and ≥ 2 × Baseline.

* Direct bilirubin data is provided unblinded during the study.
Table 12. Management of Confirmed ALT Levels $\geq 5 \times$ ULN and $\geq 2 \times$ Baseline

| ALT $\geq 10 \times$ ULN | • Permanently discontinue study drugs and unblind treatment assignment.  
|                          | • Complete hepatic questionnaire, update concomitant medications eCRF (if applicable) and obtain appropriate additional testing (serology for hepatitis A, B, and E, urine for drug screen).  
|                          | • Evaluate and manage the subject as medically appropriate.  |
| ALT $\geq 5 \times$ ULN but $< 10 \times$ ULN with symptoms and signs of hepatitis present | • Permanently discontinue study drugs and unblind treatment assignment.  
|                          | • Complete hepatic questionnaire, update concomitant medications eCRF (if applicable) and obtain appropriate additional testing (serology for hepatitis A, B, and E, urine for drug screen).  
|                          | • Evaluation and manage as medically appropriate.  |
| ALT $\geq 5 \times$ ULN but $< 10 \times$ ULN without symptoms or signs of hepatitis | • Complete hepatic questionnaire, update concomitant medications eCRF (if applicable), and obtain appropriate additional testing (serology for hepatitis A, B, and E, urine for drug screen).  
|                          | • Continue study drugs and repeat LFTs and INR within 3 days and as clinically indicated until resolution.  
|                          | • In the DB Treatment Period unblinding of study drugs will occur.  
|                          | • If ALT values during follow-up are increased from the prior values, or increasing direct bilirubin, or increasing INR, or symptoms/signs of hepatitis then permanently discontinue study drugs.  |

6.7.5 Creatinine Clearance

Creatinine clearance (CrCl) will be calculated throughout the study using Cockcroft-Gault method and estimated glomerular filtration rate (eGFR) will be calculated using the MDRD equation. CrCl values will be provided to the investigators.

If calculated CrCl is confirmed to have decreased to $< 50$ mL/minute, medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements.

In addition, the following should occur:
(1) Concomitant medication dose reduction based on CrCL should be done (if applicable).

(2) The Abbott Study Designated Physician should be contacted to discuss whether dose modification or drug substitution may be required for concomitant medications which might be impacted by the DAAs. Drug interactions between concomitant medications and the DAAs, for example, could potentially increase antihypertensive medication exposure and may reduce renal function. If anti-hypertensive medications are adjusted, vital signs must be monitored to ensure appropriate blood pressure control.

(3) Ribavirin dose should be adjusted per local label. Alternative management of RBV dose in the setting of reduced renal function will require approval of the Abbott Study Designated Physician.

(4) A urinalysis, urine for albumin, and a urine specimen for archive should be obtained.

(5) Creatinine and chemistries should be repeated within 7 days and as clinically indicated until resolution.

If CrCl does not improve by 2 scheduled study visits (CrCl values < 50 mL/min) then study drugs should be permanently discontinued, the study drug assignment should be unblinded with further medical management as appropriate.

If CrCl improves, consideration should be given to the reassessment of any dose modifications that have been made.

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 eCRFss.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics
Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott personnel:

Primary Contact: Kevin Howieson

Alternate Contact: George Liossis

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after subjects who were initially randomized to active drug have completed the Post-Treatment Week 12 Visit or prematurely discontinued study and subjects who were initially randomized to placebo have completed the DB Treatment Period and 12 weeks of open-label active treatment in the OL Treatment Period or prematurely discontinued study drug. For the primary analysis, the data will be locked after performing appropriate data cleaning. Data after Post-Treatment Week 12 for the subjects randomized to active drug and data after the
OL Treatment Period for the subjects randomized to placebo will be added to a subsequent version of the database which will be cleaned and locked at the end of the study.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and confidence intervals will be 2-sided with an α level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables.

Efficacy, safety, and demographic analyses will be performed on the intent-to-treat (ITT) population defined as all randomized subjects who receive at least one dose of double-blind study drug. The primary and the first 2 secondary efficacy endpoints (SVR₁₂, RVR and EOTR) will be assessed within subjects in the ITT population randomized to active drug in the DB Treatment Period. The last secondary endpoint will compare the percentage of subjects with ALT normalization at the Final Treatment Visit in the DB Treatment Period between the placebo and active treatment groups. Safety comparisons will be performed on data throughout the DB Treatment Period. Safety data during the OL Treatment Period and available data from the PT Period will be presented separately and no statistical comparisons will be made to data collected during the DB Treatment Period.

No data will be imputed for any efficacy or safety analysis except for the PRO questionnaires and for analyses of the HCV RNA endpoints of RVR, EOTR, and all SVR 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. The Mental and Physical Component Summary measures will not be computed if any domain is missing. For the HCVPRO total score, if a respondent answers at least 12 of the 16 items, the missing items will be imputed with the mean score of the answered items. In cases where the
respondent did not answer five or more items, the total score will be considered missing. For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items.

HCV RNA values will be selected for the analyses of HCV RNA endpoints of RVR, EOTR, and all SVR endpoints based on the defined visit windows. When there is no HCV RNA value in a visit window based on defined visit windows, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below.

If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. 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 analyses (e.g., SVR₄, SVR₁₂, SVR₂₄), 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 window.

8.1.1 Demographics

Demographics and baseline characteristics will be summarized for each treatment group 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 subgenotype (1a, 1b, or other), type of response to previous pegIFN/RBV treatment responder type (null responder, partial responder, or relapser), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), baseline HCV RNA levels [(continuous) and (≤ 800,000 IU/mL or > 800,000 IU/mL)], baseline IP-10 [(continuous) and (≤ 600 pg/mL or > 600 pg/mL)], baseline HOMA-IR (≤ 3 mU × mmol/L² or > 3 mU × mmol/L²), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, and geographic region (North America, Europe, Australia). Summary statistics
(N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI) and a one-way analysis of variance (ANOVA) with treatment arm as the factor will be used to compare treatment groups. The number and percentage of subjects will be presented for categorical variables (e.g., gender and race); treatment groups will be compared using a chi-square test.

OLTreatmentPeriod

Demographics and baseline characteristics will be summarized for all of the subjects randomized to placebo who receive at least one dose of active, open-label study drugs. Summary statistics will be presented for continuous variables and the number and percentage of subjects will be presented for categorical variables.

8.1.2 Efficacy

All efficacy analyses will be performed on the intent-to-treat (ITT) population. The primary efficacy endpoint and first two secondary efficacy endpoints will be performed on all subjects in the ITT population randomized to and receiving active study drug in the DB Treatment Period. The third secondary efficacy endpoint will be performed on the ITT population.

In order to control the Type I error rate, a fixed-sequence testing procedure will be used for the primary and secondary endpoints. Only if success has been demonstrated for the primary endpoint of SVR$_{12}$ rate will the testing proceed to the first secondary endpoint of RVR. Only if success has been demonstrated for the first secondary endpoint of RVR will the testing proceed to the next secondary endpoint EOTR. Only if success has been demonstrated for the second secondary endpoint of EOTR will the testing proceed to the final secondary endpoint of ALT normalization.

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of subjects with SVR$_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of active study drug). The primary efficacy
endpoint will be assessed on the subjects in the ITT population who were randomized to active study drug. The simple percentage of subjects with SVR$_{12}$ will be calculated and a 2-sided 95% confidence interval will be calculated using the normal approximation to the binomial. The lower bound of the 2-sided 95% confidence interval must be greater than 51% in order for the regimen to be a success.

Fifty-one percent represents a weighted combination of the SVR$_{24}$ rates in the boceprevir USPI in subjects without cirrhosis who were relapsers or partial responders to previous pegIFN/RBV treatment along with data from subjects without cirrhosis who were null responders to previous pegIFN/RBV treatment in PROVIDE.

8.1.2.2 Sensitivity Analyses for Primary Endpoint

In addition to the comparison to a 51% threshold to show antiviral activity versus none, the 2-sided 95% lower confidence bound for SVR$_{12}$ will be compared to 65% to show the efficacy of the DAA combination regimen compared to historical rate of SVR$_{24}$ of in the approved regimen of telaprevir with pegIFN and RBV in non-cirrhotic non-responders to previous pegIFN/RBV treatment.

8.1.2.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are: (1) the percentage of subjects with RVR defined as HCV RNA $<\text{LLOQ}$ at DB Week 4, (2) the percentage of subjects with EOTR defined as HCV RNA $<\text{LLOQ}$ at DB Week 12, and (3) the percentage of subjects with ALT normalization defined as ALT $\leq\text{ULN}$ at Final Treatment Visit in the DB Treatment Period for subjects with ALT $>\text{ULN}$ at Baseline.

The first two secondary efficacy endpoints (RVR and EOTR) will be assessed on the subjects in the ITT population who were randomized to active study drug. RVR and EOTR will be calculated as a simple percentage of subjects and a 2-sided 95% confidence interval will calculated using the normal approximation to the binomial. The lower bound
of the 2-sided 95% confidence interval must be greater than 51% in order for the regimen to be a success for each endpoint sequentially (RVR and then EOTR).

The third secondary endpoint will be assessed on all subjects in the ITT population comparing the percentage of subjects with ALT normalization (ALT ≤ ULN at Final Treatment Visit in the DB Treatment Period for subjects with ALT > ULN at Baseline) in the placebo and active treatment groups using Fisher's exact test. The $P$ value must be 0.05 or less in order for the regimen to be a success for this endpoint.

### 8.1.2.4 Subgroup Analysis

The percentage (and 2-sided confidence intervals) of subjects with SVR$_{12}$ for each treatment group will be presented by the following subgroups:

- Type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser);
- HCV genotype 1 subtype (1a, 1b, other);
- Baseline HCV RNA level ($\leq 800,000$ IU/mL or $> 800,000$ IU/mL);
- Baseline IP-10 ($\leq 600$ pg/mL or $> 600$ pg/mL);
- Sex (Male versus female);
- Age ($< 50$ versus $\geq 50$ years), ($< 65$ versus $\geq 65$ years);
- Race (Black versus non-black);
- Ethnicity (Hispanic versus none);
- Geographic Region (North America, Europe, Australia);
- BMI ($< 30$ or $\geq 30$ kg/m$^2$);
- Subjects with RBV dose modifications (yes/no);
- History of Diabetes (yes/no);
- History of Bleeding Disorders (yes/no);
- Former injection drug user or subject on stable opiate substitution (yes/no).
Each subgroup analysis will be performed if there is an adequate number of subjects within each subgroup level. If the lower confidence bound of the 2-sided 95% confidence interval for a subgroup is > 51%, then the regimen will be considered efficacious in the subgroup.

8.1.2.5 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized and analyzed as specified.

**DBTreatmentPeriod**

The following will be performed on ITT subjects randomized to active drug in the DB Treatment Period:

- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the DB Treatment Period using only subjects with data in each visit window (i.e., no imputation for missing data);
- the percentage of subjects meeting each and any virologic failure criteria during treatment;
- time to suppression of HCV RNA during the DB Treatment Period.

**OLTreatmentPeriod**

The following analyses will be performed on the subjects who were randomized to placebo and received at least one dose of active, open-label study drug.

- the percentage of subjects with RVR (HCV RNA < LLOQ at OL Week 4);
- the percentage of subjects with EOTR (HCV RNA < LLOQ at OL Week 12);
- the percentage of subjects with ALT normalization (ALT ≤ ULN at Final OL Treatment Visit for subjects with ALT > ULN at Baseline);
the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the OL Treatment Period using only subjects with data in each visit window (i.e., no flanking imputation);
the percentage of subjects meeting each and any virologic failure criteria during open-label treatment;
time to suppression of HCV RNA during the open-label Treatment Period.

PTPeriod

The following analyses will be performed on the subjects in the ITT population who were randomized to active study drug during the DB Treatment Period.

- the percentage of subjects with HCV RNA < LLOQ 4 weeks after the last actual dose of study drug (SVR₄);
- the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the DB Treatment Period, who subsequently relapse post-treatment within 4 weeks after the last actual dose of study drug;
- the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the DB Treatment Period, who subsequently relapse post-treatment within 12 weeks after the last actual dose of study drug.

The following analyses will be performed on the subjects in the ITT population who were randomized to active study drug including all PT Period data available at the time of the 120-day safety update.

- the percentage of subjects with HCV RNA < LLOQ 12 weeks after the last planned dose of study drug (SVR₁₂planned);
- the percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR₂₄);
The following analyses will be performed on the subjects who were randomized to placebo and received at least one dose of active, open-label study drug including all PT period data available at the time of the 120-day safety update.

- the percentage of subjects with HCV RNA < LLOQ 4 weeks after the last actual dose of study drug (SVR4);
- the percentage of subjects with HCV RNA < LLOQ 12 weeks after the last actual dose of study drug (SVR12);
- the percentage of subjects with HCV RNA < LLOQ 12 weeks after the last planned dose of study drug (SVR_{12planned});
- the percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR24);
- the percentage of subjects with HCV RNA < LLOQ 24 weeks after the last planned dose of study drug (SVR_{24planned});
- the percentage of subjects who completed OL study drug with HCV RNA < LLOQ at the Final OL Treatment Visit, who subsequently relapse post-treatment within 4 weeks after the last actual dose of OL study drug;
- the percentage of subjects who completed OL study drug with HCV RNA < LLOQ at the Final OL Treatment Visit, who subsequently relapse post-treatment within 12 weeks after the last actual dose of OL study drug;
- time to relapse at anytime post-treatment.
For all of the above analyses, the percentage of subjects with RVR, EOTR, and SVR will be calculated as a simple percentage and 2-sided 95% confidence intervals will be calculated using the normal approximation to the binomial; missing data will be imputed as described in Section 8.1. All other endpoints will be presented using data as observed, i.e., not performing any missing data imputations. From HCV RNA levels, the time to suppression on treatment and time to relapse post-treatment will be calculated for each subject, and the median time will be estimated using Kaplan-Meier methodology for right censored observations.

**8.1.3 Patient Reported Outcomes**

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

- Mean change from baseline in HCVPRO total score to each applicable post-baseline time point;
- Mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;
- Mean change from baseline in the SF-36V2 Mental Component Summary (MCS) and Physical Component Summary (PCS) scores to each applicable post-baseline time point;
- The percentage of subjects in each treatment arm with no decrease from baseline in SF-36 MCS and PCS greater than or equal to the minimal clinically important difference (MCID);
- The percentage of subjects in each treatment arm with no decrease from baseline in HCVPRO total score greater than or equal to the MCID;
- The percentage of subjects in each treatment arm with no decrease from baseline in EQ-5D-5L health index score greater than or equal to the MCID.

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit by treatment group will be provided for the HCVPRO
total score, the EQ-5D-5L health index and VAS scores, and the SF-36V2 PCS and MCS scores. For each of these scores, mean change from Baseline to Final DB Treatment Visit will be compared between treatment groups using an ANCOVA model with treatment arm as a factor and baseline score as a covariate.

For HCVPRO total score, a continuous plot by treatment group will be provided with percent change from baseline to Final DB Treatment Visit on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis.

The MCID for the SF-36V2 will be a decrease of 5 points from baseline to the final treatment visit for both the MCS and PCS scores. The MCID during treatment will be calculated for the HCVPRO total score and the EQ-5D-5L health index using Receiver Operating Characteristic (ROC) curves with a change from Baseline to Final DB Treatment Visit of –5 points in the SF-36V2 PCS and MCS summary measures as anchors. The percentage of subjects with a change from Baseline to Final DB Treatment Visit in the each of these measures > the appropriate MCID will be compared between treatment arms using Fisher's exact test.

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

8.1.4 Resistance Analyses

The following resistance variables will be tabulated and summarized for all subjects who experience virologic failure:

- The variants at each amino acid position (1) by nucleotide population sequencing at baseline compared to the prototypic reference sequence, a and (2) by nucleotide population and/or clonal sequencing for each post-baseline time point that is analyzed compared to baseline and prototypic reference sequences.
a. At least one non-failure subject will be matched for every subject experiencing virologic failure to the extent possible by HCV subgenotype, treatment-naive or type of previous pegIFN/RBV non-response, baseline HCV RNA, and IL28B genotype. Baseline samples from these matched subjects will be sequenced at baseline for comparison of the variants existing among the group of subjects who did versus the group who did not experience virologic failure.

For those subjects with virologic failure, their baseline HCV amino acid sequence as determined by population nucleotide sequencing will be compared to the prototypic standard reference amino acid sequence for each target. A listing by subject of all variants at baseline relative to the prototypic reference amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). For those subjects with virologic failure, the HCV amino acid sequence at each timepoint as determined by population sequencing will be compared with the baseline amino acid sequence. A listing by subject of all variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B).

Clonal sequencing will be performed at the time of virologic failure only if no variants are detected at signature resistance-associated amino acid positions by population sequencing. For the subset of these subjects for whom clonal sequencing is performed, the amino acid variants determined by clonal sequencing will be summarized by counting the number of clones whose amino acid sequence does not match that of the population baseline sequence at each visit and amino acid position, out of the total number of clones analyzed.

For subjects who experience virologic failure, resistance-associated signature amino acid variants will be identified by Abbott Clinical Virology and amino acid variants determined by population and/or clonal sequencing will be summarized for these signature variants within the active treatment group and within each subject, respectively. Four additional summaries (and accompanying listings) will be created for all subjects who experience virologic failure to assess the effects of amino acid substitutions based on population sequencing for each target gene on failure: 1) a summary of subjects who failed versus the matched set of subjects who did not fail by amino acid variants at signature positions detected at baseline compared to prototypic reference, 2) a summary of subjects who failed due to on-treatment virologic failure by treatment-emerged
substitutions (single or double) at signature amino acid positions compared to baseline, 3) a summary of those who failed due to relapse by post-treatment variants (single or double) at signature amino acid positions compared to baseline, and 4) the persistence of resistance-associated amino acid substitutions by a summary of subjects who failed by the substitutions at the time of failure and PT Week 24 and Week 48.

A subject who experiences virologic failure will be considered to have emerged/enriched variants if at any time point after baseline a variant (that was not present at baseline) is detectable by population sequencing, or alternatively if at any time point after baseline the increase from baseline in percentage of clones of any variant by clonal sequencing is greater than 20%. If there are at least 2 subjects with an emerged/enriched variant meeting this definition, then the number and percentage of subjects with emerged/enriched variants from baseline will be summarized by amino acid variant. A separate listing of all these subjects and the emerged variants will be provided.

8.1.5 Safety

All subjects who receive at least one dose of double-blind study drug will be included in the safety analyses. For safety analyses, data from the active and placebo treatment groups during the DB Treatment Period will be summarized, and pairwise comparisons will be performed. The data from the OL Treatment Period and PT Period will be summarized similarly, but no pairwise comparisons will be performed.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the active and placebo arms in the DB Treatment Period, treatment-emergent events are defined as any event that begins or worsens in severity after initiation of double-blind study drugs through the last dose of double-blind study drugs. The number and percentage of subjects in each treatment group with treatment-emergent adverse events will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between active and placebo groups.
using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by severity rating and relationship to study drugs.

An additional summary of treatment-emergent adverse events during the DB Treatment Period will be provided using the following definitions of treatment-emergent. For the active arm, treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of active study drugs through 30 days after the last dose of active study drugs. For the placebo arm, treatment-emergent events are defined as any event that begins or worsens in severity after initiation of placebo through the last dose of placebo.

The number and percentage of subjects having treatment-emergent adverse events will be tabulated by SOC and preferred term for adverse events occurring in the OL Treatment Period.

Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be performed if useful and appropriate.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement prior to the initial dose of study drugs. Mean changes from Baseline to each treatment visit will be summarized by treatment group. The differences between the active and placebo groups in the DB Treatment Period will be analyzed using contrasts within an ANOVA model with treatment group as the factor.
Both during the DB and OL Treatment Periods, laboratory data values will be categorized as low, normal, or high based on reference ranges of the laboratory used in this study. The number and percent of subjects who experience post-baseline shifts in clinical laboratory values from low/normal to high and high/normal to low based on the normal range will be summarized by treatment group.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant (PCS) laboratory values will be summarized by treatment group. Comparisons will be performed between the active and placebo groups in the DB Treatment Period of the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact tests.

Additional analyses will be performed if useful and appropriate.

8.1.5.3 Vital Signs Data

Vital sign measurements will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from Baseline to each treatment visit will be summarized descriptively for each treatment group. The baseline value will be the last measurement prior to the initial dose of study drugs. Mean changes will be compared between the active and placebo groups in the DB Treatment Period using contrasts within an ANOVA model with treatment group as the factor. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for PCS vital sign values will be summarized by treatment group. Comparisons will be performed between the active and placebo groups in the DB Treatment Period of the percentage of subjects with PCS vital sign values for each vital sign measurement using Fisher's exact tests.
8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and ribavirin will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

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

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version VI, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

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

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The
relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM) or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at P < 0.005, corresponding to an increase in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

In general, all continuous covariates will be entered in the model, initially in a linear fashion, with continuous covariates centered around the median value. Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored. For example:

\[ TVCL_i = \Theta(2) \text{Comedication } [1,2,\ldots] + \Theta(3) (WT_i - \text{median value}) + \Theta(4) (AGE_i - \text{median value}). \]

Where TVCL_i = Typical value of clearance for an individual i, \Theta(1) is the intercept and \Theta(2) - (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

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

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored. Exposure response relationships will be explored using a semi-mechanistic viral dynamic model and/or logistic regression analyses.
The viral dynamic model will account for target cell growth and death, infection of target cells, infected cell infection and death rate, production of virus by infected cells, and inhibition of production of virus by the various DAAs. Effect of ribavirin will be explored on infection of target cells by the virus. Models will explore mutation of the wild type to single and/or double mutant species depending on the available clinical resistance data. Additional adjustments to the structural and error models will be made during model development as appropriate.

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., RVR, EVR, SVR4, SVR12, relapse following end of treatment and breakthrough on treatment).

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

Additional analyses will be performed if useful and appropriate.

### 8.2 Determination of Sample Size

It is planned to enroll 400 subjects in a 3:1 ratio to ABT-450/r/ABT-267 + ABT-333 + RBV and placebo (300 subjects randomized to active drug and 100 subjects randomized to placebo). The primary efficacy endpoint of SVR12 is assessed within the subjects randomized to the active arm. With a sample size of 300 subjects, this study has greater than 90% power to achieve a two-sided 95% lower confidence bound greater than 51% if the underlying SVR12 rate is 61% or higher. Subjects who do not have data at Post-Treatment Week 12 (after performing the described imputation) count as failures for SVR12 so no adjustment for dropout is applicable.

### 8.3 Randomization Methods

Subjects will be randomized to ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + weight-based RBV or placebo for 12 weeks in a 3:1 ratio at the start of the study. The randomization schedule will be stratified by type of response to previous
pegIFN/RBV treatment (null responder, partial responder, or relaper) and HCV subgenotype (1a versus non-1a). After completing DB treatment, subjects randomized to placebo will receive 12 weeks of open-label treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.

The number of relapers to previous pegIFN/RBV treatment will be limited to ≤ 120 subjects. The total number of partial responders plus relapers to previous pegIFN/RBV treatment will be limited to ≤ 300 subjects.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

IL28B genotypes will be determined for each subject. Consent for determination of IL28B status will be included in the study informed consent. Additional pharmacogenetic analysis, other than IL28B analysis and mRNA analysis will only be performed if the subject has voluntarily signed and dated the IEC/IRB approved pharmacogenetic and mRNA informed consents, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The subject must provide consent specific to pharmacogenetic and mRNA testing before the pharmacogenetic and mRNA testing is performed. If the subject does not consent to the additional pharmacogenetic or mRNA testing it will not impact the subject's participation in the study.
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 the Sponsor and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by the Sponsor and will be maintained in the Trial Master File at the Sponsor.

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 Abbott personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

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

11.0 Data Quality Assurance

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

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic
information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and the Sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and the Sponsor. 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 the Sponsor 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 the Sponsor to arrange alternative archiving options.

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

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

1. I have received and reviewed the Investigator's Brochure for ABT-450, ABT-267, ABT-333 and the product labeling for ritonavir and RBV.

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)

Protocol Date: 21 August 2012

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)
15.0 Reference List

1. Weekly Epidemiological Record. No. 49, 10 December 1999, WHO.


Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by the Sponsor 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 the Sponsor, 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 the Sponsor 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 the Sponsor and/or the appropriate regulatory agency, and retaining all study-related documents until notification from the Sponsor.
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 the Sponsor.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry Bernstein</td>
<td>Project Director</td>
<td>Therapeutic Area</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Clinical Pharmacokinetics</td>
</tr>
<tr>
<td>Sabine Gerloff</td>
<td>Senior Clinical Supply Project Manager</td>
<td>Global Drug Supply</td>
</tr>
<tr>
<td>Kevin Howieson</td>
<td>Clinical Research Manager Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Senior Medical Director</td>
<td>Therapeutic Area</td>
</tr>
</tbody>
</table>
### Appendix C. Study Activities – Treatment Failure Extension

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8, OL Wk 12, Ext Wk16, and Ext Wk 20</th>
<th>Ext Wk 24 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject takes first doses of active study drugs and site calls subject to confirm start date</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Vital Signs, Weight</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test [urine (u)]&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X (u)</td>
<td>X (u)</td>
<td>X (u)</td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study drugs Dispensed</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Study drugs Collected and Compliance Reviewed</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>MEMS cap downloaded (and collected at OL Wk 12 or Premature D/C from OL Treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>HCV Resistance Sample</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Pharmacokinetic Samples</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Archive Plasma Sample</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>
### Appendix C.  Study Activities – Treatment Failure Extension (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8, OL Wk 12, Ext Wk 16, and Ext Wk 20</th>
<th>Ext Wk 24 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
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<td></td>
<td></td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Total Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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

a. Subjects randomized to Arm A will complete study procedures as outlined in Table 3, dispense drug at DB Week 12, and complete Ext Weeks 16, 20 and 24 (or DC Visit if applicable). Subjects randomized to Arm B will complete study procedures as outlined in Table 3 and will take their first dose of all study drugs the day after the last day of the DB Treatment Period as noted above in the Treatment Failure Extension Table. The site will call the subject and record the study drugs start and end dates in the electronic data capture (EDC) system and source notes.

b. Subjects will begin the PT Period after completing study drugs treatment or prematurely discontinuing the OL Treatment Period.

c. Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal.
### Appendix D. Clinical Toxicity Grades

#### Clinical Toxicity Grades for HCV Studies

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute</td>
<td>LLN – 1500/mm³</td>
<td>LLN – 1500 – 1000/mm³</td>
<td>LLN – 1000 – 500/mm³</td>
<td>LLN – 500/mm³</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>LLN – 1.5 × 10⁹/L</td>
<td>LLN – 1.5 – 1.0 × 10⁹/L</td>
<td>LLN – 1.0 – 0.5 × 10⁹/L</td>
<td>LLN – 0.5 × 10⁹/L</td>
</tr>
<tr>
<td>Eosinophil count increased</td>
<td>650 – 1500 cells/mm³</td>
<td>1501 – 5000 cells/mm³</td>
<td>&gt; 5000 cells/mm³</td>
<td>Hypereosinophilic</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>LLN – 10.0 g/dL</td>
<td>LLN – 6.2 g/dL</td>
<td>LLN – 4.9 g/dL</td>
<td>LLN – 4.0 g/dL</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>LLN – 800/mm³</td>
<td>LLN – 500/mm³</td>
<td>LLN – 200/mm³</td>
<td>LLN – 100/mm³</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>LLN – 75,000/mm³</td>
<td>LLN – 50,000/mm³</td>
<td>LLN – 25,000/mm³</td>
<td>LLN – 10,000/mm³</td>
</tr>
<tr>
<td>FTT</td>
<td>&gt; 1 – 1.5 × ULN</td>
<td>&gt; 1.5 – 2 × ULN</td>
<td>&gt; 2 × ULN</td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>LLN – 3000/mm³</td>
<td>LLN – 2000/mm³</td>
<td>LLN – 1000/mm³</td>
<td>LLN – 500/mm³</td>
</tr>
<tr>
<td>White blood cell count increased</td>
<td>10,800 – 15,000 cells/mm³</td>
<td>15,000 – 20,000 cells/mm³</td>
<td>20,000 – 25,000 cells/mm³</td>
<td>&gt; 25,000 cells/mm³</td>
</tr>
<tr>
<td><strong>CHEMISTRIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, serum, low</td>
<td>LLN – 3 g/dL</td>
<td>LLN – 3 – 2 g/dL</td>
<td>LLN – 2 g/dL</td>
<td>LLN – 2 g/dL</td>
</tr>
<tr>
<td>Bilirubin, high</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3.0 × ULN</td>
<td>&gt; 3.0 – 10.0 × ULN</td>
<td>&gt; 10.0 × ULN</td>
</tr>
<tr>
<td>BUN</td>
<td>1.25 – 2.5 × ULN</td>
<td>2.5 – 5.0 × ULN</td>
<td>5 – 10.0 × ULN</td>
<td>10 × ULN</td>
</tr>
<tr>
<td>Calcium, serum low</td>
<td>LLN – 8.0 mg/dL</td>
<td>LLN – 8.0 – 7.0 mg/dL</td>
<td>LLN – 7.0 – 6.0 mg/dL</td>
<td>LLN – 6.0 mg/dL</td>
</tr>
<tr>
<td>Calcium, serum high</td>
<td>&gt; ULN – 11.5 mg/dL</td>
<td>&gt; 11.5 – 12.5 mg/dL</td>
<td>&gt; 12.5 – 13.5 mg/dL</td>
<td>&gt; 13.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Clinical Toxicity for HCV Studies
2. International Normalized Ratio (INR), Increased
## Clinical Toxicity Grades for HCV Studies

### CHEMISTRIES

<table>
<thead>
<tr>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALCIUM, IONIZED, LOW</td>
<td>&lt; LLN – 1.0 mmol/L</td>
<td>&lt; 1.0 – 0.9 mmol/L</td>
<td>&lt; 0.9 – 0.8 mmol/L</td>
</tr>
<tr>
<td>CALCIUM, IONIZED, HIGH</td>
<td>&gt; ULN – 1.5 mmol/L</td>
<td>&gt; 1.5 – 1.6 mmol/L</td>
<td>&gt; 1.6 – 1.8 mmol/L</td>
</tr>
<tr>
<td>CHOLESTEROL HIGH</td>
<td>&gt; ULN – 300 mg/dL</td>
<td>&gt; 300 – 400 mg/dL</td>
<td>&gt; 400 – 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 7.75 mmol/L</td>
<td>&gt; 7.75 – 10.34 mmol/L</td>
<td>&gt; 10.34 – 12.92 mmol/L</td>
</tr>
<tr>
<td>CREATININE</td>
<td>1.5 – 1.7 mg/dL</td>
<td>1.8 – 2.0 mg/dL</td>
<td>2.1 – 2.5 mg/dL</td>
</tr>
<tr>
<td>GLUCOSE, SERUM, LOW</td>
<td>&lt; LLN – 55 mg/dL</td>
<td>&lt; 55 – 40 mg/dL</td>
<td>&lt; 40 – 30 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>&lt; 3.0 – 2.2 mmol/L</td>
<td>&lt; 2.2 – 1.7 mmol/L</td>
</tr>
<tr>
<td>GLUCOSE, SERUM, HIGH (Fasting)</td>
<td>&gt; ULN – 160 mg/dL</td>
<td>&gt; 160 – 250 mg/dL</td>
<td>&gt; 250 – 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 8.9 mmol/L</td>
<td>&gt; 8.9 – 13.9 mmol/L</td>
<td>&gt; 13.9 – 27.8 mmol/L</td>
</tr>
<tr>
<td>MAGNESIUM, SERUM, LOW</td>
<td>&lt; LLN – 1.2 mg/dL</td>
<td>&lt; 1.2 – 0.9 mg/dL</td>
<td>&lt; 0.9 – 0.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 0.5 mmol/L</td>
<td>&lt; 0.5 – 0.4 mmol/L</td>
<td>&lt; 0.4 – 0.3 mmol/L</td>
</tr>
<tr>
<td>MAGNESIUM, SERUM, HIGH</td>
<td>&gt; ULN – 3.0 mg/dL</td>
<td>&gt; 3.0 – 3.3 mg/dL</td>
<td>&gt; 3.3 – 3.6 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 1.23 mmol/L</td>
<td>&gt; 1.23 – 1.5 mmol/L</td>
<td>&gt; 1.5 – 1.8 mmol/L</td>
</tr>
<tr>
<td>PHOSPHATE, SERUM, LOW</td>
<td>&lt; LLN – 2.5 mg/dL</td>
<td>&lt; 2.5 – 2.0 mg/dL</td>
<td>&lt; 2.0 – 1.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 0.8 mmol/L</td>
<td>&lt; 0.8 – 0.6 mmol/L</td>
<td>&lt; 0.6 – 0.3 mmol/L</td>
</tr>
<tr>
<td>POTASSIUM, SERUM, LOW</td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>&lt; 3.0 – 2.5 mmol/L</td>
<td>&lt; 2.5 mmol/L</td>
</tr>
<tr>
<td>POTASSIUM, SERUM, HIGH</td>
<td>&gt; ULN – 5.5 mmol/L</td>
<td>&gt; 5.5 – 6.0 mmol/L</td>
<td>&gt; 6.0 – 7.0 mmol/L</td>
</tr>
<tr>
<td>PROTEIN, SERUM, LOW</td>
<td>5.5 – 6.0 g/dL</td>
<td>&lt; 5.5 – 5.0 g/dL</td>
<td>&lt; 5.0 g/dL</td>
</tr>
<tr>
<td>SODIUM, SERUM, LOW</td>
<td>&lt; LLN – 130 mmol/L</td>
<td>&lt; 130 – 120 mmol/L</td>
<td>&lt; 120 mmol/L</td>
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<tr>
<td>SODIUM, SERUM, HIGH</td>
<td>&gt; ULN – 150 mmol/L</td>
<td>&gt; 150 – 155 mmol/L</td>
<td>&gt; 155 – 160 mmol/L</td>
</tr>
<tr>
<td>TRIGLYCERIDES HIGH (Fasting)</td>
<td>150 – 300 mg/dL; 1.71 – 3.42 mmol/L</td>
<td>&gt; 300 – 500 mg/dL; 3.42 – 5.7 mmol/L</td>
<td>&gt; 500 – 1000 mg/dL; 5.7 – 11.4 mmol/L</td>
</tr>
</tbody>
</table>

1. **M13-098 Protocol**
2. **EudraCT 2012-002035-29**
### Clinical Toxicity Grades for HCV Studies\(^1,2\)

<table>
<thead>
<tr>
<th>CHEMISTRIES (continued)</th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>URIC ACID, SERUM, HIGH</td>
<td>7.5 – 10.0 mg/dL</td>
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1 Adapted from the National Cancer Institute’s Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
2 Used for all HCV development compounds.
**Document Approval**

Study M13098 - A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection - EudraCT 2012-002035-29 - 21Aug2012

**Version:** 2.0  **Date:** 21-Aug-2012 09:50:43 PM  **Abbott ID:** 08212012-00F9F6801F6D38-00002-en

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1.0 Title Page

Clinical Study Protocol M13-098

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)

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

AbbVie Investigational Product: ABT-450/Ritonavir/ABT-267, ABT-333
Date: 08 April 2013
Development Phase: 3
Study Design: This is a randomized, double-blind combination drug study.
EudraCT Number: 2012-002035-29
Investigator: Multicenter. Investigator information is on file at AbbVie.
Sponsor: AbbVie Inc (AbbVie)*
Sponsor/Emergency Contact: Tolga Baykal, MD

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 incorporate the changes summarized in the following text.

- Prohibit the use of hormonal contraceptives during study drug administration.
  
  Rationale: *Hormonal contraceptives are not expected to be effective when dosed with the DAA regimen and may be associated with an increased risk for ALT elevation.*

- Corrected typographical error for Sponsor/Emergency Contact mobile number.

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

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<tr>
<td><strong>Name of Study Drug:</strong></td>
<td><strong>Phase of Development:</strong> 3</td>
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<td>ABT-450, ritonavir, ABT-267, ABT-333</td>
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<table>
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<tr>
<th><strong>Name of Active Ingredient:</strong></th>
<th><strong>Date of Protocol Synopsis:</strong> 08 April 2013</th>
</tr>
</thead>
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<tr>
<td>ABT-450: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{{(5-methylpyrazin-2-yl)carbonylamino}-5,16-dioxo-2-(phenanthridin-6-yl oxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocycloprop[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</td>
<td></td>
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<tr>
<td>ritonavir: [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazastridecan-13-oic acid, 5-thiazolylmethyl ester</td>
<td></td>
</tr>
<tr>
<td>ABT-267: Dimethyl ([2S,5S]-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl}[2S]pyrrolidine-2,1-diyl[2S]-3-methyl-1-oxobutane-1,2-diyl})biscarbamate hydrate</td>
<td></td>
</tr>
<tr>
<td>ABT-333: (sodium N-6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl]methanesulfonamide hydrate</td>
<td></td>
</tr>
</tbody>
</table>

| Protocol Title: | |
|----------------||
| A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II) | |

| Objectives: | |
|-------------||
| The primary objectives of this study are to compare the percentage of subjects achieving a 12-week sustained virologic response, SVR12 (HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment) to the historical SVR rate of telaprevir plus pegIFN and RBV therapy and to assess the safety of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV versus placebo for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults without cirrhosis. | |
Objectives (Continued):
The secondary objectives of this study are to assess the percentage of subjects with ALT normalization (ALT ≤ ULN at the end of treatment for subjects with ALT > ULN at Baseline), the percentage of HCV genotype 1a subjects with SVR12, the percentage of HCV genotype 1b subjects with SVR12, the percentage of subjects with virologic failure during treatment, and the percentage of subjects with relapse post-treatment.

Investigators:
Multicenter, investigator information on file at AbbVie.

Study Sites:
Approximately 90

Study Population:
Non-cirrhotic, HCV genotype 1-infected adults that are null-responders, partial responders or relapsers to prior pegylated-interferon alfa-2a or 2b with RBV (pegIFN/RBV) treatment, aged 18 – 70 years of age inclusive.

Number of Subjects to be Enrolled:
Approximately 400 subjects

Methodology:
This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 co-administered with RBV in pegIFN/RBV treatment-experienced non-cirrhotic HCV genotype 1-infected adults. Approximately 400 HCV genotype 1-infected, treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind Treatment Period.

Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) weight-based RBV BID for 12 weeks.

Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + Placebo for ABT-333 250 mg BID with weight-based Placebo for RBV BID for 12 weeks followed by ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID with weight-based RBV BID for 12 weeks.

Randomization will be stratified by type of response to previous pegIFN/RBV treatment type (prior null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). Null responders will be defined by one of two definitions. The number of relapsers to previous pegIFN/RBV treatment will be limited to ≤ 120 subjects, the total number of partial responders plus relapsers to previous pegIFN/RBV treatment will be limited to ≤ 300 subjects, and the number of null responders according to definition 2 will be limited to about 25 subjects to ensure adequate representation in the presumed harder to treat null responder definition 1 population.

This study will consist of three Periods: Double-blind (DB) Treatment Period, an Open-label (OL) Treatment Period for Previous Placebo Subjects and a Post-Treatment (PT) Period for all subjects who received active drugs.
Methodology (Continued):

**DB Treatment Period**

The Sponsor, investigators and subjects will be blinded to drug assignment, virologic results and specific safety laboratory results for the duration of the DB Treatment Period. Virologic results will be reviewed and individual virologic failure criteria will be applied to those subjects randomized to active drugs by an unblinded independent reviewer. Upon reaching Week 12 or premature discontinuation of study drugs, subjects, investigators and the Sponsor will be unblinded. Subjects randomized to active drugs will enter the Post-Treatment Period; subjects randomized to placebo will enter the OL Treatment Period. Subjects randomized to placebo who prematurely discontinue placebo during the DB Treatment Period will be eligible for open-label DAA and RBV treatment at the scheduled DB Week 12 Visit and not at the time of discontinuation of placebo.

**OL Treatment Period**

After being unblinded at the Week 12 Visit, subjects initially randomized to placebo will receive 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV. Study drug, virologic results, and safety laboratory results will not be blinded during this Period. Individual subject virologic failure criteria will be evaluated and applied by the investigator. Upon completing the Open-label Treatment Period (OL Week 12) or premature discontinuation of study drug, subjects will enter the PT Period.

**PT Period**

All subjects initially randomized to active drug who complete or prematurely discontinue study drug in the DB Treatment Period and all subjects initially randomized to placebo who complete the OL Treatment Period or prematurely discontinue study drug in the OL Treatment Period, will be followed for 48 weeks in the PT Period, to monitor safety, HCV RNA and the emergence and persistence of resistant viral variants and assessments of PROs.

The following criteria will be considered evidence of virologic failure. Subjects receiving active study drug in the DB or OL Treatment Periods demonstrating any of the following will be discontinued from direct-acting antiviral agent (DAA) therapy:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log₁₀ IU/mL above nadir) at any time point during treatment,
- Failure to achieve HCV RNA < LLOQ by Week 6; or
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met for subjects on DAA therapy, the subject will discontinue study treatment.
Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:
1. Male or female and age is between 18 and 70 years, inclusive, at time of screening.
2. Subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:
   - Null responder:
     1. received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a $2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
     2. received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a $< 1 \log_{10}$ IU/mL reduction in HCV RNA at Week 4 ($\geq$ 25 days); or
   - Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
   - Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up

Viral loads documenting the type of prior non-response should be obtained during the previous pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.
3. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCVAb at the time of Screening; or
   - Positive for anti-HCV Ab and HCV RNA 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).
4. Screening laboratory result indicating HCV genotype 1-infection.
5. Per local standard practice, documented results of one of the following:
   - 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
   - A screening FibroTest score of $\leq 0.72$ and Aspartate Aminotransferase to Platelet Ratio Index (APRI) $\leq 2$; or
   - A screening FibroScan result of $< 9.6$ kPa.

Subjects with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.
6. Subject has plasma HCV RNA level $> 10,000$ IU/mL at Screening.
### Main Exclusion:

1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.
2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).
3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5%, at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
4. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir Score of >3 or Ishak score of >4.
5. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase (ALT) > $5 \times$ upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) > $5 \times$ ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
   - Albumin < Lower limit of normal (LLN)
   - Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder may be enrolled with permission of the AbbVie Study Designated Physician even if the INR > 1.5
   - Hemoglobin < LLN
   - Platelets < 120,000 cells per mm$^3$
   - Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for subjects of African descent who are black)
   - Indirect bilirubin > $1.5 \times$ ULN and direct bilirubin > ULN

### Investigational Products:

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<tr>
<td>ABT-450/ritonavir/ABT-267</td>
<td>75 mg/50 mg/12.5 mg tablet</td>
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<tr>
<td>ABT-333</td>
<td>250 mg tablet</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>200 mg tablet</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>200 mg capsule</td>
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### Doses:

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<td>ABT-450/ritonavir/ABT-267</td>
<td>150 mg/100 mg/25 mg QD</td>
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<td>ABT-333</td>
<td>250 mg BID</td>
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<tr>
<td>Ribavirin</td>
<td>RBV weight-based dosing 1000 to 1200 mg divided twice daily</td>
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### Mode of Administration:

- Oral

### Reference Therapy:

- Placebo for ABT-450/ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet
- Placebo for ABT-333 250 mg tablet
- Placebo for Ribavirin 200 mg capsule

### Dose:

- Not applicable

### Mode of Administration:

- Oral
**Duration of Treatment:**
In the DB Treatment Period, subjects will receive ABT-450/r/ABT-267 and ABT-333 co-administered with RBV or matching placebos for 12 weeks. Subjects randomized to placebo in the DB Treatment Period will receive ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks in the OL Treatment Period.

**Criteria for Evaluation:**

**Efficacy:**
HCV RNA in IU/mL will be assessed at all Treatment Period Visits and at all post-treatment visits.

**Patient Reported Outcomes (PROs):**
The change in disease-specific function and wellbeing will be assessed using the HCV Patient Reported Outcomes (HCVPRO) instrument. Health State Utility will be assessed using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L). General Health Related Quality of Life (HRQoL) will be assessed using the short form 36, version 2 (SF-36V2) non-disease specific HRQoL instrument.

**Resistance:**
For subjects receiving active drugs who do not achieve SVR, the variants at each amino acid position by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence, and the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline and the appropriate prototypic reference sequences will be tabulated and summarized.

**Pharmacokinetic:**
Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be tabulated and summarized for subjects treated with the active regimen in the DB Treatment Period and the OL Treatment Period.

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

**Statistical Methods:**

**Efficacy:**
In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure will be used to proceed through the primary and secondary efficacy endpoints in the order specified below.

The primary efficacy endpoints are:
1. SVR12: Non-inferiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; lower bound of 95% confidence interval (LCB) must exceed 60% to achieve noninferiority.
2. SVR12: Superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; LCB must exceed 70% to achieve superiority.
Statistical Methods (Continued):

Efficacy (Continued):
The hypotheses will be tested on subjects in the ITT population who were randomized to active study
drug (Arm A). To test the hypothesis that the percentage of treatment-experienced HCV genotype 1
infected subjects treated with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV (the DAA
combination regimen) who achieve SVR12 is non-inferior or superior to the historical SVR rate for the
corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with
SVR12 will be calculated with a 2-sided 95% confidence interval. The confidence interval (CI) will be
calculated using the normal approximation to the binomial distribution. The LCB must be greater than
60% in order for the regimen to be considered non-inferior, and the LCB must be greater than 70% in
order for the regimen to be considered superior to the historical SVR rate in treatment-experienced HCV
genotype 1 infected subjects treated with telaprevir plus pegIFN and RBV.

The secondary efficacy endpoints included in the fixed-sequence testing procedure are:
3. ALT normalization rate in Arm A compared to Arm B in the DB Treatment Period.
4. SVR12: In GT1a subjects, superiority of Arm A to the historical rate for telaprevir plus pegIFN and
   RBV; to demonstrate superiority, the LCB must exceed 65%.
5. SVR12: In GT1b subjects, superiority of Arm A to the historical rate for telaprevir plus pegIFN and
   RBV; to demonstrate superiority, the LCB must exceed 77%.

ALT normalization (final ALT ≤ ULN in the DB Treatment Period) will be calculated for all subjects in
the ITT population with ALT above the upper limit of normal (ULN) at baseline. To test the hypothesis
that the percentage of subjects in the active arm with ALT normalization is greater than the percentage
of subjects in the placebo arm with ALT normalization at the Final DB Treatment Visit, the percentages will
be compared using Fisher's exact test. If superiority of the active arm is demonstrated with a P value
≤ 0.05, then the DAA combination regimen is considered a success for this endpoint. To test the
hypothesis that the percentage of treatment-experienced HCV genotype 1a subjects treated in Arm A who
achieve SVR12 is superior to the historical SVR rate in the corresponding population treated with
telaprevir plus pegIFN and RBV, the percentage of subjects with SVR12 will be calculated with a 2-sided
95% CI calculated using the normal approximation to the binomial distribution. The LCB must be
greater than 65% in order for the regimen to be a success for this endpoint. To test the hypothesis that the
percentage of treatment-experienced HCV genotype 1b subjects treated in Arm A who achieve SVR12 is
superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN
and RBV, the percentage of subjects with SVR12 will be calculated with a 2-sided 95% CI calculated
using the normal approximation to the binomial distribution. The LCB must be greater than 77% in order
for the regimen to be a success for this endpoint.
**Statistical Methods (Continued):**

**Efficacy (Continued):**

Other secondary endpoints not included in the fixed-sequence testing procedure are:

- The percentage of subjects in Arm A with on-treatment virologic failure during the DB Treatment Period (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA ≥ LLOQ at the end of treatment);

- The percentage of subjects in Arm A with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The percentages and 2-sided 95% CI using the normal approximation to the binomial distribution of the subjects with virologic failure during treatment and post-treatment relapse will be calculated and summarized. These endpoints will not be part of the fixed-sequence testing procedure as no hypothesis is being tested.

**PROs:**

Exploratory analyses of the change in non-disease-specific HRQoL, HCV-specific function and wellbeing and Health State Utility will be measured using the SF-36V2, HCVPRO and EQ-5D-5L instruments, respectively. SF-36V2 and HCVPRO will be analyzed by their total/component scores, as appropriate. The EQ-5D-5L will be analyzed by utility score and by visual analogue scale (VAS) response. Changes from baseline in the patient reported outcome (PRO) summary measures will be summarized and compared between treatment arms using ANCOVA models with a treatment group factor and the baseline score as a covariate. The number and percentage of subjects without a decrease from baseline to the Final DB Treatment Visit that is greater than or equal to the minimally important difference (MID) for HCVPRO total score, SF-36v2 MCS or PCS score, and EQ-5D-5L health index score will be calculated for all subjects in each treatment group. The MID for the SF-36v2 PCS and MCS scores will each be −5 points. The MID for HCVPRO total score and EQ-5D-5L health index score will be based on Receiver Operating Characteristic (ROC) curves anchored by SF-36 MCS and SF-36 PCS decreases of 5 points.

**Resistance:**

The following resistance information will be analyzed for subjects receiving active drugs who do not achieve SVR (who have HCV RNA ≥ 1000 IU/mL): 1) the variants at each amino acid position at baseline identified by population nucleotide sequencing will be compared to the appropriate prototypic reference sequence, 2) the variants at available post-baseline time points identified by population and/or clonal nucleotide sequencing will be compared to baseline and the appropriate prototypic reference sequences, 3) the most prevalent amino acid variants found by population sequencing and amino acid variants that emerge or become enriched in isolates from at least 2 subjects of the same subgenotype will be summarized, and 4) the persistence of viral resistance will be summarized.

**Pharmacokinetic:**

Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be tabulated and summarized for subjects treated with the active regimen in the DB Treatment Period and the OL Treatment Period.
Statistical Methods (Continued):

**Safety:**
The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment arm; comparisons will be performed between the active regimen and placebo during the DB Treatment Period using Fisher's Exact test. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA term) in each treatment group is additionally categorized by rating (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 during the DB Treatment Period will be summarized by treatment group and compared between the active and placebo groups in the DB Treatment Period using contrasts within an ANOVA model with treatment group as the factor. Laboratory and vital sign values that are potentially clinically significant (PCS), according to predefined criteria, will be identified, and the percentage of subjects with potentially clinically significant values during the DB Treatment Period will be compared between groups using Fisher's exact tests.
# 1.3 List of Abbreviations and Definition of Terms

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AARDEX</td>
<td>Advanced Analytical Research on Drug Exposure</td>
</tr>
<tr>
<td>ABT-450/r</td>
<td>ABT-450 administered with ritonavir</td>
</tr>
<tr>
<td>ABT-450/r/ABT-267</td>
<td>ABT-450 co-formulated with ritonavir and ABT-267</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
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<td>Cytochrome P450 3A</td>
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<td>DAA</td>
<td>Direct-acting antiviral agent</td>
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<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<td>GAM</td>
<td>Generalized additive method</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<td>---------------------------------------------------------</td>
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<tr>
<td>GCSF</td>
<td>granulocyte colony stimulating factor</td>
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<td>Hepatitis C virus antibody</td>
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<td>HCVPRO</td>
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<td>Human immunodeficiency virus antibody</td>
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<td>IUD</td>
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<td>LCB</td>
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</tr>
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<td>LLOD</td>
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<td>LLOQ</td>
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<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
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<tr>
<td>MID</td>
<td>Minimally important difference</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger RNA</td>
</tr>
<tr>
<td>NGAL</td>
<td>Neutrophil gelatinase-associated lipocalin</td>
</tr>
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<td>NS3A</td>
<td>Nonstructural viral protein 3A</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
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<tr>
<td>NS4A</td>
<td>Nonstructural viral protein 4A</td>
</tr>
<tr>
<td>NS5A</td>
<td>Nonstructural viral protein 5A</td>
</tr>
<tr>
<td>NS5B</td>
<td>Nonstructural viral protein 5B</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Organic anion transporting polypeptide 1B1</td>
</tr>
<tr>
<td>OL</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PCS</td>
<td>Potentially clinically significant or Physical component Summary</td>
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<td>PegIFN</td>
<td>Pegylated-interferon alfa-2a or 2b</td>
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<td>PK</td>
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<td>r</td>
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<td>Ribavirin</td>
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<tr>
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<td>Ribonucleic acid</td>
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<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase PCR</td>
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<tr>
<td>RVR</td>
<td>Rapid virologic response</td>
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<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
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<td>SF-36V2</td>
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<td>SGOT</td>
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<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
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<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<tr>
<td>SVR</td>
<td>Sustained virologic response</td>
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<td>Sustained virologic response 12 weeks post-dosing</td>
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<td>SVR&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Sustained virologic response 4 weeks post-dosing</td>
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<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
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USPI United States Prescribing Information
VAS Visual analogue scale
WBC White blood cells

**Definition of Terms**

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<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Study Drugs</td>
<td>ABT-450/r/ABT-267, ABT-333, ribavirin</td>
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<td>DB Day 1</td>
<td>First day a subject took study drugs (active or placebo)</td>
</tr>
<tr>
<td>Treatment Period</td>
<td>Baseline/DB Day 1 through last dose of active drugs (DB through OL Treatment Periods)</td>
</tr>
<tr>
<td>DB Treatment Period</td>
<td>Double-Blind Treatment Period</td>
</tr>
<tr>
<td>OL Treatment Period</td>
<td>Open-Label Treatment Period</td>
</tr>
<tr>
<td>PT Period</td>
<td>Post-Treatment Period (Day after the last dose of active DAA through Post-Treatment Week 48 or Post-Treatment Discontinuation)</td>
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3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals chronically infected worldwide. While therapy for this condition has improved considerably with approval of the protease inhibitors telaprevir and boceprevir, these direct-acting antiviral agents (DAA) must be used in combination with pegylated-interferon (pegIFN) and ribavirin (RBV) for up to 48 weeks. Treatment with pegIFN and RBV may be associated with considerable, often treatment-limiting toxicities. Thus, the currently available treatment regimens are not optimal and there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment and/or decrease the need for pegIFN and RBV as components of HCV therapy.

Combinations of multiple DAAs with pegIFN and RBV may further improve sustained virologic response (SVR) rates or shorten duration of therapy. Ultimately, it is anticipated that regimens combining multiple DAAs may be curative without the need for combination pegIFN and RBV. Exploratory studies with such pegIFN and RBV sparing combination regimens in humans have been initiated, and promising short-term antiviral efficacy has been reported from IFN-free combinations (either with or without RBV) of an HCV protease inhibitor with a nucleoside polymerase inhibitor, a nonnucleoside polymerase inhibitor, and a nonstructural viral protein 5A (NS5A) inhibitor. Additionally, studies evaluating the combination of a nonstructural protein 5B (NS5B) nucleotide polymerase inhibitor and RBV have been initiated. Sustained virologic response 12 weeks post-doing (SVR12) in rates as high as 90% (9/10 subjects) have been observed in genotype 1b infection with an NS5A plus protease inhibitor combination and 100% (10/10 subjects) in genotype 2 or 3 infection with a nucleotide polymerase inhibitor plus RBV.

AbbVie currently has a number of DAA compounds in clinical development: ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor, ABT-267 is an NS5A inhibitor, and ABT-333 is a NS5B non-nucleoside polymerase inhibitor. These agents have the potential for co-administration in the treatment of HCV
infection. This double-blind, placebo-controlled study is intended to examine the safety and antiviral activity of 12 weeks treatment with ABT-450/r/ABT-267 with ABT-333 co-administered with RBV in treatment-experienced adults with chronic HCV genotype 1 infection.

**ABT-450**

ABT-450, (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-([(5-methylpyrazin-2-yl)carbonyl]amino)-5,16-dioxo-2-(phenanthridin-6-yl oxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradeca hydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate, is a NS3 protease inhibitor with nanomolar potency against genotype 1 HCV in vitro. ABT-450 is metabolized primarily by cytochrome P450 3A4 (CYP3A) and thus is dosed with ritonavir, (the combination is denoted as ABT-450/r) a potent CYP3A inhibitor, in order to enhance exposures.

ABT-450/r has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown potent antiviral activity at doses of 50/100 mg QD and greater in HCV genotype 1-infected subjects. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-450.⁹

**ABT-267**

ABT-267, dimethyl (((2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diy1)bis{benzene4,1-diy1carbamoyl(2S)pyrrolidine-2,1-diy1([2S)-3-methyl-1-oxobutane-1,2diy1])bis carbamate hydrate, is a novel NS5A inhibitor, with inhibitory concentrations in the picomolar range against genotypes 1a and 1b in subgenomic replicon systems.

ABT-267 has a favorable safety, tolerability, and pharmacokinetic profile at all doses administered to date, and has shown substantial antiviral activity during 3 days of monotherapy in HCV genotype 1-infected subjects. Additional detailed information
about preclinical toxicology, metabolism, pharmacology, and clinical data can be found in the Investigator's Brochure for ABT-267.\textsuperscript{10}

The ABT-267 formulation used in the Phase 2b study M11-652 is a HME tablet. The formulation to be used in this study is a HME co-formulation of ABT-450 and ritonavir with ABT-267. Exposures to ABT-267 from the co-formulation is comparable to that from the HME formulation used in Study M11-652.

**ABT-333**

ABT-333, (sodium N-\{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl\]naphthalen-2-yl\}methanesulfonamide), is a non-nucleoside NS5B polymerase inhibitor with inhibitory concentrations in the nanomolar range against genotypes 1a and 1b NS5B in subgenomic replicon systems. ABT-333 has been well tolerated in single and multiple dose studies in healthy volunteers, and when administered to HCV-infected subjects at doses up to 800 mg BID for up to 12 weeks. The mean $t_{1/2}$ ranged from approximately 5 to 8 hours.

ABT-333 has a favorable safety, tolerability, and pharmacokinetic profile at doses administered to date and has shown antiviral activity in HCV genotype 1-infected subjects at doses greater than 100 mg BID. Additional detailed information about preclinical toxicology, metabolism, pharmacology and clinical data can be found in the Investigator's Brochure for ABT-333.\textsuperscript{11}

The ABT-333 formulation used in the Phase 2b Study M11-652 is a 400 mg tablet. The formulation to be used in this study is a 250 mg optimized formulation of ABT-333. Exposures of the 250 mg ABT-333 dose from the optimized formulation is expected to be comparable to that from 400 mg dose of the formulation used in Study M11-652.

**Combination Dosing in HCV-Infected Subjects**

In the M12-267 study open-label ABT-450/r 150/100 mg QD was administered for 12 weeks to 11 HCV genotype 1-infected treatment-naïve subjects with host interleukin
28B (IL28B) rs12979860 CC genotype, in combination with weight-based RBV and a non-nucleoside polymerase inhibitor, ABT-072, which has antiviral activity comparable to that of ABT-333. The combination was safe and well tolerated and was associated with rapid and durable virologic suppression, with all 11 subjects achieving HCV RNA levels below the limit of quantitation by Week 4. To date, 10 of 11 subjects have achieved sustained virologic response 24 weeks post-dosing (SVR24) with one subject subsequently experiencing a late relapse at post-treatment Week 36.12

In a separate, open-label study (Study M12-746), ABT-450/r QD and ABT-333 400 mg BID were administered for 12 weeks in combination with weight based RBV to 33 treatment-naïve and 17 treatment-experienced (pegIFN/RBV non-responders and null-responders) HCV genotype 1-infected adults. ABT-450/r in this study was given at doses of 150/100 mg or 250/100 mg QD. Thirty-one of 33 treatment-naive subjects have completed 12 weeks of dosing; rapid virologic suppression was seen in all 31 subjects and all 31 (94%) achieved SVR12. No relapses have been identified to date among these subjects with durations of follow-up as long as 48 weeks. Among the 17 treatment-experienced subjects, 6 experienced breakthrough during treatment and to date 3 have experienced post-treatment relapse. The remaining 8 subjects have achieved SVR24 resulting in an overall SVR24 rate of 47% (8/17) in this treatment-experienced population.13,14

Preliminary safety results in Study M12-746 show that the regimen was generally well tolerated. There have been no serious adverse events with the majority of adverse events being reported as mild, including fatigue, pruritus, and headache. One subject in the ABT-450/r 250/100 mg and ABT-333 400 mg BID treatment arm experienced a Grade 3 ALT elevation at Week 2 and discontinued study drug dosing as a result. The subject was asymptomatic, did not have concomitant total bilirubin increases, and the ALT decreased promptly after discontinuing study drug. There were no Grade 3 or greater elevations of ALT at ABT-450/r doses less than 250/100 mg QD. A second subject in the ABT-450/r 250/100 mg and ABT-333 400 mg BID treatment arm experienced an asymptomatic Grade 3 total bilirubin elevation of 6.2 mg/dL at Week 2,
which remained at Grade 2 throughout most of the remainder 12 weeks of dosing and normalized after treatment was discontinued. The elevation was predominately due to increases in indirect bilirubin and was not associated with symptoms referable to the hepatobiliary system, or with elevated levels of transaminases or alkaline phosphatase.

**Study M11-652**

Study M11-652 is an ongoing multicenter, open-label Phase 2b study evaluating the antiviral activity, safety and pharmacokinetics of multiple ABT-450/r-based DAA combination regimens in HCV genotype 1-infected adults who are either treatment-naïve or are previous null responders to pegIFN and RBV. This study consists of 14 arms: 9 arms with planned enrollment of 440 treatment-naïve subjects and 5 arms with planned enrollment of 120 null responders. The primary and secondary efficacy endpoints compare the percentage of treatment-naïve subjects achieving SVR\textsubscript{24} across the various regimens.

Preliminary efficacy data suggest that all regimens demonstrate rapid suppression of HCV-1 RNA levels. All subjects in the 8- and 12-week treatment arms have completed study treatment and are in post-treatment follow-up. In the null responders to previous pegIFN/RBV 12-week treatment arms, the 4 drug regimen using the higher ABT-450 dose (ABT-450/r 150/100 mg once daily [QD] + ABT-267 25 mg QD + ABT-333 400 mg twice daily [BID] with RBV) achieved numerically higher SVR\textsubscript{12} results (21/22 subjects, 95%) compared to the lower dose of ABT-450/r in the 3 DAA regimen coadministered with RBV (21/23 subjects, 91%) or the 2 DAA regimen of ABT-450/r and ABT-267 coadministered with RBV (40/45 subjects, 89%).

Thus, the 4 drug regimen using the higher ABT-450 dose for 12 weeks will be used in the current study.

Preliminary resistance testing in Study M11-652 suggests that in the majority of subjects who experienced virologic failure, viral mutations were selected in the target regions corresponding to the DAAs each subject was receiving with the exception of those treated...
for 8 weeks, among whom most had populations at the time of relapse that were identical to their baseline sample.

Preliminary safety analysis showed that all study drug regimens were well tolerated for up to 24 weeks in treatment-naïve and prior null responder subjects. Approximately 1.2% discontinued study drug treatment due to adverse events. The majority of adverse events reported have been mild or moderate in severity, the most frequent including nausea, headache, fatigue, insomnia and diarrhea. Laboratory abnormalities included decreases in hemoglobin, most likely related to RBV, since mean decreases in hemoglobin from baseline to the end of treatment were greater in arms with RBV than in the arm without RBV (2.0 – 2.8 g/dL versus 0.7 g/dL). Grade 3 (or higher) elevations of alanine aminotransferase (ALT) occurred in 5 subjects (all without bilirubin elevation) all of whom were asymptomatic; some of these elevations were seen in subjects taking concomitant hormonal contraceptives. In all 5 cases ALT normalized without intervention or study drug modification or interruption. Four of these subjects were receiving ABT-450/r at a dosage of 200/100 mg which is greater than the planned ABT-450/r dose in the current study. The highest ALT level in Study M11-652 was 408 U/L. To date, the majority of subjects randomized to 24 weeks of treatment in Study M11-652 are still receiving study treatment. However, preliminary assessment of safety and efficacy suggest that these treatment regimens are comparable to the corresponding 12-week treatment regimens.

The current double-blind, placebo-controlled study is intended to examine the safety and antiviral activity of 12 weeks treatment with ABT-450/r/ABT-267 with ABT-333 co-administered with RBV in pegIFN/RBV treatment-experienced adults with chronic HCV genotype 1-infection. Additional discussion and justification of study design may be found in Section 5.6.

### 3.1 Differences Statement

The differences between this study and the previous DAA combination studies are as follows:
This is a Phase 3 DAA combination study in all types of pegIFN/RBV treatment-experienced subjects: null responders, partial responders, and relapsers. Prior Phase 2b studies have assessed only prior null responders to pegIFN/RBV.

Differences in study design: This is a Phase 3 study. Prior DAA combination studies have been conducted in an open-label fashion. This study is a double-blind, placebo-controlled study to confirm the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 co-administered with ribavirin for 12 weeks in approximately 400 treatment-experienced subjects.

This study will expose significantly more subjects to ABT-450/r/ABT-267 and ABT-333 co-administered with RBV to allow for a more robust assessment of safety and efficacy.

The DAA formulations used in this study also differ from those used in Study M11-652.

3.2 Benefits and Risks

Study M13-098 consists of two arms in which three DAAs and RBV are administered together in one arm with placebo for the DAAs and RBV in the other arm. All subjects randomized to placebo will be eligible to received active drugs after completing 12 weeks on study. Promising clinical data on interferon free regimens have been reported using combination DAA regimens; the Sponsor is currently conducting two trials, Study M11-652 and Study M12-998 which include arms evaluating interferon and ribavirin free regimens for 12-week durations.

Based on data from Study M11-652, in the null responders to previous pegIFN/RBV 12-week treatment arms, the 4 drug regimen using the higher ABT-450 dose (ABT-450/r 150/100 mg once daily [QD] + ABT-267 25 mg QD + ABT-333 400 mg twice daily [BID] with RBV) achieved high SVR12 rates. Numerically higher SVR12 results (21/22 subjects, 95%) were observed as compared to the lower 100/100 mg dose of ABT-450/r in the 3 DAA regimen coadministered with RBV (21/23 subjects, 91%). Previous analyses have reported that SVR12 has a 98% positive predictive value for
SVR\textsubscript{24}, suggesting SVR\textsubscript{12} results provide clinically meaningful assessment of long term response.\textsuperscript{15} Partial responders and relapers have had higher SVR rates than null responders in multiple regimens by other sponsors.

In Study M11-652, the regimen has been generally well-tolerated. Details about the safety of the DAAs, including data from Study M11-652 are provided in the Investigator's Brochures for the individual DAAs.

Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the ICF 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 co-administered with RBV, including the risks of toxicity and virologic failure, including the emergence of resistant variants, appear limited and manageable based on the results of ongoing trials. Given the potential high rate of cure in this population of HCV-infected subjects, the risk-benefit comparison is favorable.

4.0 Study Objective

4.1 Primary Objective

The primary objectives of this study are to compare the percentage of subjects achieving SVR\textsubscript{12} (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV (the DAA combination regimen) to the historical SVR rate of telaprevir plus pegIFN and RBV therapy and to assess the safety of the DAA combination regimen versus placebo for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults without cirrhosis.
4.2 Secondary Objective

The secondary objectives of this study are to measure the effect of the DAA combination regimen compared to placebo for 12 weeks on normalizing alanine aminotransferase (ALT) levels and demonstrate the effect of the DAA combination regimen on SVR12 in subjects with HCV genotype 1a and genotype 1b infection, and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment relapse, respectively.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT 450/r/ABT-267 and ABT-333 co-administered with RBV in pegIFN/RBV treatment-experienced non-cirrhotic HCV genotype 1-infected adults.

Approximately 400 HCV genotype 1-infected, pegIFN/RBV treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind (DB) Treatment Period at approximately 90 sites.

- Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks;
- Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + Placebo for ABT-333 250 mg BID + Placebo for RBV for 12 weeks followed by active study drug (ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV) for 12 weeks.

RBV dosing will be weight based, either 1000 mg or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID).
The duration of the study will be up to 72 weeks long (not including a screening period of up to 35 days) consisting of three periods: The DB Treatment Period, the Open-Label (OL) Treatment Period (for subjects randomized to placebo/Arm B), and the Post-Treatment (PT) Period (for all subjects who received active study drugs).

In the DB Treatment Period, randomization will be stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). Subjects on placebo will be administered open-label active study drugs for 12 weeks following completion of the DB Treatment Period. All subjects administered active study drugs will be followed for 48 weeks post-treatment to monitor for safety, HCV RNA, the emergence and/or persistence of resistant viral variants and assessment of PROs (Figure 1).

**Figure 1. Study Design**

The primary analysis will occur after subjects who were initially randomized to active drug have completed through PT Week 12 or prematurely discontinued the study and subjects who were initially randomized to placebo have completed 12 weeks of open-label active treatment or prematurely discontinued study drug. A follow-up analysis will occur after subjects who received open-label active treatment have completed through PT Week 12 or prematurely discontinued the study. All remaining data through PT Week 48 will be summarized in the end of study analysis.
Safety evaluations will occur throughout the study by a Data Monitoring Committee (DMC). See Section 5.5.2.2. Efficacy evaluations will occur throughout the DB and OL Treatment Periods and if virologic failure criteria as detailed in Section 5.4.1.1 are met, the findings will be discussed with the investigator and reviewed by the Sponsor.

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 Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 associated with the Screening Visit. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through DB 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 35 days following the Screening Visit to enroll into the study.

Screening is required prior to entering the DB Treatment Period only. Subjects randomized to placebo will not be required to re-screen prior to entering the OL Treatment Period.

Subjects should otherwise meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

The study is designed to enroll 400 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.
5.1.1.1 Rescreening

Subjects may be rescreened only once as follows:

- Subjects who meet all eligibility criteria with the exception of one exclusionary laboratory parameter may rescreen once without prior AbbVie approval with the exception of exclusionary genotype, a positive drug screen (without prescription for the positive drug, or as noted below), or a positive HIV, HBV or pregnancy test. Subjects who test positive at Screening for any of these parameters are not eligible to rescreen.

- Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine drug screen repeated. If the repeat urine drug screen is negative (except for cases in which the screen is positive for a prescribed drug), the subject may be considered eligible.

- Subjects who have multiple exclusionary laboratory results require approval from the AbbVie Study Designated Physician prior to rescreening the subject.

Subjects being rescreened because of an exclusionary eligibility parameter other than a positive urine alcohol screen must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary at the first screening attempt (with the exception of HCV genotype, IL28B genotype, FibroTest, FibroScan or liver biopsy which do not need to be repeated).

Eligible subjects who fail to enroll within 35 days of screening, regardless of the reason for falling outside the 35-day screening window, may be allowed to rescreen only once.

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 EDC systems.
5.1.2 Treatment Period

5.1.2.1 Double-Blind (DB) Treatment Period

Subjects with HCV genotype 1 who meet the eligibility criteria will be randomized via IRT in a 3:1 ratio to either active drug (ABT-450/r/ABT-267 and ABT-333 co-administered with RBV) or matching placebos on DB Day 1. The DB Treatment Period of the study consists of 12 weeks of double-blind treatment. The Sponsor, investigators and subjects will be blinded to drug assignment and virologic results for the duration of the DB Treatment Period. Virologic results will be reviewed and virologic failure criteria will be applied to those subjects randomized to active drugs by an unblinded independent reviewer. See Section 5.4.1.1 for further details. Certain safety laboratory results which, if available, could potentially be unblinding (such as hemoglobin, hematocrit, AST, ALT, total and indirect bilirubin) will also be blinded to the Sponsor, investigators and subjects. For the blinded laboratory tests if prespecified toxicity thresholds are exceeded then the relevant unblinded laboratory data will be provided to the investigator and Sponsor. See Section 6.7 for further details. In addition, a subject's study drug assignment may be unblinded as directed by the toxicity management guidelines or at the investigator's discretion, if deemed necessary for subject safety.

Sites should ensure that subjects adhere to the study visits. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drugs 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, adverse event and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment by qualified individuals at the request of the Investigator and with the agreement of the subject.

At the Week 12 Visit of the DB Period, the study drug assignment will be unblinded and subjects randomized to placebo who complete the 12-week DB Treatment Period may
enter the OL Treatment Period, consisting of 12 weeks of active therapy. Following completion or discontinuation of active therapy (either in the DB or OL Treatment Period), all subjects will enter the PT Period consisting of 48 weeks of post-treatment follow-up.

Subjects who prematurely discontinue from the DB Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as defined in Table 3 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 drug and prior to the initiation of any other anti-HCV therapy. At the Treatment Discontinuation Visit, subjects will be unblinded to study drug assignment. Subjects who were randomized to active study drug will immediately start the PT Period and be monitored for virologic failure and resistance as detailed in Section 5.1.4. Subjects who prematurely discontinue study drugs during the DB Treatment Period and who are found to be on placebo may elect to remain in the study (at the investigator's discretion) and receive active drug during the Open-Label Period. However, the subject is expected to continue to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through DB Week 12 in order to be enrolled into the OL Treatment Period.

5.1.2.2 Open-Label (OL) Treatment Period

After completing the DB Treatment Period, subjects initially randomized to placebo (Arm B) will receive 12 weeks of active treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV. Subjects will be dispensed drugs at the DB Week 12 Visit for administration starting the next day, which will become Day 1 of the OL Treatment Period. The same type of blister cards as were used for placebo will be used for active study drugs ABT-450/r/ABT-267 + ABT-333 and will be dispensed during the OL Treatment Period; open-label RBV tablets will be dispensed during the OL Treatment Period.
Sites must call subjects the next day to verify the first day of open-label, study drug administration and record this date on the eCRF and in the source documents. Study drugs, virologic results and safety laboratory results will not be blinded during the OL Treatment Period. Virologic failure criteria and toxicity management will be evaluated and applied by the investigator (Section 5.4.1.1 and Section 6.7). Some of the Open-Label Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, adverse event and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment by qualified individuals at the request of the Investigator and with the agreement of the subject. Some of the Open-Label Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, adverse event and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment by qualified individuals at the request of the Investigator and with the agreement of the subject.

Subjects who prematurely discontinue from the OL Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as defined in Table 4 and as described in Section 5.4.1. Ideally, this should occur on the day of 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. Subjects who complete or discontinue the OL Treatment Period will be monitored in the PT Period for virologic resistance as detailed in Section 5.1.3.

### 5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of active drugs will be monitored for safety, HCV RNA, the emergence and/or persistence of resistant viral variants, and assessment of PROs for an additional 48 weeks following the last dose of active study drugs. Subjects will return to the study site as outlined in Table 5 for the PT Period. The PT Period will begin the day after the last dose of active study drugs (in either the DB Treatment Period for subjects who were randomized to Arm A or the OL Treatment Period for subjects who
were randomized to Arm B). Subjects who prematurely discontinue the PT Period should return to the site for a PT Discontinuation Visit as outlined in Table 5. Some of the Post-Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, adverse event and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment at the request of the Investigator and with the agreement of the subject.

All subjects who receive at least one dose of active DAA may be offered participation in an AbbVie-sponsored observational study to evaluate the durability of virologic response for subjects who achieve SVR or to study the emergence and persistence of resistant variants in subjects who fail treatment.

All subjects who receive at least one dose of active DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered another AbbVie-sponsored treatment study including ABT-450/r + ABT-267 + pegIFN/RBV. Subjects may also be offered another non-AbbVie treatment as determined appropriate by the investigator.

5.1.4 Treatment Failure Extension

During the DB Treatment Period, if greater than or equal to 50% of null or partial responder subjects completing 12 weeks of active study drug treatment experience virologic relapse post-treatment, then the treatment will extend to 24 weeks for all ongoing subjects randomized to active regimen in the DB Treatment Period and all subjects subsequently randomized to the active regimen (see Appendix C for 24-week Study Activities table).

In addition, subjects ongoing in the OL treatment period will have OL active treatment extended to 24 weeks. Subjects randomized to the placebo group will still be administered 12 weeks of placebo; however, subjects will then receive 24 weeks of the active regimen in the OL Treatment Period. This treatment extension assessment will be applied starting when the first 10 null or partial responder subjects who complete
12 weeks of treatment relapse or reach PT Week 12, and weekly thereafter until all subjects have enrolled.

The subjects who were relapsers to previous pegIFN/RBV treatment will not be included in these assessments as their response to anti-HCV treatment is presumed to be more like subjects who are naïve to treatment. Treatment may be extended for some strata (e.g., type of response to previous pegIFN/RBV treatment or HCV subgenotype) and not for others based on the strata of the subjects experiencing relapse at a high rate.

5.2 Selection of Study Population

HCV genotype 1-infected adult subjects who are either null responders, partial responders, or relapsers to prior pegIFN/RBV treatment, and 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 and age is between 18 and 70 years, inclusive, 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
   - 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)
   - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or has a vasectomized partner(s)
   - of childbearing potential and sexually active with male partner(s):
○ currently using at least one effective method of birth control at the time of screening and agrees to use 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 DB Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during administration of study drugs).

● 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),
  ○ practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle),
  ○ sexually active with female partners only

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

  ● at Screening by serum specimen within 35 days prior to initial study drug administration, and

  ● at Baseline (prior to dosing) by urine specimen.

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

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

4. Sexually active males must be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential must agree to practice 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 DB Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Contraceptives containing ethinyl estradiol or depo-progesterone may be considered effective if used by the female partners of males subjects.)

5. Subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:

- **Null responder:**
  1. received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a $2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16); or
  2. received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a $< 1 \log_{10}$ IU/mL reduction in HCV RNA at Week 4 ($\geq$ 25 days); or

- **Partial responder:** received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment; or

- **Relapser:** received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.
Viral loads documenting the type of prior non-response should be obtained in relation to the previous pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.

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

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

8. Must voluntarily sign and date an informed consent form, approved by an IRB/IEC, prior to the initiation of any screening or study specific procedures.

9. Chronic HCV infection prior to study enrollment. Chronic HCV infection is defined as one of the following:
   - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening; or
   - Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection.

10. Screening laboratory result indicating HCV genotype 1-infection.

11. Per local standard practice, documented results of one of the following:
   - 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
   - A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
   - A screening FibroScan result of < 9.6 kPa.
Subjects with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 24 months prior to or during screening.

12. Subject has plasma HCV RNA level > 10,000 IU/mL at Screening.

**Rationale for Inclusion Criteria**

(1, 5, 9, 10 – 12) To select the appropriate subject population with sufficient disease severity for evaluation.

(7) For the safety of study subjects.

(2 – 4) RBV has known teratogenic effects.

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

**5.2.2 Exclusion Criteria**

1. History of severe, life-threatening or other significant sensitivity to any drug.

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

3. Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of study drug.

4. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol.

5. Positive test result at screening for Hepatitis B surface antigen (HBsAg) or anti-Human immunodeficiency virus antibody (HIV Ab).
6. HCV genotype performed during screening indicates co-infection with any genotype other than genotype 1.

7. Use of any medications listed below as well as those that are contraindicated for ritonavir and ribavirin within 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer, including but not limited to:

<table>
<thead>
<tr>
<th>Medications Contraindicated for Use with the Study Drug Regimen</th>
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<tbody>
<tr>
<td>Alfuzosin</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Astemizole</td>
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<td>Bepridil</td>
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<td>Bosentan</td>
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<td>Buprenorphine</td>
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<td>Carbamazepine</td>
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<td>Cisapride</td>
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<td>Clarithromycin</td>
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<td>Dronedarone</td>
</tr>
<tr>
<td>Efavirenz</td>
</tr>
<tr>
<td>Eletriptan</td>
</tr>
<tr>
<td>Eplerenone</td>
</tr>
<tr>
<td>Ergot Derivatives</td>
</tr>
<tr>
<td>Everolimus</td>
</tr>
</tbody>
</table>

* Use of hormonal contraceptives requires SDP approval.

Or
Table 2. Medications Contraindicated Because Dose Adjustments Cannot Be Readily Made Prior to or During the Blinded Placebo-Controlled Phase of the Study

| Alfentanil  | Mexiletine |
| Budesonide  | Perphenadine |
| Colchicine  | Risperadone |
| Colchicine  | Sildenafil |
| Cyclosporine| Sirolimus |
| Digoxin     | Tacrolimus (use topically is permitted) |
| Disopyramide| Tadalafil |
| Divalproex  | Thioridazine |
| Erythromycin| Vardenafil |
| Ethosuximide| Vinblastine |
| Fentanyl    | Vincristine |
| Fluticasone | Warfarin |
| Lamotrigine |           |
| Lidocaine   |           |

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.

8. Use of known strong inhibitors or inducers of cytochrome P450 3A (CYP3A), inhibitors of cytochrome P450 2C8 (CYP2C8) within 2 weeks or 10 half-lives (if known) of the respective medication/supplement, prior to study drug administration.

9. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of:

   - a positive result associated with documented short-term use or chronic stable use of a prescribed medication in that class;
• a single positive result on urine screen for alcohol is discussed in Section 5.1.1.1 on rescreening.

10. Clinically significant abnormalities, other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator.

11. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.

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

13. Any cause of liver disease other than chronic HCV infection, including but not limited to the following:
   • Hemochromatosis
   • Alpha-1 antitrypsin deficiency
   • Wilson's disease
   • Autoimmune hepatitis
   • Alcoholic liver disease
   • Drug-related liver disease

Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.
14. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - ALT > 5 × Upper limit of normal (ULN)
   - AST > 5 × ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
   - Albumin < Lower limit of normal (LLN)
   - Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated Physician
   - Hemoglobin < LLN
   - Platelets < 120,000 cells per mm$^3$
   - Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for subjects of African descent who are black)
   - Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

15. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or DB Day 1 (prior to dosing).

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

17. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-450, ABT-267, ABT-333, ritonavir or RBV.

18. Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than interferon and/or pegIFN/RBV) including previous exposure to telaprevir, boceprevir, ABT-450, ABT-267, ABT-333. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled with the
approval of the AbbVie Study Designated Physician if they can produce documentation that they received only placebo. Concurrent participation in a non-interventional, epidemiologic or registry trial may be permitted with approval by the AbbVie Study Designated Physician.

19. The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of the Screening Period.

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

**Rationale for Exclusion Criteria**

(1, 3, 8–12, 14, 15, 17, 20) To ensure safety of the subjects throughout the study.

(2, 4, 6, 7, 16, 18, 19) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.

(5, 13) To exclude subjects with liver diseases other than HCV.

**5.2.3 Prior and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of signing the consent through the DB and OL (if applicable) Treatment Periods of the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.
All medication use will be recorded until 30 days following the last dose of study drugs. Only medications associated with HCV treatment or a serious adverse event (SAE) will be collected thereafter.

The AbbVie study-designated physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior HCV Therapy

All study subjects must have previously received pegIFN and RBV and failed treatment (either on treatment or via relapse post-treatment). These subjects should have documentation of pegIFN and RBV combination treatment history, including start and stop dates and HCV RNA levels to document the type of non-response in the source.

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

Prior or current use of any other investigational or commercially available anti-HCV agents other than interferon and/or pegIFN/RBV, including telaprevir, boceprevir, 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 or herbal supplements within 2 weeks or within 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to initial study drug administration through 2 weeks following discontinuation of study drug dosing. Subjects must be consented prior to discontinuing any prohibited medications or herbal supplements for the purpose of meeting study inclusion criteria.
Investigator should confirm that concomitant medication can be administered with DAAs (including ritonavir) and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. The investigator can also review the label(s) for the concomitant medication(s) for additional information.

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

5.2.3.3 Prohibited Therapy

In addition to the medications listed above in Table 1 and Table 2; use of known strong inhibitors or inducers of CYP3A, or inhibitors of CYP2C8 is prohibited within 2 weeks or 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to the initial dose of study drug through the first 2 weeks after the subject has completed active study drugs.

Alprazolam, diazepam, clonazepam, clorazepate, estazolam and flurazepam, may be contraindicated depending on the anticipated duration, dose and frequency of use. Individuals on these medications must contact the AbbVie Study Designated Physician to verify if the use of these medications is exclusionary.

Hormonal contraceptives (including oral, topical, injectable or implantable varieties) may not be used from 2 weeks prior to the first dose of study drug until 2 weeks after the end of study drug dosing unless approved by the Study Designated Physician. Post-menopausal hormone replacement therapy may be used at the discretion of the Investigator.

Anti-HCV medications other than those specified in the protocol will not be allowed during either the DB or OL Treatment Periods of the study.

Use of hematopoietic growth factors is not permitted during this study without the approval of the AbbVie Study Designated Physician. Management of hematologic
growth factor therapy is the responsibility of the investigator; growth factors will not be provided by the Sponsor, and the Sponsor will not reimburse for the expense of growth factors or their use.

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

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in Table 3, Table 4, and Table 5.
### Table 3. Study Activities – Double-Blind (DB) Treatment Period

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C from DB Treatment&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
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<tr>
<td>Provide RBV Medication Guide and Partner Risk Fact Sheet&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Pregnancy Test [serum (s) urine (u)]&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X (s)</td>
<td>X (u, s)</td>
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<tr>
<td>Liver Biopsy or FibroTest or FibroScan&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Pharmacogenetic Sample (optional)&lt;sup&gt;i&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> DB = Double-Blind; <sup>b</sup> EOT = End of Treatment; <sup>c</sup> D/C = Discontinuation; <sup>d</sup> Include only for women of childbearing potential; <sup>e</sup> Normally measured on Day 1; <sup>f</sup> ECG on Day 1 and Week 12; <sup>g</sup> Serum samples (s) are collected at Wk 4, 8, and 12; <sup>h</sup> For those with cirrhosis or abnormal liver function test results; <sup>i</sup> Not available for all patients.
### Table 3. Study Activities – Double-Blind (DB) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>DB Wk 12 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C from DB Treatment&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Messenger RNA (mRNA) Sample (optional)</td>
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<td>Total Insulin</td>
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<td>Concomitant Medication Assessment</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Adverse Event Assessment</td>
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<td>X</td>
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<tr>
<td>Patient Reported Outcomes Instruments (PROs)&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>Study Drugs Dispensed</td>
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<td>Medication Event Monitoring System (MEMS) cap dispensed</td>
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<tr>
<td>Study Drugs Collected, MEMS Cap Downloaded and Compliance Reviewed</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
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<td></td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
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<td>HCV RNA Samples</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Archive Serum Sample</td>
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</table>
### Table 3. Study Activities – Double-Blind (DB) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>DB Day 1(^a)</th>
<th>DB Wk 1</th>
<th>DB Wk 2</th>
<th>DB Wk 4</th>
<th>DB Wk 6</th>
<th>DB Wk 8</th>
<th>DB Wk 10</th>
<th>DB Wk 12 (EOT)(^{b,c})</th>
<th>Premature D/C from DB Treatment(^c)</th>
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</thead>
<tbody>
<tr>
<td>Interferon gamma-induced protein 10 (IP-10) Sample</td>
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<td>Urine Albumin(^n)</td>
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</tbody>
</table>

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

a. All procedures will be performed prior to first dose.
b. Subjects randomized to Arm B and beginning the OL Treatment Period should have all procedures completed prior to dosing OL Day 1.
c. Subjects randomized to Arm A should begin the PT Period after the subject completes or prematurely discontinues study drugs treatment in this period.
d. Where applicable/locally available.
e. Height will be measured at the Screening Visit only.
f. Evaluate DB day 1 ECG prior to dosing to determine eligibility
g. Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal.
h. For subjects who have not had a qualifying liver biopsy within the previous 24 months.
i. If the optional Pharmacogenetic sample is not collected at DB Day 1, it may be collected at any other visit during the study.
j. SF-36V2, EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L), and Hepatitis C Virus Patient Reported Outcomes Instrument (HCVPRO) should be administered before any study procedures including unblinding and in the order listed.
k. Subjects randomized to Arm B will have study drugs and a MEMS cap dispensed for open-label RBV at the DB Week 12 Visit.
l. MEMS cap will be collected at the DB Week 12 or Premature D/C visit (if applicable).
m. Subjects randomized to active study drugs will proceed to the PT Period (Table 5). Subjects randomized to Arm B will begin the OL Treatment Period (Table 4) after completing DB Week 12 with active study drugs dispensed to begin dosing the next day (OL Day 1).
Table 3. Study Activities – Double-Blind (DB) Treatment Period (Continued)

n. May also be done as part of toxicity management (Section 6.7.5).

* In the event that the treatment failure extension parameters are met (Section 5.4.1.1) subjects will attend visits as outlined in Table 3 and then upon unblinding will be extended to the 24-week active treatment duration as outlined in Appendix C.
Table 4. Study Activities – Open-Label (OL) Treatment Period

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8</th>
<th>OL Wk 10</th>
<th>OL Wk 12 (EOT)&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>Premature D/C from OL Treatment&lt;sup&gt;ab&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Subject takes first doses of active study drugs and site calls subject to confirm start date</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Physical Exam</td>
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<td>Vital Signs, Weight</td>
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<td>Hematology/Chemistry/Urinealysis/Coagulation Panel</td>
<td>X X X X X X</td>
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<tr>
<td>Pregnancy Test [urine (u)]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X (u) X (u) X (u) X (u)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Concomitant Medication Assessment</td>
<td>X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adverse Event Assessment</td>
<td>X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drugs Dispensed</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drugs Collected, MEMS Cap Downloaded and Compliance Reviewed</td>
<td>X X X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td>X X X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Resistance Sample</td>
<td>X X X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic Samples</td>
<td>X X X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X X X X X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
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</table>
Table 4. Study Activities – Open-Label (OL) Treatment Period (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8</th>
<th>OL Wk 10</th>
<th>OL Wk 12 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C from OL Treatment&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Total Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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

a. Take first doses of all study drugs the day after the last day of the DB Treatment Period. The site will call the subject and record the study drug start dates in the electronic data capture (EDC) system and source notes. The study drug end date of all drugs will be recorded in EDC and the source at OL Week 12 or Premature D/C.

b. Subjects will begin the PT Period after completing study drug treatment or prematurely discontinuing the OL Treatment Period.

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

d. MEMS cap will be collected at the OL Week 12 or Premature D/C visit.
**Table 5. Study Activities – Post-Treatment (PT) Period**

<table>
<thead>
<tr>
<th>Activity</th>
<th>PT Wk 2</th>
<th>PT Wk 4</th>
<th>PT Wk 8</th>
<th>PT Wk 12</th>
<th>PT Wk 24</th>
<th>PT Wk 36</th>
<th>PT Wk 48 or PT D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs and Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Monthly Pregnancy Test (females)(^a)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PRO Instruments(^b)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medication Assessment(^c)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Assessment(^d)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>HCV Resistance Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA Sample (Optional)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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

\(^a\) Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or who are confirmed post-menopausal. At PT Weeks 16, 20 and 28, subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

\(^b\) SF-36V2, EQ-5D-5L, and HCVPRO should be administered before any study procedures and in the order listed. Subjects who were randomized to placebo and completed the OL Treatment Period do not need to complete PRO instruments during the PT Period.

\(^c\) Only medications related to the treatment of HCV and medications prescribed in association with an SAE will be collected after 30 days post-dosing.

\(^d\) Only SAEs will be collected after 30 days post-dosing.

Note: Day 1 of the PT Period will be defined as the day after the last dose of active study drug treatment (in either the DB Treatment Period, for subjects randomized to active drug or the OL Treatment Period for subjects randomized to Arm B and treated with open-label active drug).
5.3.1.1 Study Procedures

The study procedures outlined in Table 3 through Table 5 are discussed in detail in this section, with the exception of the assessment of concomitant medications (Section 5.2.3.2), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), the monitoring of treatment compliance (Section 5.5.6) and the collection of adverse event information (Section 6.4).

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from the subject before any study procedures are performed. All subjects will be given the RBV Medication Guide (where applicable/locally available). Male subjects will be given an additional copy of the RBV Medication Guide (where applicable/locally available) and a RBV Partner Risk Fact Sheet to share with their female partner(s). 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, alcohol and injection drug use, will be taken from each subject during the Screening Visit. The subject's medical history will be updated at the DB Day 1 Visit. This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Table 3 and Table 4 (if applicable), or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on DB Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.
Vital Signs, Weight, Height

Body temperature (oral), blood pressure, pulse and body weight will be measured at the visits specified in Table 3 and Table 4 (if applicable) and Table 5. The vital signs performed on DB Day 1 will serve as the baseline for clinical assessment. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

12-lead Electrocardiogram

A 12-lead resting ECG will be obtained at the visits specified in Table 3 and Table 4 (if applicable), or upon subject discontinuation (or as clinically needed). The DB Day 1 reading will serve as the baseline assessment. When an ECG is scheduled on the same day as a blood collection, the ECG will be obtained prior to the blood collection.

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

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

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

The original ECG tracing will be retained in the subject's records at the study site.
Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 6 at the visits specified in Table 3 and Table 4 (if applicable) and Table 5.

Blood samples for serum chemistry tests should ideally be collected following a minimum 8-hour fast (with the exception of the Screening Visit, which may be 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. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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

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

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

For sites in Canada, Mexico, Puerto Rico, USA:

Covance
8211 SciCor Drive
Indianapolis, IN 46214 USA
For sites in Czech Republic, Denmark, France, Germany, Ireland, Italy, Netherlands, Portugal, Russia, Spain, Turkey, United Kingdom:

Covance
7 rue Marcinhes
1217 Geneva
Meyrin Switzerland

For sites in Australia:

Covance (Asia) Pte Ltd
1 International Business Park
#01-01 The Synergy
Singapore 609917
## Table 6. Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Creatinine</td>
<td>Ketones</td>
</tr>
<tr>
<td>Red Blood Cell (RBC) count</td>
<td>Total bilirubin (^a)</td>
<td>pH</td>
</tr>
<tr>
<td>White Blood Cell (WBC) count</td>
<td>Direct and indirect bilirubin</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Blood</td>
</tr>
<tr>
<td>Bands</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Alkaline phosphatase</td>
<td>Urobinogen</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Sodium</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Basophils</td>
<td>Potassium</td>
<td>Leukocyte esterase</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Calcium</td>
<td>Microscopic (reflex)</td>
</tr>
<tr>
<td>Platelet count (estimate not</td>
<td>Inorganic phosphorus</td>
<td>Albumin (^c)</td>
</tr>
<tr>
<td>acceptable)</td>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>Cholesterol</td>
<td>Urine Archive Specimen (^f)</td>
</tr>
<tr>
<td>Prothrombin Time/INR</td>
<td>Total protein</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>time (aPTT)</td>
<td>Triglycerides</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Albumin</td>
<td></td>
</tr>
</tbody>
</table>

### Additional Tests

| HBsAg \(^d\)                        | Anti-HCV Ab \(^d\)                                     | Urine and Serum Human                       |
| Anti-HIV Ab \(^d\)                  | FSH (females) \(^d\)                                   | Chorionic Gonadotropin (hCG) (females) \(^e\) |
| Opiates \(^a\)                      | Barbiturates \(^d\)                                    |                                              |
| Amphetamines \(^d\)                 | Cocaine \(^d\)                                         |                                              |
| Cocaine \(^d\)                      | Benzodiazepines \(^d\)                                 |                                              |
| Alcohol \(^d\)                      | Phencyclidine \(^d\)                                   |                                              |
| Propoxyphene \(^d\)                 | Methadone \(^d\)                                       |                                              |
| Urine and Serum Human               | Opiates \(^a\)                                         |                                              |
| HCV panel                           | Barbiturates \(^d\)                                    |                                              |
| Hepatitis A Antibody, Total \(^E\) | Amphetamines \(^d\)                                   |                                              |
| Hepatitis E Virus IgG \(^G\)        | Cocaine \(^d\)                                         |                                              |
| Hepatitis E Virus IgM \(^G\)        | Benzodiazepines \(^d\)                                 |                                              |
| Hemoglobin A1 \(^c\)                | Phencyclidine \(^d\)                                   |                                              |
| IP-10                               | Methadone \(^d\)                                       |                                              |
| IL28B \(^d\)                        | Opiates \(^a\)                                         |                                              |
| HCV genotype and subtype \(^d\)     | Methadone \(^d\)                                       |                                              |
| Pharmacogenetic sample (optional)   | Total insulin                                          |                                              |
| mRNA sample (optional)              | HCV RNA                                                |                                              |
|                                    | Hepatitis B Panel \(^g\)                               |                                              |
|                                    | Hepatitis A Antibody, Total \(^E\)                     |                                              |
|                                    | Hepatitis E Virus IgG \(^G\)                           |                                              |
|                                    | Hepatitis E Virus IgM \(^G\)                           |                                              |
|                                    | Hemoglobin A1 \(^c\)                                   |                                              |
|                                    | IP-10                                                  |                                              |
|                                    | IL28B \(^d\)                                           |                                              |
|                                    | HCV genotype and subtype \(^d\)                        |                                              |
|                                    | Pharmacogenetic sample (optional)                      |                                              |
|                                    | mRNA sample (optional)                                 |                                              |
Table 6. Clinical Laboratory Tests (Continued)

a. Component of FibroTest.
b. Performed only during Screening Period for FibroTest, if needed.
c. Collected at DB Day 1 and if Creatinine Clearance level < 50 mL/minute. See Section 6.7.5 Creatinine Clearance for details.
d. Performed only at Screening.
e. Urine pregnancy testing is not required after DB Day 1 for female subjects who are confirmed to be post-menopausal or who have a documented history of prior bilateral tubal ligation, bilateral oophorectomy or hysterectomy.
f. Performed if Creatinine Clearance level < 50 mL/minute. See Section 6.7.5 Creatinine Clearance for details.
g. Performed for management of transaminase elevations. See Section 6.7.4 for details.

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

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

The management of laboratory abnormalities that may occur during the study, including procedures for blinded laboratory measurements, are described in Section 6.7.

Pregnancy Test

A serum pregnancy test will be performed at Screening and DB Day 1 for all female subjects and analyzed by the central laboratory. In addition, a urine pregnancy test will be performed for female subjects at all the visits specified in Table 3 and Table 4 (if applicable) and Table 5. All urine pregnancy tests will be performed on-site during the study visit if there is a scheduled visit, as specified in Table 3, Table 4 (if applicable) and monthly for a minimum of 7 months after the discontinuation of RBV, or according to the local RBV label and/or consistent with local treatment guidelines for RBV. A urine
pregnancy test will be performed for all female subjects at DB Day 1, and thereafter, urine pregnancy tests are not required after DB Day 1 for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of postmenopausal status by history and as measured by FSH will be obtained at the Screening Visit only.

During the PT Period where there is not a scheduled study visit, female subjects of childbearing potential 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; site personnel should contact these female study subjects to capture the results of any study-related pregnancy tests performed at home. The pregnancy test results will only be recorded in the subject's source records.

If the subject elects to return to the study site for an unscheduled visit for pregnancy testing, the results of the urine pregnancy test will be recorded in the subject's source records. If a serum pregnancy test is collected, the sample will be analyzed by the central lab and reported in the database.

If urine pregnancy result is positive a confirmatory hCG serum test should be collected and sent to the central lab.

**Concomitant Medication Assessment**

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) from 2 weeks prior to study drug administration through 30 days after last dose of study drug will be recorded in the eCRF at each study visit indicated in Table 3, Table 4. Thereafter, only medications related to the treatment of HCV and medications prescribed in association with an SAE will be recorded in the eCRF at each study visit indicated in Table 5.
Hepatitis and HIV Screen

HBsAg, anti-HCVAb and anti-HIV Ab will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these results per local regulations, if necessary. The anti-HIV Ab results will not be reported by the central laboratory to the clinical database.

Urine Screens for Drugs of Abuse

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed in Table 6. A positive screen is exclusionary, with the exception of a positive screen associated with documented short-term use or chronic stable use of a prescribed medication in that class.

Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine drug screen repeated. If the repeat urine drug screen is negative (except for cases in which the screen is positive for a prescribed drug), the subject may be considered eligible (Section 5.1.1.1).

These analyses will be performed by the certified central laboratory chosen for the study.

HCV Genotype and Subtype

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

Liver Diagnostic Testing

Subjects who have not had a qualifying liver biopsy within the previous 24 months but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo liver biopsy or non-invasive testing (FibroTest/APRI or FibroScan) prior to enrollment. Selection of liver biopsy or non-invasive testing performed should be based on local standard practice. Subjects with a FibroScan result that is ≥ 9.6 kPa, a FibroTest
result that is $\geq 0.73$ or an APRI $> 2$ must have a liver biopsy showing no evidence of cirrhosis within 24 months of screening, or in the absence of an available biopsy result within 24 months of Screening, may undergo a liver biopsy to rule out cirrhosis. Subjects with an exclusionary non-invasive test may be enrolled only if the biopsy performed within the previous 24 months or during the Screening period shows no evidence of cirrhosis.

**Pharmacogenetic Blood Samples**

**IL28B sample**

One required whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected from each subject at Screening for Interleukin 28B (IL28B) analysis. This sample will not be used for any testing other than IL28B genotypes.

**Optional Pharmacogenetic Sample**

A separate optional whole blood sample will be collected on DB 1 from those subjects who choose to participate and consent to additional pharmacogenetic analysis. If this sample is not collected at DB Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent for this optional sample is discussed in Section 9.3.

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

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

Subjects who consent to participate in the mRNA substudy will have blood samples taken as indicated in Table 3, Table 4 (if applicable) and Table 5.

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

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

The optional blood samples for mRNA must be collected at the visits specified in Table 3, Table 4 (if applicable) and Table 5.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-450, ABT-267, ABT-333 or drugs of these classes continues but no longer than 20 years.

**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 3 and Table 5. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all visits and will ensure that a response is entered for all items.

In this study, PRO instruments should be consistently presented so that subjects complete the SF-36V2 instrument first, the EQ-5D-5L, and finally the HCVPRO. PRO instruments should be completed prior to drug administration on DB Day 1 and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

As previously noted, subjects who were randomized to placebo during the DB Treatment Period and completed the OL Treatment Period do not need to complete PRO instruments during the OL or PT Periods.
Short Form 36 – Version 2 Health Status Survey

The SF-36V2 is a general 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 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Scoring is totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36V2 scores indicate a better state of health. Completion of the SF-36V2 should require approximately 10 minutes.

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

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

HCV Patient Report Outcomes (HCVPRO) Instrument

The HCVPRO has been developed specifically to capture the function and wellbeing impact of HCV conditions and treatment. The HCVPRO contains 16 items important to HCV patients; items are totaled to a summary score. Higher HCVPRO score indicates a better state of health. Completion of the HCVPRO should require approximately 5 minutes.

Randomization and Assignment of Subject Numbers

All screening activities must be completed and reviewed prior to randomization. Screening numbers will be unique 6-digit numbers and will begin with 100301, with the
first three digits representing the investigative site and the last three digits representing the subjects at that site. Subjects who meet the eligibility criteria may proceed to randomization via the IRT system at the DB Day 1 Visit.

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

**MEMS Caps**

At the DB Day 1 Visit subjects will be assigned 1 MEMS cap for the RBV bottle. To ensure that a dosing event is recorded for the first dose of study drug at the site on DB Day 1, the site should place the MEMS cap on the RBV bottle before dispensing the first dose. Additionally, at each visit, site personnel should download the MEMS dosing history data from the MEMS cap, review, and counsel the patient as appropriate regarding compliance. Additional information regarding Treatment Compliance and MEMS can be found in Section 5.5.7.

**HCV RNA Samples**

Plasma samples for HCV RNA levels will be collected as indicated in Table 3, Table 4 (if applicable) and Table 5. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. The lower limit of detection (LLOD) is 15 IU/mL and results below LLOD are reported as "HCV RNA not detected"; the LLOQ for this assay is 25 IU/mL and results below LLOQ but detectable are reported as "< 25 IU/mL HCV RNA detected."

**HCV Resistance Testing Sample**

A plasma sample for HCV resistance testing will be collected at the study visits, indicated in Table 3, Table 4 (if applicable) and Table 5.
Archive Plasma and Serum Sample

Archive plasma and serum samples will be collected at the study visits, indicated in Table 3, Table 4 (if applicable) and Table 5. Archive plasma and serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

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

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 3, Table 4 (if applicable) and Table 5. The IP-10 testing is exploratory and may not be provided to the investigator.

5.3.1.2 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 should be taken together with food and the PM dose of ABT-333 and RBV should be taken together with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for assay of ABT-267, possible ABT-267, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, as well as ritonavir and RBV (if applicable) will be collected by venipuncture at each study visit specified in Section 5.3.1 (irrespective of study drug dosing time).

The time that each blood sample is collected will be recorded to the nearest minute.
5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and RBV will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and RBV will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory. An inventory of the samples included will accompany the package.

Covance CLS will then ship the ABT-267, ABT-333, ABT-450, ritonavir, and RBV samples to:

Sample Receiving
Dept. R43F, Bldg. AP13A, Room 2310
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085

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

Plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, and RBV will be determined using validated assay methods under the supervision of the Sponsor's Drug Analysis Department. Plasma concentrations of metabolites of ABT-450 and ABT-267, and other metabolites of ABT-333 may also be determined using non-validated methods.

5.3.3 Efficacy Variables

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

5.3.3.1 Primary Variable

The primary endpoint is the percentage of subjects with SVR$_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of active study drugs).

5.3.3.2 Secondary Variables

The secondary endpoints are:

- The percentage of subjects with ALT normalization (ALT ≤ ULN at Final Treatment Visit for subjects with ALT > ULN at Baseline);
- The percentage of HCV genotype 1a subjects with SVR$_{12}$;
- The percentage of HCV genotype 1b subjects with SVR$_{12}$;
- The percentage of subjects with virologic failure during treatment;
- The percentage of subjects with post-treatment relapse.
5.3.4 Resistance Variables

The following resistance analyses will be performed for subjects receiving active drug who do not achieve SVR: the variants at each amino acid position at baseline identified by population nucleotide sequencing will be compared to the appropriate prototypic reference sequence, and the variants identified by population and/or clonal nucleotide sequencing at available post-baseline time points will be compared to baseline and the appropriate prototypic reference sequences.

5.3.5 Safety Variables

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

5.3.6 Pharmacokinetic Variables

Individual plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, ribavirin and possible metabolites of ABT-450, ABT-267 and ABT-333 (other than ABT-333 M1) will be tabulated and summarized.

5.3.7 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN and RBV and to some pegIFN-free regimens. IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B genotype results may be analyzed as part of a multi-study assessment of IL28B and response to 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 results of additional pharmacogenetic analyses may not be reported with the clinical study report.

DNA samples from subjects who separately consent for additional pharmacogenetic analysis may be analyzed for genetic factors contributing to the subject's response to study
treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response (including IL28B). Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. Pharmacogenetic analyses will be limited to studying response to HCV therapy; no other analyses will be performed.

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

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

If, during the course of study drug administration, the subject prematurely discontinues during the DB or OL Treatment Periods, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 3 and Table 4. It is recommended that this Visit occur on the day of study drug discontinuation, however, this Visit should occur within 2 days following their final dose of study drugs and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator
feels are necessary to treat the subject's condition. Following discontinuation of study drugs, the subject will be treated in accordance with the investigator's best clinical judgment. The dosing end dates and reason for discontinuation will be recorded in the eCRF. If the subject received any active study drugs, the subject should then begin the PT Period where the subject will be monitored for 48 weeks for the development and persistence of resistance to the DAAs.

Subjects prematurely discontinuing from the DB period and who on unblinding are found to have been randomized to placebo may elect to remain in the study (at the investigator's discretion) and receive active treatment during the Open-Label Period. However, the subject is expected to continue to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through the DB Week 12 Visit, in order to be eligible to enter the OL Treatment Period and receive active treatment.

If a subject discontinues from the PT Period the subject should return for PT discontinuation procedures as defined in Table 5. The reason for discontinuation from the PT Period will also be recorded in the Study Discontinuation eCRF.

If a subject is discontinued with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved (Section 6.7).

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drugs (including RBV) to that subject must be discontinued immediately. Specific instructions regarding subject pregnancy can be found in Section 6.6. Subjects will continue to be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.
5.4.1.1 Virologic Failure Criteria

During the DB Treatment Period of the study, the virologic results will be reviewed and virologic failure criteria will be applied to those subjects randomized to active drugs by an unblinded independent reviewer who will provide information to the investigators to assist with managing these subjects according to the criteria below. No virologic failure criteria will be applied to subjects randomized to placebo during the DB Treatment Period. During the OL Treatment Period, investigators will be unblinded to virologic data and will manage subjects according to the criteria below.

The following criteria will be considered evidence of virologic failure leading to discontinuation of study drug while the subject is being treated with active drugs:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements > 1 log\textsubscript{10} IU/mL above nadir) at any time point during treatment;
- Failure to achieve HCV RNA < LLOQ by Week 6;
- Confirmed HCV RNA ≥ LLOQ (defined as two consecutive HCV RNA measurements ≥ LLOQ) at any point during treatment after HCV RNA < LLOQ.

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

If any of the above criteria are met, the subject will discontinue study treatment (Section 5.4.1).

Subjects with HCV RNA < LLOQ at the end of treatment and who have a confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point in the post-treatment period will be considered to have relapsed. Confirmation of an HCV RNA ≥ LLOQ in the post-treatment period should be completed as soon as possible.
During the DB Treatment Period, if greater than or equal to 50% of null or partial responder subjects completing 12 weeks of active study drug treatment experience virologic relapse post-treatment, then the treatment will extend to 24 weeks for all ongoing subjects randomized to active regimen in the DB Treatment Period and all subjects subsequently randomized to the active regimen (see Appendix C for 24-week Study Activities table).

In addition, subjects ongoing in the OL treatment period will have OL active treatment extended to 24 weeks. Subjects randomized to the placebo group will still be administered 12 weeks of placebo; however, subjects will then receive 24 weeks of the active regimen in the OL Treatment Period. This treatment extension assessment will be applied starting when the first 10 null or partial responder subjects who complete 12 weeks of treatment relapse or reach PT Week 12, and weekly thereafter until all subjects have enrolled.

The subjects who were relapsers to previous pegIFN/RBV treatment will not be included in these assessments as their response to anti-HCV treatment is presumed to be more like subjects who are naïve to treatment. Treatment may be extended for some strata (e.g., type of response to previous pegIFN/RBV treatment or HCV subgenotype) and not for others based on the strata of the subjects experiencing relapse at a high rate.

5.4.2 Discontinuation of Entire Study

The Sponsor 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 the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will notify the investigator and subsequently provide written instructions for study termination.
5.5 Treatments

5.5.1 Treatments Administered

Each dose of blinded and open-label DAA study drugs (ABT-450/r/ABT-267 and ABT-333) or placebo for DAAs and open-label RBV will be dispensed in the form of tablets. Each dose of double-blind RBV or matching placebo for RBV will be dispensed as capsules. Study drugs will be dispensed at the visits listed in Table 3 and Table 4 (if applicable).

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 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

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 capsules during the DB Treatment Period and will be provided as tablets during the OL Treatment Period. Ribavirin has weight-based dosing 1000 to 1200 mg divided twice daily per local label. (For example, for subjects weighing < 75 kg, RBV may be taken orally as 2 tablets [or capsules] in the morning and 3 tablets [or capsules] in the evening which corresponds to a 1000 mg total daily dose. For subjects weighing ≥ 75 kg RBV may be taken orally as 3 tablets [or capsules] in the morning and 3 tablets [or capsules] in the evening which corresponds to a 1200 mg total daily dose.)

Subjects will be instructed to take study medication at the same time(s) every day. All study drugs should be taken with food.

Following enrollment, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Table 3 and Table 4 (if applicable). Study drugs must not be dispensed without contacting the IRT system, and only for
subjects enrolled in the study through the IRT system. At the end of the DB and OL Treatment Period or at the Premature Discontinuation Visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit (Section 5.3.1.1).

At DB Day 1 subjects will be administered study drugs by the study site personnel and receive instructions for self administration of all study drugs from Study Day 2 through Study Week 12 of the DB Treatment Period. Subjects will be administered study drugs on DB Day 1 and the date and time of administration of each drug will be recorded. Subjects entering the OL Treatment Period will be given drugs at the DB Week 12 Visit, along with instructions to begin dosing the next day. The site will call the subject on OL Day 1 and record the first date of dose.

All subjects who receive at least one dose of active DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered another AbbVie-sponsored treatment study including ABT-450/r + ABT-267 + pegIFN/RBV. Subjects may also be offered another non-AbbVie treatment as determined appropriate by the investigator.

5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 7.
### Table 7. Identity of Investigational Products

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Manufacturer</th>
<th>Mode of Administration</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/r/ABT-267</td>
<td>Abbott/AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>75 mg/ 50 mg/12.5 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABT-450/r/ABT-267 placebo</td>
<td>Abbott/AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>0 mg</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott/AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>ABT-333 placebo</td>
<td>Abbott/AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>0 mg</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Roche or Generic Manufacturer</td>
<td>Oral</td>
<td>Tablet</td>
<td>200 mg</td>
</tr>
<tr>
<td>Ribavirin capsules</td>
<td>Table: Roche or Generic Manufacturer Capsule: Abbott/AbbVie or Fisher Clinical Services for Abbott/AbbVie</td>
<td>Oral</td>
<td>Hard Gelatin Capsule</td>
<td>200 mg</td>
</tr>
<tr>
<td>Placebo for Overencapsulated Ribavirin</td>
<td>Abbott/AbbVie</td>
<td>Oral</td>
<td>Hard Gelatin Capsule</td>
<td>0 mg</td>
</tr>
</tbody>
</table>

### 5.5.2.1 Packaging and Labeling

Blinded 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 (or matching placebo) and 16 ABT-450/r/ABT-267 75 mg/50 mg/12.5 mg tablets (or matching placebo) for a total of 32 tablets per blinded 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 1 ABT-333 tablet or placebo) with a picture of a sun, and which should be taken in the evening (1 ABT-333 tablet or placebo) with a picture of a moon. The additional day of study drug in each blister card is identified as row "X".
Blinded overencapsulated ribavirin (or matching placebo) will be supplied to the site in bottles containing 96 capsules each to be used during the DB Treatment Period.

Ribavirin (open-label) tablets will be supplied to the site in bottles containing 168 tablets each to be used during the OL Treatment Period.

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

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

### 5.5.2.2 Storage and Disposition of Study Drugs

**Table 8. Storage and Disposition of Study Drug**

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Storage Conditions</th>
</tr>
</thead>
</table>
| ABT-450/\(r\)/ABT-267 and ABT-333 or placebo blister cards | 15°C to 25°C (59°F to 77°F)  
Australia: Store below 25°C |
| Open label Ribavirin bottles | 15°C to 25°C (59°F to 77°F)  
Australia: Store below 25°C |
| Ribavirin or placebo bottles | 15°C to 25°C (59°F 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 system and identify the subject as a screen failure.
Subjects who are enrolled will retain their subject number, assigned at the Screening Visit, throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique study drug bottle/kit numbers and a unique randomization number. The randomization number will be used only by the Sponsor for loading the treatment assignments into the database. The study drug kit numbers and randomization 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 use will be provided to each site. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

5.5.4 Selection and Timing of Dose for Each Subject

Study drug dosing will be initiated at the DB Day 1 Visit. ABT-450/r/ABT-267 will be dosed QD; ABT-333 and RBV will be dosed BID. Thus with normal dosing, 2 ABT-450/r/ABT-267 tablets, 1 ABT-333 tablet, should be taken in the morning, and 1 ABT-333 tablet should be taken in the evening.

RBV should be dosed BID, e.g., 2 to 3 tablets (or capsules) taken in the morning, and 3 RBV tablets (or capsules) should be taken in the evening.

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 should be taken together with food and the PM dose of ABT-333 and RBV should be taken with food.

5.5.5 Blinding

Treatment assignment during the DB Treatment Period will remain blinded to the investigator, subject and Sponsor during the 12-week treatment period. ABT-450/r/ABT-267 and ABT-333 or matching placebos will be provided as tablets, and RBV or matching placebo will be provided as capsules.
During the DB Treatment Period, measures to prevent implicit unblinding by laboratory results will be used. Specifically, the results of HCV RNA, hemoglobin, hematocrit, ALT, AST, bilirubin (indirect and total), will be blinded to the investigator, subject and Sponsor until the DB Week 12 or Premature D/C Visit, unless criteria for virologic failure or relevant predefined toxicity are met, in which case the relevant laboratory data will be unblinded to the investigator, subject and Sponsor, see Section 5.5.5.3.

A subject's study drug assignment may be unblinded as part of toxicity management, at the investigator's discretion, if deemed necessary for subject safety or at premature discontinuation. If a subject's treatment assignment is formally unblinded during the DB treatment period then the previously blinded laboratory tests, i.e., HCV RNA levels, transaminases, bilirubin (indirect and total), hemoglobin and hematocrit, will be provided to the investigator and the Sponsor unblinded.

In the setting of premature discontinuation of double-blind study drug for toxicity management or virologic failure (for those subjects on active drug), the investigator, subject and Sponsor will be unblinded to study drug assignment via IRT. Subjects prematurely discontinuing and who on unblinding are found to have been randomized to placebo may elect to remain in the study (at the Investigator's discretion) and receive active treatment during the Open-Label Period. However, the subject is expected to attend all remaining DB Treatment Period study visits and perform all remaining study procedures through the DB Week 12 Visit, in order to be eligible to enter the OL Treatment Period and receive active treatment. During the OL Treatment Period, open-label ribavirin tablets and ABT-450/r/ABT-267 and ABT-333 blister cards will be supplied. Subjects prematurely discontinuing and who on unblinding are found to have been randomized to active study drugs will enter the PT Period. During the blinded period, an unblinded independent reviewer will review HCV RNA data and provide guidance related to virologic failure (Section 5.4.1.1).

The Sponsor or the unblinded independent reviewer must be notified before the blind is broken unless identification of the study drugs is required for medical emergency, i.e., a situation in which the knowledge of the specific blinded treatment will affect the
immediate management of the subject/patient's conditions (e.g., antidote is available). In which case, the Sponsor or the unblinded independent reviewer must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF.

5.5.5.1 Blinding of Investigational Product

ABT-450/r/ABT-267 and ABT-333 or matching placebos will be provided as tablets and blinded study medication will be identical in appearance. During the DB Treatment Period, RBV and matching placebos will be provided as capsules and will be identical in appearance. During the OL Treatment Period open-label RBV will be supplied as tablets with the ABT-450/r/ABT-267 and ABT-333 tablets.

The IRT system will dispense the appropriate treatment during the DB and OL Treatment Periods.

5.5.5.2 Data Monitoring Committee (DMC)

An independent DMC will review safety data from this study and provide recommendations to the Sponsor as per the DMC charter. The charter also describes DMC membership, which will include individuals with experience in the management of patients with chronic HCV infection, and member responsibilities. The DMC will receive interim summaries of safety data according to a schedule and format specified in the charter. After each review, the DMC will communicate its recommendations to the Sponsor. The Sponsor will retain sole responsibility for study management, communication with study sites and regulatory authorities.

5.5.5.3 Blinding of Other Study Data

DAA therapy exerts a normalizing effect on the levels of hepatic transaminases, ABT-450 may cause a transient asymptomatic elevation of indirect bilirubin and RBV exposure may reduce hemoglobin/hematocrit levels in a characteristic manner. Consequently, provision of transaminases, bilirubin and/or hemoglobin and hematocrit values during the
DB Treatment Period might implicitly unblind a subject's study assignment. In order to preserve the blinded nature of the DB Treatment Period, there will be blinding of the HCV RNA levels, transaminases, bilirubin (indirect and total), hemoglobin and hematocrit. Unblinding of any of these laboratory data may occur for the investigator, subject and Sponsor as required for toxicity management (Section 6.7) or in the setting of protocol defined virologic failure.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drugs only to subjects enrolled in the study in accordance with the protocol. The study drugs must not be used for reasons other than that 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 regards to virologic response and potential development of resistance. Subjects will be administered study drugs at the site at the DB Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

Subjects will be instructed to bring all blister cards of ABT-450/r/ABT-267 and ABT-333, and all bottles of RBV (full, partial, or empty) to the study site at each visit indicated in Table 3 and Table 4 (if applicable). At every DB or OL Treatment Period visits, study site personnel will inspect the contents of the blister cards and bottles and record the exact number of remaining tablets of ABT-450/r/ABT-267 and ABT-333 and tablets or capsules of RBV. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Reconciliation in IRT should occur only when the card or bottle is returned to the site at the dispensation visits during the DB Treatment Period in Table 3. During the OL Treatment Period, reconciliation in IRT should be performed when the blister cards are
returned at the dispensation visits in Table 4; open-label RBV for subjects in Arm B may be re-dispensed, therefore IRT reconciliation should occur when drugs are returned and not re-dispensed.

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

### 5.5.7 MEMS Caps

All subjects will utilize a MEMS monitor (cap), manufactured by AARDEX on the bottles for RBV. The MEMS cap will be used to obtain daily dosing histories for RBV for all subjects; this data will also be used to determine the dosing dates and times of all the DAAs. In addition, MEMS data will be provided to the investigator to guide treatment compliance discussions and will be the primary data used to assess PK time relative to dose.

The MEMS cap is a threaded cap containing an internal electronic clock, with an integrated electronically erasable programmable read-only memory, a special micro-switch and battery. Once fastened onto the medication bottle, the MEMS cap silently records the date and time of all dosing events (event = opening + closing). This electronic monitor provides a means of objectively measuring a subject's adherence with the study medication.

At the DB Day 1, subjects will be assigned one MEMS cap that will be placed on the RBV bottles in place of the original cap. The original cap should be saved so it can be placed back on the bottle upon return by the subject in order to store returned study drug.

The MEMS cap must only be used by the subject to whom it was assigned. Each MEMS cap has a unique serial number that must be recorded in the subject's source.
documentation. It is suggested that the subject’s subject number be written on his or her MEMS cap in permanent ink.

The subjects will be instructed to open the bottle when it is time to take the medicine, to remove the proper amount of medication and promptly close the bottle, then ingest the prescribed dose. The subject should be instructed to transfer the MEMS cap to the next full bottle of study drug at the same time that they take their last dose from the current in-use bottle.

The MEMS cap will be collected from the subject at the completion of study drugs as applicable. If MEMS caps cannot be imported into a participating study country or if other issues preclude the use of MEMS cap at a site(s), dosing histories will not be obtained using the MEMS caps for subjects enrolled at that site(s). Additional instructions for the subject on how to use the MEMS cap will be provided by the Sponsor.

5.5.8 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drugs will be kept by the investigator and will include lot number, POR number, number of tablets/capsules dispensed, subject number, initials of person who dispensed study drugs and date dispensed for each subject. An overall accountability of the study drugs will be performed and verified by the Sponsor monitor throughout the DB and OL Treatment Periods. Final accountability will be performed by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug blister card or bottle, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the blister cards/bottles are damaged, the subject will be requested to return the remaining study drugs to the site. Replacement study drugs may only be dispensed to the subject by contacting the IRT system. Study drug replacement and an explanation of
the reason for the misplaced or damaged study drug will be documented within the IRT system. Study drug start/end dates will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each blister card/bottle, number of tablets/capsules remaining in each one returned, and the date of reconciliation will be documented in the IRT system. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original blister cards and 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 or capsules of each type of study drug returned in each blister card and each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The 3 DAA regimen of ABT-450/r/ABT-267 + ABT-333 with RBV is being evaluated in the current study based on data from Phase 2 Study M12-746 and Study M11-652 in treatment-experienced subjects treated for 12 weeks. Available data from Study M11-652 indicate that the 3 DAA + RBV regimen using the higher ABT-450 dose (ABT-450/r 150/100 mg once daily [QD] + ABT-267 25 mg QD + ABT-333 400 mg twice daily [BID] with RBV) achieved high SVR_{12} rates in the null responders to previous pegIFN/RBV when administered for 12 weeks. Numerically higher SVR_{12} results (21/22 subjects, 95%) were observed as compared to the lower 100/100 mg dose of ABT-450/r in the 3 DAA regimen coadministered with RBV (21/23 subjects, 91%) or the 2 DAA regimen of ABT-450/r and ABT-267 coadministered with RBV (40/45 subjects, 89%). The 2 DAA arm of 150/100 mg QD ABT-450/r + 400 mg BID ABT-333 + RBV had a much lower SVR_{4} rate (8 of 17 subjects, 47%) in Study M12-746 as compared to the 3 DAA + RBV arm in Study M11-652. Thus, the 3 DAA + RBV regimen dosed for 12
weeks provides the highest possibility of achieving SVR in treatment-experienced genotype 1 subjects.

The 3 DAA combination of ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + ABT-267 25 mg QD + RBV BID is being evaluated at 2 different durations – 12- and 24-week in treatment-experienced subjects in the Phase 2b study. Available data indicate that the SVR4 rates for the 12-week arm are very high (21 of 22 subjects, 95%) and none of the 18 subjects who were suppressed at end-of-treatment relapsed by 12-weeks post-treatment suggesting that 12 weeks of treatment will be sufficient for the 3 DAA + RBV combination in treatment-experienced subjects. Additionally, modeling and simulations predict minimal effect in SVR rates for durations longer than 12 weeks with the 3 DAA + RBV regimen in treatment-experienced subjects. While shorter durations have not been studied in treatment-experienced subjects, data from treatment naïve subjects indicate that due to the high relapse rates following 8-week of dosing with 3 DAAs + RBV, durations lower than 12-week will not be adequate in treatment-experienced subjects. Thus, 12 weeks of dosing with the 3 DAA + RBV is considered to be the optimal duration of treatment in HCV treatment-experienced subjects.

A placebo-controlled study in treatment-experienced subjects is justified based on the following:

Infeasibility of enrolling a study with an active comparator arm: Despite the improvement in SVR rate with the addition of telaprevir and boceprevir to pegIFN/RBV over a regimen of pegIFN/RBV alone, many physicians recommend to delay treatment, and many patients are deferring treatment because of the toxicity associated with the currently approved protease inhibitor/pegIFN/RBV regimens. Experts have confirmed that studies which include a pegIFN containing comparator would be difficult to enroll or to retain adequate numbers of subjects in the IFN-containing arm.

Active comparator which contains pegIFN cannot be effectively blinded. Because of the high rate of adverse events associated with administration of the protease inhibitors (rash,
anorectal symptoms, and anemia with telaprevir and anemia and neutropenia with boceprevir), and pegIFN (influenza like illness, injection site reactions, myalgias and pancytopenia), the ability to effectively blind a protease inhibitor/pegIFN/RBV comparator arm is limited. Even within a double dummy design where subjects randomized to receive the pegIFN-free DAA combination with RBV are given sham injections and placebo protease inhibitor and subjects randomized to receive protease inhibitor/pegIFN/RBV are given placebo DAA combination, the characteristic side effect profile of the protease inhibitor/pegIFN/RBV regimen will make the treatment randomization obvious to both subjects and investigators. As patients will likely be attracted to the trial because of the possibility that they will receive a pegIFN-free regimen, effective unblinding may disincentivize patients randomized to the active comparator arm from continuing to participate in the study. In addition, poor adherence to a protease inhibitor/pegIFN/RBV regimen because of its perceived inferiority may result in development of protease inhibitor resistance mutations that could limit future treatment options. Premature discontinuations in the protease inhibitor/pegIFN/RBV arm of the study due to dissatisfaction with the assigned regimen would necessarily be counted as failures, thus the SVR rate for the active comparator will likely be inaccurately low. Early discontinuation of a large portion of the comparator arm may also give an inaccurate safety profile with which to compare the pegIFN-free DAA regimen. Thus, high rates of discontinuation of the active comparator arm may affect the quality and validity of comparison of safety and efficacy, and bias the study in favor of the investigational combination DAA regimen.

Antiviral activity in the placebo group is expected to be negligible. Because of the bias likely to arise with an pegIFN-based active comparator, as described above, and because the primary efficacy endpoint (SVR12) is objective, comparison of the pegIFN-free DAA regimen results to efficacy and safety results in the package inserts of approved regimens is more likely to provide a meaningful assessment of the Phase 3 study results compared to the current standard of care.
Comparison of active drug to placebo in a blinded fashion provides a highly effective method to assess safety and tolerability of the DAA + RBV regimen in the population for whom the treatment will ultimately be utilized. Given the potential for patients chronically infected with HCV to report symptoms or adverse events unrelated to DAA therapy, the placebo control group allows characterization of adverse events in an untreated, chronically HCV-infected population. The open-label period allows the subjects initially randomized to placebo access to active DAA therapy.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. Clonal sequencing and population sequencing methods are experimental. SF-36V2 and EQ-5D-5L PRO instruments are standards in the literature and thoroughly validated; the HCVPRO is preliminarily validated.

5.6.3 Justification of Primary and Secondary Endpoint Success Criteria

Historical SVR rates, as reported in the telaprevir US Prescribing Information (USPI),\textsuperscript{16} for telaprevir plus pegIFN and RBV treatment in treatment-experienced subjects without cirrhosis from the REALIZE trial are presented in Table 9. The rates are based on a weighted average of relapsers, partial responders, and null responders, with the weighting reflecting the distribution of subjects expected to enroll in Study M13-098.

SVR rates for treatment-experienced subjects by subgenotype are provided in Table 10. Because data are not available in the package inserts on treatment-experienced subjects without cirrhosis by subgenotype, data from the REALIZE study were used, with an adjustment factor to account for the exclusion of cirrhotic subjects in Study M13-098. Thus, to establish historical control rates relevant to Study M13-098, SVR rates in Table 10 were increased by 0.5%, 12.0%, and 9.2% for relapsers, partial responders, and
null responders, respectively. A weighted average of the corresponding SVR rates was calculated to reflect the population expected to enroll in Study M13-098.

**Table 9. Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced, Without Cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>REALIZE&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All T12/P48&lt;sup&gt;b&lt;/sup&gt; n/N (%)</td>
<td>Projected Enrollment in Study M13-098 (%)</td>
<td>Population-Based Weighted Average % [95% CI]</td>
</tr>
<tr>
<td>Prior relapsers</td>
<td>198/229 (86)</td>
<td>30</td>
<td>65 [60, 70]</td>
</tr>
<tr>
<td>Prior partial responders</td>
<td>46/65 (71)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Prior null responders</td>
<td>40/97 (41)</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.

<sup>b</sup> All GT1 treatment-experienced subjects without cirrhosis in the REALIZE study.
Table 10. Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced Subjects by Subgenotype

<table>
<thead>
<tr>
<th></th>
<th>REALIZE†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT1a (Pooled T12/PR48) n/N (%)</td>
</tr>
<tr>
<td>Relapsers</td>
<td>119/142 (83.8)</td>
</tr>
<tr>
<td>Partial responders</td>
<td>26/55 (47.3)</td>
</tr>
<tr>
<td>Null responders</td>
<td>24/88 (27.3)</td>
</tr>
</tbody>
</table>

GT1a = genotype 1a; GT1b = genotype 1b
† US Prescribing Information for INCIVEK™ (telaprevir). Vertex Pharmaceuticals Incorporated; Cambridge, MA.
For a regimen to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV therapy in genotype 1-infected subjects without cirrhosis, the lower confidence bound for the SVR rate for that regimen must exceed the upper bound of the 95% confidence interval for telaprevir plus pegIFN and RBV therapy (i.e., 70%). To be considered non-inferior to the historical SVR rate for telaprevir plus pegIFN and RBV, a margin of 10.5% is used. Thus, non-inferiority to the historical SVR rate for telaprevir based therapy is obtained by showing that the lower confidence bound is greater than 60%. The superiority thresholds in genotype 1a and genotype 1b subjects are 65% and 77%, respectively, as described in Table 2.

5.6.4 Suitability of Subject Population

The selection of subjects infected with HCV genotype 1 virus will allow for the assessment of safety, pharmacokinetics and antiviral activity of ABT-450/r, ABT-267, ABT-333 and RBV dosed in combination. HCV-infected subjects with transaminase levels up to 5 times the ULN will be allowed to enroll, as many with chronic HCV infection who are otherwise healthy have stable elevations of AST and ALT levels (≤ 5 × ULN) and are considered representative of the population who will receive ABT-450/r, ABT-267, and ABT-333. The age range selected for this study, 18 through 70 years, is also intended to be representative of the target population. Similarly, a substantial portion of the HCV-infected population has a relatively high BMI. Because of the acceptable safety and pharmacokinetic profiles of ABT-450/r, ABT-267 and ABT-333 demonstrated across Phase 1 and Phase 2 studies which enrolled subjects with a similar BMI range, this protocol will enroll subjects with a BMI less than 38 kg/m². Patients chronically (rather than acutely) infected with HCV comprise the target population for DAA-based regimens. This study will enroll subjects who are prior non-responders to treatment with pegIFN/RBV, but are considered eligible for treatment currently. Subjects who are naïve to treatment, those with more advance liver disease, such as cirrhosis, and those co-infected with HIV-1 are also in the target population. These groups may respond differently to pegIFN-free DAA regimens and are being evaluated in separate studies.
5.6.5 Selection of Doses in the Study

Doses of the three DAAs to be used in this study have shown significant antiviral activity and have been shown to be generally safe and well tolerated both as monotherapy, in combination with pegIFN + RBV, and in combination with each other and RBV. Of note, coadministration of ABT-450/r, ABT-267 and ABT-333 at the doses planned for use in this study do not clinically significantly impact plasma exposures compared to administration as single agents thus dose adjustments based on drug interactions are not required.

**ABT-450**

The ABT-450/r doses of 100/100 and 150/100 mg evaluated in the Phase 2 studies using the ABT-450 SDD tablet provided high ITT SVR_{12} rates in treatment-naïve (100% and 95%, respectively) and treatment-experienced (91% and 95.5%, respectively) subjects when dosed with ABT-333 and ABT-267 + RBV. The higher ABT-450 dose of 150 mg, administered with 100 mg ritonavir has been selected to advance into Phase 3 studies as it provides an optimal balance between safety and suppression of resistant variants.

In combination with other DAAs ± RBV, the highly fit, moderately resistant R155K viral variant was observed in a lower fraction of patients who had virologic failure at the 150/100 and 200/100 mg ABT-450/r dose (SDD tablet of ABT-450) as compared to the 100/100 mg ABT-450/r dose. This finding is consistent with monotherapy data for ABT-450/r where the higher 200/100 mg dose of ABT-450/r selected fewer resistant variants including R155K as compared to the lower 50/100 and 100/100 mg doses of ABT-450/r. Higher ABT-450 doses were also associated with higher SVR_{24} rates when combined with pegIFN and RBV. Thus based on resistance profile and SVR_{24} data with pegIFN + RBV, higher doses provide better efficacy. However, ABT-450 doses of 200/100 and 250/100 mg (SDD tablet) were associated with a greater incidence of asymptomatic grade 3+ ALT elevations (~4% at doses ≥ 200/100 versus < 0.5% at lower doses) suggesting that doses < 200/100 mg SDD tablet might have a more favorable safety profile.
The ABT-450 150 mg dose from the ABT-450/r/ABT-267 co-formulation planned for this study has a ~60% higher exposure as compared to the 150/100 mg SDD formulation but the exposure is ~50% lower than that from the 200/100 mg SDD formulation. The 150 mg ABT-450 dose from the coformulation will hence minimize the incidence of asymptomatic, transient Grade 3 ALT elevations while maximizing virologic suppression and minimizing the appearance of resistant variants.

**ABT-333**

An ABT-333 dose of 250 mg BID using the optimized tablet formulation that is expected to provide exposures comparable to the 400 mg BID dose used in Phase 2 studies and has been selected to advance into Phase 3 studies. This is based on comparable efficacy and better safety profile compared to exposures at higher ABT-333 doses.

Comparable viral load decline following monotherapy (approximately 1 log10 IU/mL) was observed at exposures greater than that achieved with the 400 mg BID dose evaluated in Phase 2 studies. Additionally, the 400 and 800 mg BID doses resulted in identical SVR rates (63%) when combined with pegIFN and RBV for 12 weeks followed by 36 weeks of pegIFN + RBV, indicating that increasing ABT-333 dose > 400 mg BID did not improve efficacy. Additionally, available data from the Phase 2b study indicates that when ABT-333 400 mg BID dose is combined with ABT-450, ABT-267 and RBV for 12 weeks, very high SVR12 rates were observed in treatment-naïve and treatment-experienced subjects (> 90%).

While both the 400 mg BID and 800 mg BID doses of ABT-333 in combination with pegIFN and RBV were well tolerated by HCV-infected subjects for 12 weeks, the 800 mg BID dose was associated with a greater mean hemoglobin reduction compared to the 400 mg BID dose and compared to placebo plus pegIFN and RBV.

The optimized formulation used in the current study has a higher bioavailability and is expected to provide comparable exposures to the 400 mg tablet formulation used in Phase 2 studies. Hence, the ABT-333 dose in the current study is the 250 mg optimized
formulation dosed BID as it provides exposures that maximizes efficacy and a superior safety profile compared to higher ABT-333 doses.

**ABT-267**

An ABT-267 dose of 25 mg has been selected to advance into Phase 3 studies. Compared to higher doses, the 25 mg QD dose provided comparable viral load decline following monotherapy and lower potential to decrease ABT-450 exposures.

Following 2 to 3 days of ABT-267 monotherapy at doses of 1.5 mg to 200 mg QD, the 25 mg dose of ABT-267 showed viral load decline comparable to higher doses with none of the rebound between doses seen at lower doses. Preliminary resistance analysis following monotherapy suggests that doses significantly greater than 25 mg would be needed to improve the resistance profile as a variety of NS5A resistant mutants were observed following monotherapy with doses of 5 to 200 mg. In addition, higher ABT-267 doses have been associated with decreases in ABT-450 exposures; the ABT-267 200 mg dose resulted in ~80% lower ABT-450 exposures when ABT-450 250 mg was dosed with 100 mg ritonavir. Hence doses > 25 mg could decrease the exposures of the "anchor" molecule ABT-450, without providing significant benefit in terms of improved efficacy. Additionally, available data from the Phase 2b study indicates that when ABT-267 25 mg QD dose is combined with ABT-450, ABT-333 and RBV for 12 weeks, very high SVR12 rates were observed in treatment-naïve and treatment-experienced subjects (> 90%).

The co-formulated ABT-450/r/ABT-267 formulation used in the current study has ABT-267 bioavailability comparable to the ABT-267 25 mg tablet used in Phase 2 studies. Hence, the ABT-267 dose in the current study is the 25 mg dose, as it provides exposures that maximizes efficacy without compromising ABT-450 exposures.

**RBV**

The daily dose of RBV in this study is 1000 to 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 is selected for this
study because its safety profile has been well characterized when administered with pegIFN, including the incidence of hemolytic anemia, and there are well-defined dose reduction criteria in the event of RBV-induced anemia. In addition, this dose was studied in the absence of pegIFN in Studies M12-267, M12-746, M12-998 and M11-652 and was found to be generally safe and well tolerated and resulted in high SVR rates.

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. 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 associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.
6.1 Definitions

6.1.1 Adverse Event

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

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

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

6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the Sponsor as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of Subject</td>
<td>An event that results in the death of a subject.</td>
</tr>
<tr>
<td>Life-Threatening</td>
<td>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.</td>
</tr>
<tr>
<td>Hospitalization or Prolongation of Hospitalization</td>
<td>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.</td>
</tr>
<tr>
<td>Congenital Anomaly</td>
<td>An anomaly detected at or after birth, or any anomaly that results in fetal loss.</td>
</tr>
<tr>
<td>Persistent or Significant Disability/Incapacity</td>
<td>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).</td>
</tr>
<tr>
<td>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome</td>
<td>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.</td>
</tr>
</tbody>
</table>
For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.2 Adverse Event Severity

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

**Mild**
The adverse event is transient and easily tolerated by the subject.

**Moderate**
The adverse event causes the subject discomfort and interrupts the subject's usual activities.

**Severe**
The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug. Assessment of relatedness will be made with respect to the DAAs (ABT-450/r/ABT-267 and ABT-333) and with respect to RBV:

**Reasonable Possibility**
An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, the Sponsor will consider the event associated.
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for a serious adverse event.

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

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

Figure 2. Adverse Event Collection

<table>
<thead>
<tr>
<th>SAEs</th>
<th>SAEs and Non-Serious AEs</th>
<th>SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Signed</td>
<td>Study Drug Start</td>
<td>Study Drug Stopped</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elicited and/or Spontaneously Reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of Study</td>
</tr>
</tbody>
</table>

6.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify the Antiviral Safety Management Team within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the EDC system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be faxed to the Antiviral Safety Management Team within 24 hours of being made aware of the serious adverse event.

FAX to: [redacted]
For serious adverse event concerns, contact the Antiviral Safety Team at:

Antiviral Safety Team  
AbbVie  
Dept. R477, Bldg. AP30-3  
1 North Waukegan Road  
North Chicago, IL  60064

Office: 

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

Primary Study Designated Physician:

Tolga Baykal, MD  
Medical Director

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 documents used for SUSAR reporting in the EU countries will be the most current versions of the Investigator's Brochures or Labels.
6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with the DB Day 1 Visit and 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 Sponsor within 1 working day of the site becoming aware of the pregnancy. Subjects who report a positive pregnancy test during the DB or OL Treatment Period must be notified to stop all study medication (Section 5.4.1). Subjects will continue to be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected by the sponsor. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to 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 D. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 and Section 6.7.2.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or the Sponsor as having a "reasonable possibility" of being related to the study drugs (Section 6.3). 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.

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

During the study, timeliness of EDC data entry to reflect blinded or unblinded study drug interruptions and/or blinded or unblinded RBV dose modifications and consequent required adverse events ensures that the AbbVie Safety Team (medical monitor, safety monitor) and the DMC have the data necessary for signal detection at safety data review and DMC meetings. The investigator should ensure that any study drug interruptions or RBV dose modifications and consequent required adverse events are entered into the appropriate eCRFs.

Safety surveillance, via regular review of safety labs will be performed by the Sponsor personnel who are blinded to study assignment and/or its designee. If during these reviews, an issue is identified which warrants discontinuation of study drug by a subject, the investigator will be notified.

The toxicity management guidelines below should be followed. In the DB Period, unblinding of study drug assignment may occur as directed by the toxicity management guidelines. In addition, a subject's study drug assignment may be unblinded at the investigator's discretion, if deemed necessary for subject safety. Subjects who are unblinded may remain on study drug except as described below.

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

Subjects who develop a study drug-related (reasonable possibility) mild or moderate adverse event or Grade 1 or 2 laboratory abnormality (other than those discussed separately in Toxicity Management Sections for hemoglobin parameters [Section 6.7.3],

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total bilirubin and hepatic transaminase parameters [Section 6.7.4] and creatinine clearance parameters [Section 6.7.5]) may continue study drugs with follow-up per study protocol. In the DB Period unblinding of study drug assignment does not need to occur. If the adverse event or laboratory parameter does not improve or normalize within 2 scheduled study visits and an etiology other than study drug has not been determined, then the AbbVie Study Designated Physician can be contacted to further discuss subject management. Subjects may continue study drugs; study drug interruption is not required.

6.7.2 Grades 3 or 4 Laboratory Abnormalities and Severe or Serious Adverse Events

Grade 3 – 4 Laboratory Abnormalities

With the exception of Grade 3 or higher elevations in uric acid, total cholesterol or triglycerides, if a subject experiences a Grade 3 or greater laboratory parameter during the study (other than those discussed in the toxicity management Sections 6.7.3 through 6.7.5 below), the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the study drugs should be interrupted and the laboratory parameter followed until it reaches Grade 1. In the DB Period for a confirmed Grade 3 – 4 laboratory abnormality as above, unblinding of study drug assignment is not required by protocol. The study drugs can be restarted if the laboratory parameter reaches Grade 1 within 7 days of study drug interruption. If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued. If the abnormality does not improve to Grade 1 or less within 7 days of interruption, the study drugs should be permanently discontinued.

If the investigator believes that the confirmed Grade 3 – 4 laboratory abnormality can be managed medically without interruption of study drug, then the AbbVie Study Designated Physician should be contacted to discuss continued study drug administration and medical management. If the laboratory abnormality does not improve with medical management within 2 scheduled study visits, then study drugs should be interrupted and the laboratory abnormality followed. The study drugs can be restarted if the laboratory parameter
reaches Grade 1 within 7 days of study drug interruption. If the laboratory abnormality recurs upon restart, then study drugs should be permanently discontinued. If the laboratory abnormality does not improve within 7 days, then study drugs should be permanently discontinued.

**Severe Adverse Event**

If a subject experiences a severe drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed in Sections 6.7.3 through 6.7.5 below) during the study, the study drugs should be interrupted. In the DB Treatment Period for a drug-related severe adverse event, unblinding of study drug assignment is not required by protocol. Study drugs may be restarted if the adverse event improves or resolves within 7 days of the interruption. If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued. If the adverse event does not improve or resolve within 7 days of the interruption the study drugs should be permanently discontinued.

If the investigator believes that the severe drug-related (reasonable possibility) adverse event can be managed medically without interruption, then the AbbVie Study Designated Physician should be contacted to discuss continued study drug administration with medical management. If the severe adverse event does not improve with medical management within 2 scheduled study visits, then study drugs should be interrupted. If the severe adverse event improves within 7 days of the interruption, then study drugs may be restarted. If the severe adverse event recurs upon restart, then study drugs should be permanently discontinued. If the severe adverse event does not improve within 7 days of the interruption, then study drugs should be permanently discontinued.

For a drug-related (reasonable possibility) severe adverse event, unblinding is not required by protocol.

If a subject experiences a non drug-related (no reasonable possibility) severe adverse event study drugs may be continued; unblinding is not needed.
A severe adverse event and any associated dose interruptions (or discontinuations) should be entered into the appropriate eCRFs.

**Serious Adverse Event**

If a subject experiences a serious drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed in Sections 6.7.3 through 6.7.5 below) during the study, study drugs should be permanently discontinued, and in the DB Period unblinding should occur. If the investigator believes that the serious drug-related (reasonable possibility) adverse event can be managed medically without permanent discontinuation of study drug, then the AbbVie Study Designated Physician should be contacted to discuss continued study drug administration and medical management. If study drug requires interruption longer than 7 days, the subject should have study drug permanently discontinued.

If a subject experiences a serious adverse event considered unrelated (no reasonable possibility) to study drugs, study drugs may be continued. If the study drugs are interrupted because it is deemed necessary for clinical management the interruption should not exceed 7 days.

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

**6.7.3 Management of Decreases in Hemoglobin**

Reductions in hemoglobin are a well characterized side effect of ribavirin exposure. Therefore in order to avoid implicit unblinding during the DB Treatment Period of the study the results of hemoglobin testing will be blinded unless confirmed hemoglobin values meet or exceed predefined toxicity thresholds (Table 12), in which case current and
preceding hemoglobin and hematocrit values will be unblinded to the investigator and Sponsor as will all subsequent values.

If a subject experiences a hemoglobin decrease (as outlined in Table 11 and Table 12), an alert will be provided to the investigator which will require the test to be repeated. If the hemoglobin decrease is confirmed, the investigator and Sponsor will receive a confirmatory alert, as well as the abnormal hemoglobin and hematocrit values and all preceding hemoglobin and hematocrit values. If a RBV dose reduction is required (as outlined in Table 12) the dose should be reduced in a manner consistent with the local RBV label. Alternative management of the RBV dose in the setting of reduced renal function will require approval of the AbbVie Study Designated Physician.

Hemoglobin abnormalities (and relevant unblinding in the DB Treatment Period) should be managed according to Table 12. Management will be different for subjects with or without a history of known cardiac disease.

Use of hematologic growth factors such as erythropoietin or filgrastim or blood transfusions is not recommended; and is permitted only with approval of the AbbVie Study Designated Physician. If these agents are to be used in the DB Treatment period, study drug treatment should be unblinded for appropriate management. Management of hematologic growth factor therapy is the responsibility of the investigator, and growth factors will not be provided or reimbursed by the Sponsor.

Alternative management of hemoglobin decreases including unblinding of study drugs or of hemoglobin data in the DB Period outside of these criteria requires approval of the AbbVie Study Designated Physician.
### Table 11. Indications for Unblinding of Hemoglobin (Hb) and Hematocrit Levels During the DB Period and the Nature of Hb Data Unblinded

<table>
<thead>
<tr>
<th>Hemoglobin (Hb) Level (Confirmed)</th>
<th>Hb Unblinding Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level &lt; 10g/dL, no cardiac disease</td>
<td>• Unblind subject’s current and prior Hb and hematocrit data to Investigator and Sponsor.</td>
</tr>
<tr>
<td>Hb level &lt; 12g/dL, stable cardiac disease</td>
<td>• All subsequent Hb and hematocrit data will also be unblinded.</td>
</tr>
<tr>
<td>A Hb decline ≥ 2 gm/dL over a 4-week period with Hb levels ≥ 12 g/dL for a subject with cardiac disease</td>
<td></td>
</tr>
<tr>
<td>A Hb decline ≥ 4 gm/dL between study visits with a Hb that is either:</td>
<td></td>
</tr>
<tr>
<td>• ≥ 12 g/dL (with stable cardiac disease); or</td>
<td></td>
</tr>
<tr>
<td>• ≥ 10 g/dL (no cardiac disease history)</td>
<td></td>
</tr>
</tbody>
</table>

When Hb/hematocrit results are blinded it can be assumed that Hb levels are ≥ 10 g/dL (no history of cardiac disease) or ≥ 12 g/dL with stable cardiac disease) and without either of markers of decline described above.

### Table 12. Management of Hemoglobin Decreases

<table>
<thead>
<tr>
<th>Hemoglobin in Patients with No Cardiac Disease History</th>
<th>Study drugs may be continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt; 10.0 g/dL, but ≥ 8.5g/dL</td>
<td>Reduce RBV dose and continue to monitor hemoglobin per protocol</td>
</tr>
<tr>
<td></td>
<td>If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose</td>
</tr>
<tr>
<td></td>
<td>If Hb decreases to &lt; 8.5 g/dL see appropriate row below</td>
</tr>
<tr>
<td></td>
<td>In the DB Treatment Period, unblinding of study drugs will occur</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>Permanently discontinue all study drugs and in the DB Treatment Period unblinding of the study drugs will occur</td>
</tr>
<tr>
<td></td>
<td>Manage the subject as medically appropriate</td>
</tr>
<tr>
<td></td>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event</td>
</tr>
<tr>
<td>Hemoglobin decrease of ≥ 4g/dL between two scheduled study visits but hemoglobin ≥ 10 g/dL</td>
<td>Manage the subject as medically appropriate</td>
</tr>
<tr>
<td></td>
<td>Study drugs may be continued</td>
</tr>
<tr>
<td></td>
<td>In the DB Treatment Period unblinding of study drug will occur</td>
</tr>
</tbody>
</table>
### Table 12. Management of Hemoglobin Decreases (Continued)

<table>
<thead>
<tr>
<th>Hemoglobin Decrease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hb ≥ 12 g/dL) without symptoms and/or signs of cardiac disease</td>
<td>Study drug may be continued and in the DB Treatment Period unblinding of study drugs will occur. Reduce RBV dose. Continue to monitor hemoglobin levels per protocol. If a subsequent hemoglobin result is greater than the level that triggered the dose reduction, the investigator may elect to increase RBV; with gradual dose increases in 200 mg increments towards original dose. If hemoglobin does not increase; investigator may manage the subject as medically appropriate. If hemoglobin decreases to &lt; 12 g/dL see appropriate row below.</td>
</tr>
<tr>
<td>Hemoglobin decrease ≥ 4g/dL between study visits but hemoglobin ≥ 12 g/dL</td>
<td>Investigator should manage subject as medically appropriate, but study drugs may be continued. In the DB Treatment Period unblinding of study drugs will occur.</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12.0 g/dL, but ≥ 8.5 g/dL</td>
<td>Study drugs may be continued but in the DB period unblinding of study drugs will occur. Reduce RBV dose and continue to monitor hemoglobin per protocol. If hemoglobin increases to ≥ 12 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose. If hemoglobin &lt; 12 g/dL despite 4 weeks at the reduced RBV dose, permanently discontinue all study drugs (if alternative management of study drugs is considered then the SDP should be contacted); otherwise manage as medically appropriate. Enter the discontinuation into appropriate eCRFs and create corresponding adverse event*.</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>Permanently discontinue all study drugs; manage subject as medically appropriate*. Enter discontinuation into appropriate eCRFs and create corresponding adverse event. In the DB Treatment Period unblinding of study drugs will occur.</td>
</tr>
</tbody>
</table>

* For subjects unblinded who are found to be on placebo, see Section 5.4.1 Discontinuation of Individual Subjects.
6.7.4 Management of Transaminase Elevations

As discussed in Section 3.0, ABT-450/r is associated with transient asymptomatic increases in total and indirect bilirubin. Furthermore, treatment with direct acting anti-HCV agents may have a normalizing effect on ALT levels. Therefore in order to avoid implicit unblinding during the DB Treatment Period the results of hepatic transaminases, ALT and AST, and total and indirect bilirubin will be blinded unless confirmed ALT values meet or exceed predefined toxicity thresholds (Table 14) in which case current and preceding ALT, AST, and bilirubin values will be unblinded to the investigator and Sponsor as will all subsequent values (Table 13).

If a subject experiences an ALT level \( \geq 5 \times \text{ULN} \) and \( \geq 2 \times \text{baseline} \), an alert will be provided to the investigator which will require the test to be repeated. If the ALT is confirmed \( \geq 5 \times \text{ULN} \) and \( \geq 2 \times \text{baseline} \), the investigator and Sponsor will receive a confirmatory alert, as well as the abnormal ALT, AST and indirect and total bilirubin values at that visit and the ALT, AST and indirect and total bilirubin values from all proceeding visits.

Management guidelines for elevations in ALT are provided in Table 14.

For subjects presenting with clinical jaundice the investigator may contact the Study designated physician to initiate unblinding of ALT, AST, bilirubin (total and indirect) and hemoglobin. Alternative management of transaminase elevations or other liver chemistry abnormality outside of these criteria including unblinding of study drugs or unblinding of liver chemistries requires approval of the AbbVie Study Designated Physician.
Table 13. Indications for Unblinding of ALT levels during the DB Period and the Nature of Hepatic Chemistry Data Unblinded

<table>
<thead>
<tr>
<th>ALT Level (Confirmed)</th>
<th>ALT, (ALT Bilirubin) Unblinding Activities</th>
</tr>
</thead>
</table>
| ALT ≥ 5 × ULN and ≥ 2 × Baseline | • Unblind subject's current and prior ALT, AST and bilirubin*(total and indirect) data to investigator and Sponsor.  
| | • All subsequent ALT, AST and bilirubin data will also be unblinded |

When ALT results are blinded it can be assumed that ALT levels are < 5 × ULN or ≥ 5 × ULN and ≤ 2 × Baseline.

* Direct bilirubin data is provided unblinded throughout the study.

Table 14. Management of Confirmed ALT Levels Greater than or Equal to 5 × ULN and Greater than or Equal to 2 × Baseline

| ALT ≥ 10 × ULN or ALT ≥ 5 × ULN but < 10 × ULN with symptoms and signs of hepatitis present | • Permanently discontinue study drugs and if during the DB period, unblind treatment assignment.*  
| | • Complete hepatic questionnaire, update concomitant medications eCRF (if applicable) and obtain appropriate additional testing (e.g., serology for hepatitis A, B, and E, urine for drug screen).  
| | • Evaluate and manage the subject as medically appropriate. |

| ALT ≥ 5 × ULN but < 10 × ULN without symptoms or signs of hepatitis | • Complete hepatic questionnaire, update concomitant medications eCRF (if applicable), and obtain appropriate additional testing (e.g., serology for hepatitis A, B, and E, urine for drug screen).  
| | • Continue study drugs and repeat LFTs and INR within 3 days and as clinically indicated until resolution.  
| | • In the DB Treatment Period unblinding of study drugs will occur.  
| | • If ALT values during follow-up are increased from the prior values, or increasing direct bilirubin, or increasing INR, or symptoms/signs of hepatitis then permanently discontinue study drugs. |

* Subjects unblinded during DB period and found to be on placebo, see Section 5.4.1, Discontinuation of Individual Subjects.

6.7.5 Creatinine Clearance

Creatinine clearance (CrCl) will be calculated throughout the study using Cockcroft-Gault method and estimated glomerular filtration rate (eGFR) will be calculated using the MDRD equation. CrCl values will be provided to the investigators.
If a subject experiences a calculated CrCl level < 50 mL/minute, an alert will be provided to the investigator which will require the test to be repeated. If calculated CrCl is confirmed to have decreased to < 50 mL/minute, medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements.

In addition, the following should occur:

(1) Concomitant medication dose reduction based on CrCl should be done (if applicable).

(2) The AbbVie Study Designated Physician should be contacted to discuss whether dose modification or drug substitution may be required for concomitant medications which might be impacted by the DAAs. Drug interactions between concomitant medications and the DAAs, for example, could potentially increase antihypertensive medication exposure and may reduce renal function. If anti-hypertensive medications are adjusted, vital signs must be monitored to ensure appropriate blood pressure control.

(3) Ribavirin dose should be adjusted per local label. Alternative management of RBV dose in the setting of reduced renal function will require approval of the AbbVie Study Designated Physician.

(4) A urine specimen should be obtained for urinalysis (including urine for albumin) and a separate urine specimen for archive should be obtained.

(5) Creatinine and chemistries should be repeated within 7 days and as clinically indicated until resolution.

If CrCl does not improve by 2 scheduled study visits (CrCl values < 50 mL/min) then study drugs should be permanently discontinued, the study drug assignment should be unblinded with further medical management as appropriate.

If CrCl improves, consideration should be given to the reassessment of any dose modifications that have been made.
The investigator should ensure that any concomitant medication changes, RBV dose reductions, and study drug discontinuations, as well as consequent related adverse events are entered into the appropriate eCRFs.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following AbbVie personnel:

Primary Contact: Kevin Howieson

Alternate Contact: George Liossis

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

8.1 Statistical and Analytical Plans

The primary analysis will occur after subjects who were initially randomized to active drug have completed the Post-Treatment Week 12 Visit or prematurely discontinued from the study and subjects who were initially randomized to placebo have completed the DB Treatment Period and 12 weeks of open-label active treatment in the OL Treatment Period or prematurely discontinued study drug. A follow-up analysis will occur after subjects who received open-label active treatment have completed the PT Week 12 Visit or prematurely discontinued the study. All remaining data through PT Week 48 will be summarized in the end of study analysis. For the primary and follow-up analyses, the data will be locked after performing appropriate data cleaning. Data after Post-Treatment Week 12 (for subjects who received placebo and open-label active drug) and after Post-Treatment Week 24 (for subjects who were initially randomized to active drug) will be added to a subsequent version of the database which will be cleaned and locked at the end of the study. If the duration of active treatment is extended to 24 weeks, then the subjects whose treatment was extended to 24 weeks of active treatment will be presented separately from the subjects assigned to 12 weeks of active treatment. The primary and secondary efficacy analyses will be assessed on subjects assigned to 12 weeks of active treatment in the DB Treatment Period. The primary safety comparison will be between subjects assigned to 12 weeks of placebo or active treatment in the DB Treatment Period.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and confidence intervals will be 2-sided with an α level of 0.05. Descriptive statistics will be provided, such as the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables.

Efficacy, safety, and demographic analyses will be performed on the intent-to-treat (ITT) population defined as all randomized subjects who receive at least one dose of
double-blind study drug. The primary and all secondary (other than ALT normalization) efficacy endpoints will be assessed within subjects in the ITT population randomized to active drug in the DB Treatment Period. The first secondary endpoint will compare the percentage of subjects with ALT normalization at the Final Treatment Visit in the DB Treatment Period between the placebo and active treatment groups. Safety comparisons will be performed on data from the DB Treatment Period. Safety data during the OL Treatment Period and available data from the PT Period will be presented separately and no statistical comparisons will be made to data collected during the DB Treatment Period.

No data will be imputed for any efficacy or safety analysis with the exception of the following PRO data and 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. The Mental and Physical Component Summary measures will not be computed if any domain is missing. For the HCVPRO total score, if a respondent answers at least 12 of the 16 items, the missing items will be imputed with the mean score of the answered items. In cases where the respondent did not answer five or more items, the total score will be considered missing. For EQ-5D-5L index and VAS scores, no imputation will be performed for missing items.

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

If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. 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 analyses (e.g., SVR$_4$, SVR$_{12}$, SVR$_{24}$), 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 window.

### 8.1.1 Demographics

**DB Treatment Period**

Demographics and baseline characteristics will be summarized for each treatment group in the ITT population. Demographics include age, weight, height, and BMI, and the frequency of sex, race, ethnicity, age groups (< 55 or $\geq$ 55 years and < 65 or $\geq$ 65 years), birth year (< 1945, 1945 – 1965, or $>$ 1965), BMI group (< 30 or $\geq$ 30 kg/m$^2$), geographic region (North America, Europe, or Australia), and country. Baseline characteristics will include HCV genotype 1 subgenotype (1a, 1b, or other), type of response to previous pegIFN/RBV treatment responder type (null responder (definition 1 or 2), partial responder, or relapser), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), baseline HCV RNA levels ([continuous] and (< 800,000 IU/mL or $\geq$ 800,000 IU/mL]), baseline IP-10 ([continuous] and (< 600 pg/mL or $\geq$ 600 pg/mL]), baseline HOMA-IR ($< 3$ mU $\times$ mmol/L$^2$ or $\geq$ 3 mU $\times$ mmol/L$^2$), tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker) status, former injection drug user (yes, no), history of bleeding disorders (yes, no), history of diabetes (yes, no), history of depression or bipolar disorder (yes/no), and baseline fibrosis stage (F0-F1, F2, $\geq$ F3).

Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and BMI) and a one-way analysis of variance (ANOVA) with treatment arm as the factor will be used to compare treatment groups. The number and percentage of subjects will be presented for categorical variables (e.g., gender and race); treatment groups will be compared using a chi-square test.

**OL Treatment Period**

Demographics and baseline characteristics will be summarized for all of the subjects randomized to placebo who receive at least one dose of active, open-label study drugs.
Summary statistics will be presented for continuous variables and the number and percentage of subjects will be presented for categorical variables.

8.1.2 Efficacy

All efficacy analyses will be performed on the intent-to-treat (ITT) population. The primary efficacy endpoint and all of the secondary efficacy endpoints, except for ALT normalization, will be performed on all subjects in the ITT population randomized to and receiving active study drug in the DB Treatment Period. The secondary efficacy endpoint of ALT normalization will be performed on the ITT population.

In order to control the Type I error rate, a fixed-sequence testing procedure will be used for the primary (SVR12) and secondary efficacy endpoints in the order numbered below. That is, only if success has been demonstrated for the primary endpoint of noninferiority of the SVR12 rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (1) will the testing continue to the second primary endpoint of superiority of the SVR12 rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (2). Similarly, only if success has been demonstrated for the second primary endpoint (2) will testing continue to the first secondary endpoint of ALT normalization (3). If success has been demonstrated for the first secondary endpoint of ALT normalization (3), then testing will continue to the next secondary endpoint (4). Similarly, testing will continue through the other numbered secondary endpoints only if success was met for the preceding endpoint; otherwise, statistical testing will stop.

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoints in the fixed-sequence testing procedure are ordered as follows:

1. SVR12: Non-inferiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; lower confidence bound (LCB) of 95% confidence interval must exceed 60% to achieve non-inferiority.
2. **SVR\textsubscript{12}:** Superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; LCB must exceed 70% to achieve superiority.

The following hypotheses will be tested on subjects in the ITT population who were randomized to active study drug (Arm A). To test the hypothesis that the percentage of pegIFN/RBV treatment-experienced HCV genotype 1 infected subjects treated with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV who achieve SVR\textsubscript{12} is non-inferior or superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR\textsubscript{12} will be calculated with a 2-sided 95% confidence interval (CI). The confidence interval will be calculated using the normal approximation to the binomial distribution. The LCB must be greater than 60% in order for the regimen to be considered non-inferior, and the LCB must be greater than 70% in order for the regimen to be considered superior to the historical SVR rate in pegIFN/RBV treatment-experienced HCV genotype 1 infected subjects treated with telaprevir plus pegIFN and RBV.

The value of 70% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN and RBV represents the upper bound of the 95% two-sided confidence interval based on a population-based weighted average of SVR rates in treatment-experienced HCV genotype 1-infected subjects in the REALIZE study included in the product labeling for telaprevir (Section 5.6.3).

### 8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included in the fixed-sequence testing procedure are:

3. **ALT normalization rate in Arm A compared to Arm B, in the DB Treatment Period.**

4. **SVR\textsubscript{12}:** In GT1a subjects, superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; to demonstrate superiority, the LCB must exceed 65%.
5. **SVR₁₂**: In GT1b subjects, superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; to demonstrate superiority, the LCB must exceed 77%.

ALT normalization (ALT ≤ ULN at Final Treatment Visit in the DB Treatment Period) will be calculated for all subjects in the ITT population with ALT above the upper limit of normal (ULN) at baseline. To test the hypothesis that the percentage of subjects with ALT normalization in the active treatment group is greater than the percentage of subjects with ALT normalization in the placebo treatment group, the percentage of subjects will be compared using Fisher's exact test. If superiority of the active arm is demonstrated with a \( P \) value ≤ 0.05, then the DAA combination regimen is considered a success for this endpoint. To test the hypothesis that the percentage of treatment-experienced HCV genotype 1a infected subjects treated in Arm A who achieve SVR₁₂ is superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR₁₂ will be calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must be greater than 65% in order for the regimen to be a success for this endpoint. To test the hypothesis that the percentage of treatment-experienced HCV genotype 1b infected subjects treated in Arm A who achieve SVR₁₂ is superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR₁₂ will be calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must be greater than 77% in order for the regimen to be a success for this endpoint.

Other secondary endpoints not included in the fixed-sequence testing procedure are:

- The percentage of subjects in Arm A with on-treatment virologic failure during the DB Treatment Period (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA ≥ LLOQ at the end of treatment);
- The percentage of subjects in Arm A with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after
the last dose of study drug among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

The percentages and 2-sided 95% confidence intervals using the normal approximation to the binomial distribution of the subjects with virologic failure during treatment and post-treatment relapse will be calculated and summarized. These endpoints will not be part of the fixed-sequence testing procedure as no hypothesis is being tested.

**8.1.2.3 Subgroup Analysis**

The percentage (and 2-sided confidence intervals) of subjects with SVR\textsubscript{12} for each treatment group will be presented by the following subgroups:

- Type of response to previous pegIFN/RBV treatment (null responder [also by definitions 1 and 2], partial responder, or relapser);
- HCV genotype 1 subtype (1a, 1b, other);
- Baseline HCV RNA level (< 800,000 IU/mL or \( \geq 800,000 \) IU/mL);
- IL28B genotype (CC or non-CC);
- Sex (Male versus female);
- Age (< 55 versus \( \geq 55 \) years), (< 65 versus \( \geq 65 \) years);
- Birth year (< 1945, 1945 to 1965, > 1965);
- Race (Black versus non-black);
- Ethnicity (Hispanic versus no ethnicity);
- Geographic Region (North America, Europe, or Australia) and country (as appropriate);
- BMI (< 30 or \( \geq 30 \) kg/m\(^2\));
- Baseline IP-10 (< 600 pg/mL or \( \geq 600 \) pg/mL);
- Baseline HOMA-IR (< 3 mU × mmol/L\(^2\) or \( \geq 3 \) mU × mmol/L\(^2\));
- Subjects with RBV dose modifications (yes/no);
History of Diabetes (yes/no);
History of Bleeding Disorders (yes/no);
History of depression or bipolar disorder (yes/no);
Former injection drug user (yes/no);
Baseline fibrosis stage (F0–F1, F2, or ≥ F3).

Each subgroup analysis will be performed if there is an adequate number of subjects within each subgroup level. For each subgroup, the lower confidence bound of the 2-sided 95% confidence interval will be compared to > 60%.

8.1.2.4 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized and analyzed as specified.

DB Treatment Period

The following will be performed on ITT subjects randomized to active drug in the DB Treatment Period:

- the percentage of subjects with RVR (HCV RNA < LLOQ at DB Week 4);
- the percentage of subjects with EOTR (HCV RNA < LLOQ at DB Week 12);
- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the DB Treatment Period using only subjects with data in each visit window (i.e., no imputation for missing data);
- the percentage of subjects meeting each and any virologic failure criteria during treatment;
- time to suppression of HCV RNA during the DB Treatment Period.
**OL Treatment Period**

The following analyses will be performed on the subjects who were randomized to placebo and received at least one dose of active, open-label study drug.

- the percentage of subjects with RVR (HCV RNA < LLOQ at OL Week 4);
- the percentage of subjects with EOTR (HCV RNA < LLOQ at OL Week 12);
- the percentage of subjects with ALT normalization (ALT ≤ ULN at Final OL Treatment Visit for subjects with ALT > ULN at Baseline);
- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the OL Treatment Period using only subjects with data in each visit window (i.e., no imputation for missing data);
- the percentage of subjects with on-treatment virologic failure during the OL Treatment Period;
- the number of subjects with virologic rebound at each visit in the OL Treatment Period;
- the percentage of subjects who failed to have confirmed suppression of HCV RNA during the OL Treatment Period;
- time to suppression of HCV RNA during the OL Treatment Period.

**PT Period**

The following analyses will be performed by treatment arm on all randomized subjects who received active study drug either during the DB (Arm A) or OL (Arm B) Treatment Periods, at the time of the primary or follow-up analysis database locks based on data availability.

- the percentage of subjects with HCV RNA < LLOQ 4 weeks after the last actual dose of study drug (SVR₄) in the DB or OL Period (OL and DB active treated subjects separately);
- the percentage of subjects with HCV RNA < LLOQ 12 weeks after the last actual dose of open-label, active study drug (SVR₁₂) in the OL Period;
• the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the DB or OL Treatment Period, who subsequently relapse post-treatment within 4 weeks after the last actual dose of study drug (OL and DB active treated subjects separately);

• the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the OL Treatment Period, who subsequently relapse post-treatment within 12 weeks after the last actual dose of study drug.

The following analyses will be performed on all randomized subjects who received active study drug (either in the DB or OL Treatment Periods) including all available PT Period data.

• the percentage of subjects with HCV RNA < LLOQ 12 weeks after the last planned dose of study drug (SVR_{12\text{planned}});

• the percentage of subjects with HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR_{24});

• the percentage of subjects with HCV RNA < LLOQ 24 weeks after the last planned dose of study drug (SVR_{24\text{planned}});

• the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the DB or OL Treatment Period, who subsequently relapse at any time post-treatment;

• the percentage of subjects who achieved SVR_{12} who subsequently relapsed;

• time to relapse (day of the first of two consecutive HCV RNA values ≥ LLOQ used) at anytime post-treatment.

The percentage of subjects with RVR, EOTR, and SVR will be calculated as a simple percentage and 2-sided 95% confidence intervals will be calculated using the normal approximation to the binomial distribution; missing data will be imputed as described in Section 8.1. All other endpoints will be presented using data as observed, i.e., not performing any missing data imputations. From HCV RNA levels, the time to
suppression on treatment and time to relapse post-treatment will be calculated for each subject, and the median time will be estimated using Kaplan-Meier methodology for right censored observations.

### 8.1.3 Patient Reported Outcomes

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

- Mean change from baseline in HCVPRO total score to each applicable post-baseline time point;
- Mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;
- Mean change from baseline in the SF-36V2 Mental Component Summary (MCS) and Physical Component Summary (PCS) scores to each applicable post-baseline time point;
- The percentage of subjects in each treatment arm without a decrease from baseline to the Final DB Treatment Visit in SF-36 MCS and PCS greater than or equal to the minimally important difference (MID);
- The percentage of subjects in each treatment arm without a decrease from baseline to the Final DB Treatment Visit in HCVPRO total score greater than or equal to the MID;
- The percentage of subjects in each treatment arm without a decrease from baseline to the Final DB Treatment Visit in EQ-5D-5L health index score greater than or equal to the MID.

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit by treatment group will be provided for the HCVPRO total score, the EQ-5D-5L health index and VAS scores, and the SF-36V2 PCS and MCS scores. For each of these scores, mean change from Baseline to Final DB Treatment Visit
will be compared between treatment groups using an ANCOVA model with treatment arm as a factor and baseline score as a covariate.

For HCVPRO total score, SF-36v2 MCS and PCS score, and EQ-5D-5L health index score and VAS, a continuous plot by treatment group will be provided with percent change from baseline to Final DB Treatment Visit on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis.

The MID for the SF-36v2 will be a decrease of 5 points from baseline to the final treatment visit for both the MCS and PCS scores. The MID during treatment will be calculated for the HCVPRO total score and the EQ-5D-5L health index using Receiver Operating Characteristic (ROC) curves with a change from Baseline to Final DB Treatment Visit of –5 points in the SF-36v2 PCS and MCS summary measures as anchors. The percentage of subjects with a change from Baseline to Final DB Treatment Visit in the each of these measures > the appropriate MID will be compared between treatment arms using Fisher's exact test.

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

### 8.1.4 Resistance Analyses

The genes of interest for sequencing in this study are those encoding NS3 protease domain (amino acids 1–181), NS5A domain 1 (amino acids 1–215), and NS5B amino acids 300–591. For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology.

Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of products of amplification. Therefore, if the HCV RNA level at the time of virologic failure is < 1000 IU/mL, the sample closest in time after the failure with an HCV RNA level ≥ 1000 IU/mL will be used.
The following resistance variables will be tabulated and summarized for all subjects receiving active drugs who did not achieve SVR regardless of the reason and who have resistance data available:

- The variants at each amino acid position (1) by nucleotide population sequencing at baseline compared to the appropriate prototypic reference sequence, and (2) by nucleotide population and/or clonal sequencing for each post-baseline time point that is analyzed compared to baseline and the appropriate prototypic reference sequences.
  a. At least two non-failure subjects will be matched for every subject (treated with active drug) experiencing virologic failure to the extent possible by HCV subgenotype, type of previous pegIFN/RBV non-response, baseline HCV RNA level, and IL28B genotype. Baseline samples from these matched subjects will be sequenced for comparison of the variants existing among the group of subjects who did versus the group who did not experience virologic failure.

For those subjects who did not achieve SVR, their baseline HCV amino acid sequence as determined by population nucleotide sequencing will be compared to the appropriate prototypic reference amino acid sequence for each DAA target. A listing by subject of all variants at baseline at signature resistance-associated amino acids relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). For those subjects who do not achieve SVR, the HCV amino acid sequence at each timepoint analyzed post-baseline as determined by population sequencing will be compared with the baseline amino acid sequences. A listing by subject of all variants relative to the baseline and appropriate prototypic reference amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). In addition, listings by subject of variants at signature resistance-associated amino acid positions relative to baseline and the appropriate prototypic reference amino acid sequences will be provided.

Clonal sequencing of a given target (NS3, NS5A, or NS5B) will be performed at the time of virologic failure only if no variants are detected at signature resistance-associated amino acid positions by population sequencing. For the subset of samples for which clonal sequencing is performed, the amino acid variants determined by clonal sequencing
will be summarized by counting the number of clones whose amino acid sequence does not match that of the population baseline sequence at each visit and amino acid position, out of the total number of clones analyzed.

For subjects who do not achieve SVR, signature resistance-associated amino acid variants determined by population and/or clonal sequencing will be summarized for each drug target and subject. Four additional summaries (and accompanying listings) will be created for all subjects who experience virologic failure to assess the effects of amino acid substitutions based on population sequencing for each target gene on failure: 1) a summary of subjects who failed versus the matched set of subjects who did not fail by amino acid variants at signature positions detected at baseline compared to the appropriate prototypic reference, 2) a summary of subjects who failed due to on-treatment virologic failure by treatment-emerged variants (single or double) at signature amino acid positions compared to baseline, 3) a summary of those who failed due to relapse by post-treatment emerged variants (single or double) at signature amino acid positions compared to baseline, and 4) the persistence of resistance-associated amino acid substitutions by a summary of subjects who failed by the substitutions at the time of failure and PT Week 24 and Week 48.

A subject who does not achieve SVR will be considered to have emerged/enriched variants if at any time point after baseline a variant (that was not detected at baseline) is detectable by population sequencing, or alternatively if at any time point after baseline the increase from baseline in percentage of clones of any variant by clonal sequencing is greater than 20%. If there are at least 2 subjects of the same subgenotype with an emerged/enriched variant meeting this definition, then the number and percentage of subjects with emerged/enriched variants from baseline will be summarized by subgenotype amino acid position, and variant. A separate listing of all these subjects and the emerged variants by target will be provided.

To evaluate linkage between emerged or enriched variants by population sequencing, when post-baseline variants are present within a target at 2 or more signature resistance-associated amino acid positions, and no mixture is detected at either position, these will be
reported as linked variants. A listing by subject and time point of the linked variants will be provided. Furthermore, where clonal sequencing is performed, the number of clones that have the same multiple variants within a DAA target at 2 signature resistance-associated amino acid positions will be determined. A listing by subject and time point of the linked variants will be provided.

8.1.5 Safety

All subjects who receive at least one dose of double-blind study drug will be included in the safety analyses. For safety analyses, data from the active and placebo treatment groups during the DB Treatment Period will be summarized, and pairwise comparisons will be performed. The data from the OL Treatment Period and PT Period will be summarized similarly, but no pairwise comparisons will be performed.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the active arms (DB or OL active), treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of active study drugs through 30 days after the last dose of active study drugs. For the placebo arm in the DB Treatment period, treatment-emergent events are defined as any event that begins or worsens in severity after initiation of placebo through the last dose of placebo. The number and percentage of subjects in each treatment group with treatment-emergent adverse events will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between the DB active and placebo groups using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events also will be provided by severity rating and relationship to study drugs.

The number and percentage of subjects having treatment-emergent adverse events will be tabulated by SOC and preferred term for adverse events occurring in the OL Treatment Period.
Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be performed if useful and appropriate.

### 8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement prior to the initial dose of study drugs. Mean changes from Baseline to each treatment visit will be summarized by treatment group. The differences between the active and placebo groups in the DB Treatment Period will be analyzed using contrasts within an ANOVA model with treatment group as the factor.

Changes from baseline to the post-treatment visits will be calculated after active treatment in the DB or OL treatment periods.

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

In addition, the number and percentage of subjects with values meeting pre-specified criteria for Potentially Clinically Significant (PCS) laboratory values during treatment will be summarized by treatment group. Comparisons will be performed between the active and placebo groups in the DB Treatment Period of the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact tests.

Additional analyses will be performed if useful and appropriate.
8.1.5.3 Vital Signs Data

Vital sign measurements will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from Baseline to each treatment visit will be summarized descriptively for each treatment group. The baseline value will be the last measurement prior to the initial dose of study drugs. Mean changes will be compared between the active and placebo groups in the DB Treatment Period using contrasts within an ANOVA model with treatment group as the factor. Changes from baseline to the post-treatment visits will be calculated after active treatment in the DB or OL treatment periods. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for PCS vital sign values during treatment will be summarized by treatment group. Comparisons will be performed between the active and placebo groups in the DB Treatment Period of the percentage of subjects with PCS vital sign values for each vital sign measurement using Fisher's exact tests.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ritonavir and ribavirin will be tabulated for each subject and group. Summary statistics will be computed for each time and visit.

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

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software (Version VI, or higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent
volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The evaluation criteria described below will be used to examine the performance of different models.

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

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using either stepwise forward selection method, or generalized additive method (GAM) or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at P < 0.005, corresponding to an increase in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

In general, all continuous covariates will be entered in the model, initially in a linear fashion, with continuous covariates centered around the median value. Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates may also be explored. For example:
TVCLi = + Theta(2) (Comedication [1,2,⋯] + Theta(3) (WTi-median value) + Theta(4) (AGEi - median value).

Where TVCLi = Typical value of clearance for an individual i, Theta(1) is the intercept and Theta(2) - (4) are regression parameters relating the fixed effects (weight and age centered on the median value) to clearance.

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

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

The viral dynamic model will account for target cell growth and death, infection of target cells, infected cell infection and death rate, production of virus by infected cells, and inhibition of production of virus by the various DAAs. Effect of ribavirin will be explored on infection of target cells by the virus. Models will explore mutation of the wild type to single and/or double mutant species depending on the available clinical resistance data. Additional adjustments to the structural and error models will be made during model development as appropriate.

Logistic regression analyses will explore the relationship between exposure and one or more virologic endpoints (e.g., RVR, EVR, SVR₄, SVR₁₂, relapse following end of treatment and breakthrough on treatment).

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

8.2 Determination of Sample Size

It is planned to enroll 400 subjects in a 3:1 ratio to ABT-450/r/ABT-267 + ABT-333 + RBV and placebo (300 subjects randomized to active drug and 100 subjects randomized to placebo). The primary efficacy endpoint of SVR_{12} is assessed within the subjects randomized to the active arm (Arm A). With a sample size of 300 subjects and assuming that 85% of the subjects in Arm A will achieve SVR_{12}, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 60% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 70% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).^{18-20} Subjects who do not have data at Post-Treatment Week 12 (after performing the described imputation) count as failures for SVR_{12} so no adjustment for dropout is applicable.

8.3 Randomization Methods

Subjects will be randomized to ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + weight-based RBV or placebo for 12 weeks in a 3:1 ratio at the start of the study on DB Day 1. The randomization schedule will be stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). After completing DB treatment, subjects randomized to placebo will receive 12 weeks of open-label treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.

The number of relapsers to previous pegIFN/RBV treatment will be limited to \( \leq 120 \) subjects. The total number of partial responders plus relapsers to previous pegIFN/RBV treatment will be limited to \( \leq 300 \) subjects. The number of null responders with a \( < 1 \log_{10} \) IU/mL HCV RNA reduction at Week 4 who received at least 4 weeks of pegIFN/RBV (null responder definition 2) will be limited to about 25 subjects.
9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

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

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

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

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 Abbott personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.
Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

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

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and the Sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and the Sponsor. 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 the Sponsor 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 the Sponsor to arrange alternative archiving options.

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

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

1. I have received and reviewed the Investigator's Brochure for ABT-450, ABT-267, ABT-333 and the product labeling for ritonavir and RBV.

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)

Protocol Date: 08 April 2013

Signature of Principal Investigator ___________________________ Date ____________

Name of Principal Investigator (printed or typed) _____________________________________________________________
15.0 Reference List

1. Weekly Epidemiological Record. No. 49, 10 December 1999, WHO.


Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by the Sponsor 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 the Sponsor, 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 the Sponsor 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 the Sponsor and/or the appropriate regulatory agency, and retaining all study-related documents until notification from the Sponsor.
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 the Sponsor.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolga Baykal</td>
<td>Medical Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Sabine Kaleta</td>
<td>Senior Clinical Supply Project Manager</td>
<td>Global Drug Supply</td>
</tr>
<tr>
<td>George Lioissis</td>
<td>Clinical Research Manager</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Senior Medical Director</td>
<td>Clinical</td>
</tr>
</tbody>
</table>
Appendix C. Study Activities – Treatment Failure Extension

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8, OL Wk 10, OL Wk 12, Ext Wk 16, and Ext Wk 20</th>
<th>Ext Wk 24 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject takes first doses of active study drugs and site calls subject to confirm start date</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical Exam</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs, Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test [urine (u)]&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Adverse Event Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study drugs Dispensed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Study drugs Collected and Compliance Reviewed</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEMS cap downloaded (and collected at OL Wk 12 or Premature D/C from OL Treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>HCV Resistance Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pharmacokinetic Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
### Appendix C. Study Activities – Treatment Failure Extension (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>OL Day 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OL Wk 1</th>
<th>OL Wk 2</th>
<th>OL Wk 4</th>
<th>OL Wk 6</th>
<th>OL Wk 8, OL Wk 10, OL Wk 12, Ext Wk 16, and Ext Wk 20</th>
<th>Ext Wk 24 (EOT)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Total Insulin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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

a. Subjects randomized to Arm A will complete study procedures as outlined in Table 3, dispense drug at DB Week 12, and complete Ext Weeks 16, 20 and 24 (or D/C Visit if applicable). Subjects randomized to Arm B will complete study procedures as outlined in Table 3 and will take their first dose of all study drugs the day after the last day of the DB Treatment Period as noted above in the Treatment Failure Extension Table. The site will call the subject and record the study drugs start and end dates in the electronic data capture (EDC) system and source notes.

b. Subjects will begin the PT Period after completing study drugs treatment or prematurely discontinuing the OL Treatment Period.

c. Urine pregnancy testing is not required after the DB Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal.
### Appendix D. Clinical Toxicity Grades

#### Clinical Toxicity Grades for HCV Studies

<table>
<thead>
<tr>
<th>HEamatology</th>
<th>Grade 1 Toxicity</th>
<th>Grade 2 Toxicity</th>
<th>Grade 3 Toxicity</th>
<th>Grade 4 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absolute Neutrophil Count Decreased</strong></td>
<td>&lt; LLN – 1500/mm³</td>
<td>&lt; 1500 – 1000/mm³</td>
<td>&lt; 1000 – 500/mm³</td>
<td>&lt; 500/mm³</td>
</tr>
<tr>
<td><strong>Eosinophil Count Increased</strong></td>
<td>650 – 1500 cells/mm³</td>
<td>1501 – 5000 cells/mm³</td>
<td>&gt; 5000 cells/mm³</td>
<td>Hyper eosinophilic</td>
</tr>
<tr>
<td><strong>Hemoglobin Decreased</strong></td>
<td>&lt; LLN – 10.0 g/dL</td>
<td>&lt; 10.0 – 8.0 g/dL</td>
<td>&lt; 8.0 – 6.5 g/dL</td>
<td>&lt; 6.5 g/dL</td>
</tr>
<tr>
<td><strong>International Normalized Ratio (INR), Increased</strong></td>
<td>&gt; 1 – 1.5 × ULN</td>
<td>&gt; 1.5 – 2 × ULN</td>
<td>&gt; 2 × ULN</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphocyte Count Decreased</strong></td>
<td>&lt; LLN – 800/mm³</td>
<td>&lt; 800 – 500/mm³</td>
<td>&lt; 500 – 200/mm³</td>
<td>&lt; 200/mm³</td>
</tr>
<tr>
<td><strong>Platelets Decreased</strong></td>
<td>&lt; LLN – 75,000/mm³</td>
<td>&lt; 75,000 – 50,000/mm³</td>
<td>&lt; 50,000 – 25,000/mm³</td>
<td>&lt; 25,000/mm³</td>
</tr>
<tr>
<td><strong>FTT</strong></td>
<td>&gt; 1 – 1.5 × ULN</td>
<td>&gt; 1.5 – 2 × ULN</td>
<td>&gt; 2 × ULN</td>
<td></td>
</tr>
<tr>
<td><strong>White Blood Cell Count Decreased</strong></td>
<td>&lt; LLN – 3000/mm³</td>
<td>&lt; 3000 – 2000/mm³</td>
<td>&lt; 2000 – 1000/mm³</td>
<td>&lt; 1000/mm³</td>
</tr>
<tr>
<td><strong>White Blood Cell Count Increased</strong></td>
<td>10,800 – 15,000 cells/mm³</td>
<td>&gt; 15,000 – 20,000 cells/mm³</td>
<td>&gt; 20,000 – 25,000 cells/mm³</td>
<td>&gt; 25,000 cells/mm³</td>
</tr>
</tbody>
</table>

#### Chemistries

<table>
<thead>
<tr>
<th>Albumin, Serum, Low</th>
<th>&lt; LLN – 3 g/dL</th>
<th>&lt; 3 – 2 g/dL</th>
<th>&lt; 2 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILIRUBIN, High</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3.0 × ULN</td>
<td>&gt; 3.0 – 10.0 × ULN</td>
</tr>
<tr>
<td>BUN</td>
<td>1.25 – 2.5 × ULN</td>
<td>&gt; 2.5 – 5.0 × ULN</td>
<td>&gt; 5 – 10.0 × ULN</td>
</tr>
<tr>
<td>Calcium, Serum, Low</td>
<td>&lt; LLN – 8.0 mg/dL</td>
<td>&lt; 8.0 – 7.0 mg/dL</td>
<td>&lt; 7.0 – 6.0 mg/dL</td>
</tr>
<tr>
<td>Calcium, Serum, High</td>
<td>&gt; ULN – 11.5 mg/dL</td>
<td>&gt; 11.5 – 12.5 mg/dL</td>
<td>&gt; 12.5 – 13.5 mg/dL</td>
</tr>
</tbody>
</table>

150
### Clinical Toxicity Grades for HCV Studies[^1][^2]

<table>
<thead>
<tr>
<th>CHEMISTRIES (continued)</th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CALCIUM, IONIZED</strong>, LOW</td>
<td>&lt; LLN – 1.0 mmol/L</td>
<td>&lt; 1.0 – 0.9 mmol/L</td>
<td>&lt; 0.9 – 0.8 mmol/L</td>
<td>&lt; 0.8 mmol/L</td>
</tr>
<tr>
<td><strong>CALCIUM, IONIZED</strong>, HIGH</td>
<td>&gt; ULN – 1.5 mmol/L</td>
<td>&gt; 1.5 – 1.6 mmol/L</td>
<td>&gt; 1.6 – 1.8 mmol/L</td>
<td>&gt; 1.8 mmol/L</td>
</tr>
<tr>
<td><strong>CHOLESTEROL HIGH</strong></td>
<td>&gt; ULN – 300 mg/dL</td>
<td>&gt; 300 – 400 mg/dL</td>
<td>&gt; 400 – 500 mg/dL</td>
<td>&gt; 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 7.75 mmol/L</td>
<td>&gt; 7.75 – 10.34 mmol/L</td>
<td>&gt; 10.34 – 12.92 mmol/L</td>
<td>&gt; 12.92 mmol/L</td>
</tr>
<tr>
<td><strong>CREATININE</strong></td>
<td>1.5 – 1.7 mg/dL</td>
<td>1.8 – 2.0 mg/dL</td>
<td>2.1 – 2.5 mg/dL</td>
<td>&gt; 2.5 mg/dL or requires dialysis</td>
</tr>
<tr>
<td><strong>GLUCOSE, SERUM</strong>, LOW</td>
<td>&lt; LLN – 55 mg/dL</td>
<td>&lt; 55 – 40 mg/dL</td>
<td>&lt; 40 – 30 mg/dL</td>
<td>&lt; 30 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>&lt; 3.0 – 2.2 mmol/L</td>
<td>&lt; 2.2 – 1.7 mmol/L</td>
<td>&lt; 1.7 mmol/L</td>
</tr>
<tr>
<td><strong>GLUCOSE, SERUM</strong>, HIGH (Fasting)</td>
<td>&gt; ULN – 160 mg/dL</td>
<td>&gt; 160 – 250 mg/dL</td>
<td>&gt; 250 – 500 mg/dL</td>
<td>&gt; 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 8.9 mmol/L</td>
<td>&gt; 8.9 – 13.9 mmol/L</td>
<td>&gt; 13.9 – 27.8 mmol/L</td>
<td>&gt; 27.8 mmol/L or acidosis</td>
</tr>
<tr>
<td><strong>MAGNESIUM, SERUM</strong>, LOW</td>
<td>&lt; LLN – 1.2 mg/dL</td>
<td>&lt; 1.2 – 0.9 mg/dL</td>
<td>&lt; 0.9 – 0.7 mg/dL</td>
<td>&lt; 0.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 0.5 mmol/L</td>
<td>&lt; 0.5 – 0.4 mmol/L</td>
<td>&lt; 0.4 – 0.3 mmol/L</td>
<td>&lt; 0.3 mmol/L</td>
</tr>
<tr>
<td><strong>MAGNESIUM, SERUM</strong>, HIGH</td>
<td>&gt; ULN – 3.0 mg/dL</td>
<td>&gt; 3.0 – 8.0 mg/dL</td>
<td>&gt; 8.0 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; ULN – 1.23 mmol/L</td>
<td>&gt; 1.23 – 3.30 mmol/L</td>
<td>&gt; 3.30 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>PHOSPHATE, SERUM</strong>, LOW</td>
<td>&lt; LLN – 2.5 mg/dL</td>
<td>&lt; 2.5 – 2.0 mg/dL</td>
<td>&lt; 2.0 – 1.0 mg/dL</td>
<td>&lt; 1.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 0.8 mmol/L</td>
<td>&lt; 0.8 – 0.6 mmol/L</td>
<td>&lt; 0.6 – 0.3 mmol/L</td>
<td>&lt; 0.3 mmol/L</td>
</tr>
<tr>
<td><strong>POTASSIUM, SERUM</strong>, LOW</td>
<td>&lt; LLN – 3.0 mmol/L</td>
<td>&lt; 3.0 – 2.5 mmol/L</td>
<td>&lt; 2.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>POTASSIUM, SERUM</strong>, HIGH</td>
<td>&gt; ULN – 5.5 mmol/L</td>
<td>&gt; 5.5 – 6.0 mmol/L</td>
<td>&gt; 6.0 – 7.0 mmol/L</td>
<td>&gt; 7.0 mmol/L</td>
</tr>
<tr>
<td><strong>PROTEIN, SERUM</strong>, LOW</td>
<td>5.5 – 6.0 g/dL</td>
<td>&lt; 5.5 – 5.0 g/dL</td>
<td>&lt; 5.0 g/dL</td>
<td></td>
</tr>
<tr>
<td><strong>SODIUM, SERUM</strong>, LOW</td>
<td>&lt; LLN – 130 mmol/L</td>
<td>&lt; 130 – 120 mmol/L</td>
<td>&lt; 120 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>SODIUM, SERUM</strong>, HIGH</td>
<td>&gt; ULN – 150 mmol/L</td>
<td>&gt; 150 – 155 mmol/L</td>
<td>&gt; 155 – 160 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalization may be indicated</td>
<td>&gt; 160 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRIGLYCERIDES HIGH</strong> (Fasting)</td>
<td>150 – 300 mg/dL; 1.71 – 3.42 mmol/L</td>
<td>&gt; 300 – 500 mg/dL; 3.42 – 5.7 mmol/L</td>
<td>&gt; 500 – 1000 mg/dL; 5.7 – 11.4 mmol/L</td>
<td>&gt; 1000 mg/dL; &gt; 11.4 mmol/L</td>
</tr>
</tbody>
</table>

[^1]: M13-098 Protocol Amendment 3
[^2]: EudraCT 2012-002035-29

Hospitalization may be indicated.
## Clinical Toxicity Grades for HCV Studies\(^1,2\)

<table>
<thead>
<tr>
<th>CHEMISTRYS (continued)</th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>URIC ACID, SERUM, HIGH</td>
<td>7.5 – 10.0 mg/dL</td>
<td>10.1 – 12.0 mg/dL</td>
<td>12.1 – 15.0 mg/dL</td>
<td>&gt; 15.0 mg/dL</td>
</tr>
<tr>
<td>ENZYMES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/SGPT</td>
<td>&gt; ULN – 3.0 × ULN</td>
<td>&gt; 3.0 – 5.0 × ULN</td>
<td>&gt; 5.0 – 20.0 × ULN</td>
<td>&gt; 20.0 × ULN</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>&gt; ULN – 3.0 × ULN</td>
<td>&gt; 3.0 – 5.0 × ULN</td>
<td>&gt; 5.0 – 20.0 × ULN</td>
<td>&gt; 20.0 × ULN</td>
</tr>
<tr>
<td>ALKALINE PHOSPHATASE</td>
<td>&gt; ULN – 2.5 × ULN</td>
<td>&gt; 2.5 – 5.0 × ULN</td>
<td>&gt; 5.0 – 20.0 × ULN</td>
<td>&gt; 20.0 × ULN</td>
</tr>
<tr>
<td>AMYLASE</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>× ULN</td>
<td>&gt; 2.0 – 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
<tr>
<td>LIPASE</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 2.0 × ULN</td>
<td>&gt; 2.0 – 5.0 × ULN</td>
<td>&gt; 5.0 × ULN</td>
</tr>
</tbody>
</table>

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 E. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 3.0 Introduction
Subsection Study M11-652
Fourth paragraph, fifth sentence previously read:

Grade 3 (or higher) elevations of ALT occurred in 5 subjects (all without bilirubin elevation) all of whom were asymptomatic.

Has been changed to read:

Grade 3 (or higher) elevations of alanine aminotransferase (ALT) occurred in 5 subjects (all without bilirubin elevation) all of whom were asymptomatic; some of these elevations were seen in subjects taking concomitant hormonal contraceptives.

Section 5.2.1 Inclusion Criteria
Following fifth bullet in Criterion 2
Sub-bullet previously read:

○ currently using at least one effective method of birth control at the time of screening and agrees to use 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 DB Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label (Note: Contraceptives containing ethinyl estradiol or depo-progesterone are not considered effective during drug treatment).

Has been changed to read:

○ currently using at least one effective method of birth control at the time of screening and agrees to use 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 DB Day 1 and
for 7 months after stopping study drug or as directed by the local ribavirin label (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during administration of study drugs).

Table 1. Medications Contraindicated for Use with the Study Drug Regimen

Add: new medication

"Hormonal contraceptives*"

Table 1. Medications Contraindicated for Use with the Study Drug Regimen

Add: footnote "*"

* Use of hormonal contraceptives requires SDP approval.

Section 5.2.3.3 Prohibited Therapy

Add: third paragraph

Hormonal contraceptives (including oral, topical, injectable or implantable varieties) may not be used from 2 weeks prior to the first dose of study drug until 2 weeks after the end of study drug dosing unless approved by the Study Designated Physician. Post-menopausal hormone replacement therapy may be used at the discretion of the Investigator.

Appendix B. List of Protocol Signatories

Previously read:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolga Baykal</td>
<td>Medical Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kevin Howieson</td>
<td>Clinical Research Manager Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sabine Kaleta</td>
<td>Senior Clinical Supply Project Manager</td>
<td>Global Drug Supply</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Rejeev Menon</td>
<td>Director</td>
<td>Clinical Pharmacokinetics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Senior Medical Director</td>
<td>Clinical</td>
</tr>
</tbody>
</table>
Has been changed to read:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolga Baykal</td>
<td>Medical Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Sabine Kaleta</td>
<td>Senior Clinical Supply Project Manager</td>
<td>Global Drug Supply</td>
</tr>
<tr>
<td>George Liossis</td>
<td>Clinical Research Manager</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Senior Medical Director</td>
<td>Clinical</td>
</tr>
</tbody>
</table>
1.0 Title Page

**Statistical Analysis Plan**

**Study M13-098**

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE II)

**Date:** 30 September 2013
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3.0 Introduction

This is the first version of the statistical analysis plan (SAP) for Study M13-098. Study M13-098 examines the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 co-administered with ribavirin (RBV) for 12 weeks in pegylated-interferon (pegIFN) with RBV (P/R) treatment-experienced adults with genotype 1, chronic hepatitis C virus (HCV) infection, without cirrhosis. Throughout the SAP, the combination of direct-acting antiviral agents (DAAs) with RBV, ABT 450/r/ABT-267 + ABT-333 + RBV, will be denoted as "DAA combination regimen" for simplicity.

The SAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be utilized. A primary analysis, follow-up analysis, and end of study analysis will be conducted for Study M13-098 (defined in Section 4.4). Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objectives of this study are to compare the SVR$_{12}$ rates (the percentage of subjects achieving a 12-week sustained virologic response (SVR$_{12}$) [HCV RNA < lower limit of quantification (LLOQ) of 25 IU/mL 12 weeks after the last actual dose of study drug]) of 12 weeks of treatment with ABT 450/r/ABT-267 and ABT-333 co-administered with RBV (DAA combination regimen) to the historical SVR rate of telaprevir plus pegIFN and RBV therapy and to assess the safety of the DAA combination regimen compared to placebo for 12 weeks in P/R treatment-experienced HCV genotype 1-infected adults without cirrhosis.

The secondary objectives of this study are to measure the effect of the DAA combination regimen compared to placebo on normalizing alanine aminotransferase (ALT) levels and demonstrate the effect of the DAA combination regimen on SVR$_{12}$ in subjects with HCV
genotype 1a and genotype 1b infection and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and post-treatment relapse, respectively.

4.2 Design Diagram

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 co-administered with RBV in P/R treatment-experienced HCV genotype 1-infected adults without cirrhosis. Approximately 400 HCV genotype 1-infected, treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind (DB) Treatment Period at approximately 90 sites.

- Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks;
- Arm B: Placebo for (ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV*) for 12 weeks followed by open-label ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks.

* RBV weight based, 1000 mg to 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID)

Randomization will be stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a). Subjects on placebo who complete the DB Treatment Period will be administered open-label active study drug for 12 weeks following the DB Treatment Period. All subjects administered active study drug will be followed for 48 weeks post-treatment to test for durability of SVR and emergence or persistence of DAA resistance associated variants. A study schematic is shown below (Figure 1).
The duration of the study will be 60 weeks (for subjects randomized to Arm A) or 72 weeks (for subjects randomized to Arm B), not including a screening period of up to 35 days, consisting of a DB Treatment Period, an Open-Label (OL) Treatment Period for subjects randomized to placebo (Arm B), and a Post-Treatment (PT) Period for all subjects who receive at least one dose of active study drug.

**Double-Blind Treatment Period**

Subjects with HCV genotype 1 who meet the eligibility criteria will be randomized in a 3:1 ratio to either active drug (ABT-450/r/ABT-267 and ABT-333 co-administered with RBV) or matching placebos on Day 1. Subjects will receive blinded study drug for 12 weeks. Upon reaching Week 12 or premature discontinuation of study drug, all subjects will be unblinded. Subjects randomized to active drug will enter the PT Period; subjects randomized to placebo will enter the OL Treatment Period at the end (Week 12) of the DB Treatment Period.

**Open-Label Treatment Period**

After completing the Week 12 Visit of the DB Treatment Period, subjects initially randomized to placebo will receive 12 weeks of open-label treatment with the DAA combination regimen. Subjects will be dispensed drug at the DB Week 12 Visit for administration starting the next day, which will become Day 1 of the OL Treatment Period.
Period (OL Day 1). Upon completing the OL Treatment Period (OL Week 12) or premature discontinuation of open-label study drug, subjects will enter the PT Period.

**Post-Treatment Period**

All subjects who receive at least one dose of active drug will be monitored for HCV RNA, adverse events, quality of life, and for the emergence and/or persistence of DAA-resistant viral variants for an additional 48 weeks following the last dose of active study drug. The PT Period will begin the day after the last dose of active study drug (in either the DB Period for subjects randomized to active drug or the OL Treatment Period for subjects randomized to placebo).

### 4.3 Sample Size

This study is planned to enroll 400 subjects in a 3:1 ratio to the DAA combination regimen or placebo (300 subjects randomized to active drug and 100 subjects randomized to placebo). The primary efficacy endpoint of SVR$_{12}$ is assessed within the subjects randomized to Arm A. With a sample size of 300 subjects and assuming that 85% of the subjects in Arm A will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 95% lower confidence bound greater than 60% and greater than 90% power to demonstrate superiority with a 2-sided 95% lower confidence bound greater than 70% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4). No adjustment for dropout is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR$_{12}$.

### 4.4 Primary Analysis

The primary analysis will occur after subjects who were initially randomized to active drug (Arm A) have completed the DB Treatment Period through Post-Treatment Week 12 or prematurely discontinued study and subjects who were initially randomized to placebo (Arm B) have completed the DB Treatment Period and 12 weeks of open-label active treatment in the OL Treatment Period or prematurely discontinued study drug. For the
primary analysis, data will be locked after performing appropriate data cleaning. Results from the primary analysis (e.g., SVR_{12} data for Arm A subjects) will be described in the primary clinical study report (CSR) and submitted to regulatory agencies as part of the NDA/MAA submission.

A follow-up analysis will occur after Arm B subjects who received open-label active treatment have completed the PT Week 12 Visit or prematurely discontinued from the study (at a time point corresponding to the 4 month safety update for the US NDA). Data collected after the primary and follow-up analyses will be added to a new version of the database which will be cleaned and locked at the end of the study and included in the final CSR.

All analyses will be conducted by statisticians at AbbVie according to the methodologies specified in this SAP. No interim efficacy analyses will be performed prior to the primary analysis database lock. There is no intention of stopping the study early based on efficacy findings from the primary analysis. The intention is to follow all subjects who receive active drug for 48 weeks following active treatment.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

**Intent-to-Treat (ITT) Population**

All randomized subjects who receive at least one dose of blinded study drug will be included in the ITT population. The data from the ITT population will be presented by the treatment group assigned at the time of randomization (Arm A or Arm B).

Efficacy analyses will be performed on the ITT population.

**Safety Population**

All randomized subjects who receive at least one dose of blinded study drug will be included in the safety population.
Safety and demographic analyses will be performed on the safety population according to actual treatment received during the entire DB Treatment Period even if this differs from the randomized treatment assignment. If all subjects take the treatment to which they were randomly assigned, the Safety Population will be the same as the ITT population.

**Open-Label (OL) Population**

All subjects randomized to Arm B who receive at least one dose of active, open-label study drug will be included in the OL population. All analyses of data collected during and after the OL Treatment Period will be performed on the OL population.

### 5.2 Variables Used for Stratification of Randomization

Subjects will be randomized to Arm A (active DAA combination regimen) or Arm B (placebo) for 12 weeks in a 3:1 ratio at the start of the study. The randomization schedule will be stratified by type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and HCV subgenotype (1a versus non-1a).

### 6.0 Analysis Conventions

#### 6.1 Definition of Baseline and Final Assessment

**Definition of Baseline**

The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received. All assessments on DB Day 1 should be performed prior to administering the first dose of study drug per protocol. The baseline value is therefore determined by the last non-missing measurement collected on or before the first day of study drug administration.

If multiple measurements are recorded on the same day, the last measurement recorded prior to dosing will be used as Baseline. If these multiple measurements occur at the same time or time is not available, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as the baseline value. This same baseline value will be used for the DB, OL, and PT Periods.
Definition of DB Study Days (Days Relative to the First Dose of DB Study Drug)

DB Study Days are calculated for each time point in the DB Treatment Period relative to the first dose of double-blind (active or placebo) study drug. DB Study Days are negative values when the time point of interest is prior to the first DB study drug dose day. DB Study Days are positive values when the time point of interest is after the first DB study drug dose day. There is no DB Study Day 0. For the DB Treatment Period, DB Study Day 1 is the day of the first dose of double-blind (active or placebo) study drug.

Definition of Active Study Days (Days Relative to the First Dose of Active Study Drug)

Active Study Days will be defined for all subjects who receive at least one dose of active (double-blind or open-label) study drug. Active Study Day 1 is the day of the first dose of active (double-blind or open-label) study drug.

For subjects randomized to Arm A, DB Study Days and Active Study Days are equivalent. For subjects randomized to placebo (Arm B) and in the OL population, Active Study Days are based on the first dose of open-label, active study drug.

Definition of (Active) Study Drug End Days (Days Relative to the Last Dose of Active Study Drug)

For all subjects who receive at least one dose of active study drug, study drug end days are calculated relative to the last dose of active study drug. The last day of active study drug is defined as Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

Definition of Final Treatment Value

The final treatment value for each subject is the last non-missing measurement collected after Study Day 1 within a treatment period as defined below.
During the DB Treatment Period, the Final DB Treatment Value is defined separately for placebo and active subjects. For subjects randomized to placebo (Arm B), the Final DB Treatment Value is defined as the last non-missing measurement collected after DB Study Day 1 and no more than 2 days after the last dose of placebo and on or before OL Day 1 (if applicable). All assessments on DB Week 12 should be performed prior to administering the first dose of open-label, active study drug per protocol. Therefore, for subjects who started open-label dosing on the day they finished placebo, the assessments collected on OL Day 1 can be included in the Final DB Treatment window. For subjects randomized to active study drug (Arm A), the Final DB Treatment Value is defined as the last non-missing measurement collected after DB Study Day 1 and within 2 days of the last dose of active study drug (i.e., on or before Study Drug End Day 2).

During the OL Treatment Period, for subjects randomized to placebo who receive open-label study drug, the Final OL Treatment Value is defined as the last non-missing measurement collected after OL Day 1 and on or before Study Drug End Day 2.

**Definition of Final Post-Treatment Value**

The final post-treatment value for each subject treated with active drug is the last non-missing measurement collected after Study Drug End Day 2.

**6.2 Definition of Analysis Windows**

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 1, Table 2, and Table 3 describe how efficacy data are assigned to protocol-specified time points during the DB Treatment, OL Treatment, and PT Periods, respectively. All time points and corresponding time windows are defined based on the blood sample collection date.

*Table 4* will be used for visit windows of analyses of health-related quality of life (QoL) patient reported outcomes (PROs) collected throughout the study.
If more than one assessment is included in a time window, the assessment closest to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. The only exception to this is for the SVR windows (e.g., SVR_4, SVR_12, SVR_24, SVR_{12planned}, and SVR_{24planned}); for these windows, the last value in the window will be used.

If multiple measurements are made on the same day for a safety laboratory parameter or a vital sign parameter, the average of the values will be used in analyses. For summaries of shifts from baseline and potentially significant values, multiple values on the same day will not be averaged; all values will be considered for these analyses.

For laboratory data and vital signs, the time windows specified in Table 5, Table 6, and Table 7 describes how data are assigned to protocol specified time points during the DB Treatment, OL Treatment, and PT Periods, respectively.
### Table 1. Analysis Time Windows for HCV RNA and Resistance Endpoints (Double-Blind Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (DB Study Day)</th>
<th>Time Window (DB Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB Day 1/Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤ 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>DB Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>DB Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>DB Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>DB Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>DB Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>DB Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>DB Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Final DB Treatment Visit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of DB study drug</td>
<td></td>
</tr>
<tr>
<td>SVR&lt;sub&gt;12planned&lt;/sub&gt; c (active arm)</td>
<td>168</td>
<td>141 to 210</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;24planned&lt;/sub&gt; c (active arm)</td>
<td>252</td>
<td>211 to 294</td>
</tr>
</tbody>
</table>

<sup>a</sup> Day of first dose of double-blind study drug.

<sup>b</sup> The last value within the window will be used to define Final. For subjects randomized to active, the upper bound of the Final window is Study Drug End Day ≤ 2. For subjects randomized to placebo, it is on or before the day of first dose of open-label active drug and within 2 days of the last dose of placebo.

<sup>c</sup> For SVR windows, the last value in the window will be used. SVR windows will be used for subjects randomized to the active arm.

Note: All data, except for SVR<sub>12planned</sub> and SVR<sub>24planned</sub>, must also be within 2 days of the last dose of DB study drug. The result closest to the scheduled time point will be used, except for SVR<sub>12planned</sub> and SVR<sub>24planned</sub>. For SVR windows, the last value in the window will be used.
Table 2. Analysis Time Windows for HCV RNA and Resistance Endpoints During the Open-Label Treatment Period (OL Population)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Active Study Day)</th>
<th>Time Window (Active Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OL Day 1</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
</tr>
<tr>
<td>OL Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>OL Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>OL Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>OL Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>OL Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>OL Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>OL Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Final OL Treatment Visit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of OL study drug</td>
<td></td>
</tr>
<tr>
<td>SVR&lt;sub&gt;12planned&lt;/sub&gt;</td>
<td>168</td>
<td>141 to 210</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;24planned&lt;/sub&gt;</td>
<td>252</td>
<td>211 to 294</td>
</tr>
</tbody>
</table>

<sup>a</sup> OL visits are applicable for subjects randomized to Arm B (placebo) who received at least one dose of open-label, active study drug.

<sup>b</sup> Day of first dose of open-label (active) study drug.

<sup>c</sup> The last value within the window will be used to define Final. The upper bound of the Final window is Study Drug End Day ≤ 2.

<sup>d</sup> For SVR windows, the last value in the window will be used. SVR windows will be used for subjects randomized to placebo (Arm B) who received at least one dose of open-label (active) study drug.

Note: All data, except for SVR<sub>12planned</sub> and SVR<sub>24planned</sub>, must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used, except for SVR<sub>12planned</sub> and SVR<sub>24planned</sub>. For SVR windows, the last value in the window will be used.
Table 3. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 2</td>
<td>14</td>
<td>3 to 21</td>
</tr>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>22 to 42</td>
</tr>
<tr>
<td>Post-Treatment Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>71 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24</td>
<td>168</td>
<td>127 to 210</td>
</tr>
<tr>
<td>Post-Treatment Week 36</td>
<td>252</td>
<td>211 to 294</td>
</tr>
<tr>
<td>Post-Treatment Week 48</td>
<td>336</td>
<td>295 to 378</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;12&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;24&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>168</td>
<td>127 to 210</td>
</tr>
</tbody>
</table>

a. Post-Treatment Visits are applicable for subjects who received at least one dose of active (double-blind or open-label) study drug.

b. For SVR windows, the last value in the window will be used.

Note: The result closest to the scheduled time point will be used, except for SVR<sub>4</sub>, SVR<sub>12</sub>, and SVR<sub>24</sub>. Data must also have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of active study drug.
### Analysis Time Windows for PRO Instruments

**Table 4.**

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(DB Study Day)</td>
<td>(DB Study Days Range)</td>
</tr>
<tr>
<td>DB Day 1/Baseline</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≤ 1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>DB Week 4</td>
<td>28</td>
<td>2 to 42</td>
</tr>
<tr>
<td>DB Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>DB Week 12</td>
<td>84</td>
<td>71 to 98</td>
</tr>
<tr>
<td>Final DB Treatment Visit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of DB study drug</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day</th>
<th>Time Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Study Drug End Day)</td>
<td>(Study Drug End Days Range)</td>
</tr>
<tr>
<td>Post-Treatment Week 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>Post-Treatment Week 12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>168</td>
<td>127 to 252</td>
</tr>
<tr>
<td>Post-Treatment Week 48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>336</td>
<td>253 to 378</td>
</tr>
<tr>
<td>Final Post-Treatment Visit&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt; 2 days after last dose of active study drug</td>
<td></td>
</tr>
</tbody>
</table>

---

a. SF-36v2, HCVPRO, and EQ-5D-5L are collected at Baseline, DB Week 4, DB Week 8, and DB Week 12 for all randomized subjects. SF-36v2, HCVPRO, and EQ-5D-5L are collected at Post-Treatment Weeks 4, 12, 24, and 48 for subjects randomized to active drug. PRO instruments are not collected during the OL Treatment Period.

b. Day of first dose of double-blind study drug. A value is considered to be Baseline if it is the last non-missing value on or before DB Study Day 1.

c. The last value within the window will be used to define the final on-treatment value. For subjects randomized to active, the upper bound of this Final window is Study Drug End Day ≤ 2. For subjects randomized to placebo, it is on or before the day of first dose of open-label active drug and within 2 days of the last dose of placebo.

d. The last value within the Post-Treatment Period window will be used to define the final post-treatment value. The lower bound of this Final window is Study Drug End Day 3.

Note: The result closest to the scheduled time point will be used. For visits through DB Week 12, data must also be within 2 days of the last dose of DB study drug. For post-treatment visits, data must also have Study Drug End Day > 2 where Study Drug End Day 0 is defined as the day of the last dose of active study drug.
## Table 5. Laboratory Data and Vital Sign Visit Windows (Double-Blind Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Time</th>
<th>Nominal Day (DB Study Day)</th>
<th>Time Window (DB Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB Day 1/Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>≤ 1</td>
</tr>
<tr>
<td>DB Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>DB Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>DB Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>DB Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>DB Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>DB Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>DB Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Final DB Treatment Visit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of DB study drug</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Day of first dose of double-blind study drug.

<sup>b</sup> The last value within the window will be used to define Final. For subjects randomized to active, the upper bound of the Final window is Study Drug End Day ≤ 2. For subjects randomized to placebo, it is on or before the day of first dose of open-label active drug and within 2 days of the last dose of placebo.

Note: The result closest to the scheduled time point will be used. Data must also be within 2 days of the last dose of DB study drug.
## Table 6. Laboratory Data and Vital Sign Visit Windows During the Open-Label Treatment Period (OL Population)

<table>
<thead>
<tr>
<th>Scheduled Time&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Nominal Day (Active Study Day)</th>
<th>Time Window (Active Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OL Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
</tr>
<tr>
<td>OL Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>OL Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>OL Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>OL Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>OL Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>OL Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>OL Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Final OL Treatment Visit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of OL study drug</td>
<td></td>
</tr>
</tbody>
</table>

a. OL visits are applicable for subjects randomized to Arm B (placebo) who received at least one dose of open-label, active study drug.

b. Day of first dose of open-label (active) study drug.

c. The last value within the window will be used to define Final. The upper bound of the Final window is Study Drug End Day ≤ 2.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day ≤ 2.
Table 7. Laboratory Data and Vital Sign Visit Windows (Post-Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Time</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 2</td>
<td>14</td>
<td>3 to 21</td>
</tr>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>22 to 42</td>
</tr>
<tr>
<td>Post-Treatment Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>71 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24</td>
<td>168</td>
<td>127 to 210</td>
</tr>
<tr>
<td>Post-Treatment Week 36</td>
<td>252</td>
<td>211 to 294</td>
</tr>
<tr>
<td>Post-Treatment Week 48</td>
<td>336</td>
<td>295 to 378</td>
</tr>
<tr>
<td>Final Post-Treatment Visit(^a)</td>
<td>&gt; 2 days after last dose of active study drug</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The last value within the Post-Treatment Period window will be used to define the final post-treatment value. The lower bound of this Final window is Study Drug End Day 3.

Note: Post-Treatment Visits are applicable for subjects who received at least one dose of active (double-blind or open-label) study drug. The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2 where Study Drug End Day 0 is defined as the day of the last dose of active study drug.

6.3 Missing Data Imputation

Data will be imputed for HCV RNA analyses of RVR, EOTR, and SVR and for analyses of QoL questionnaires.

HCV RNA

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 6.2. If an HCV RNA value is missing within a study visit window, then the missing HCV RNA value will be imputed via a flanking imputation approach. When there is no HCV RNA value in a defined visit window, the HCV RNA values immediately preceding and succeeding the window will be used for the flanking imputation regardless of the values chosen in the preceding and succeeding windows. If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and the succeeding value, then the HCV RNA level will be imputed as 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.

If an HCV RNA value is missing within the SVR windows, then a flanking imputation including backward imputation approach will be used. The flanking imputation approach will be used first. If the SVR window is still missing an HCV RNA value, then a backward imputation approach will be carried out where if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window.

If a subject starts another treatment for HCV, then all HCV RNA values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses. The subject will be considered a failure for summaries of viral response at all time points after the start of the new HCV treatment.

**HCV RNA < LLOQ Analyses for RVR, EOTR, and SVR**

If a subject is missing an HCV RNA value for the visit window associated with the analysis of RVR, EOTR, or SVR after performing the imputations described above, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value for this visit will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

**HCV RNA < LLOD Analyses for RVR, EOTR, and SVR**

When summarizing RVR, EOTR, and SVR using the LLOD, only data from the central laboratory will be used and the flanking imputation will only consider values that are undetectable. If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable HCV RNA levels at both the preceding value and the succeeding value, then the HCV RNA level will be imputed as undetectable at this visit for this subject. For SVR analyses, if there is no value in the appropriate window after the flanking imputation but there is an HCV RNA value after the window, then it will be used to impute the response.
in the SVR window. In other words, if the HCV RNA value after the window is undetectable, then the subject will be imputed as an SVR responder; otherwise, the subject will be considered a failure.

**HCV RNA Analyses for Relapse and Virologic Failure**

If HCV RNA values from the central laboratory are missing but a local laboratory value is present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.

**Quality of Life Questionnaires**

If more than 4 items of the 16-item HCV-PRO are missing responses, then the total score is set to missing. When 4 or fewer items are missing, the mean of the non-missing items will be used to impute the responses for the missing item(s) and a total score will be calculated.

For EQ-5D-5L, no imputation will be performed for missing items.

For SF-36 QoL questionnaires, if a respondent answers at least 50% of the items in a multi-item scale of SF-36, 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. The Mental and Physical Component measure will not be computed if any domain is missing.

### 7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

Demographics, baseline characteristics, medical history, and previous/concomitant medications will be summarized by treatment group for the DB Treatment Period on the safety population. In addition, demographics and baseline characteristics will be summarized for the OL population.
7.1 Demographic and Baseline Characteristics

Demographics include age, weight, body mass index (BMI), and the frequency of sex, race, ethnicity, age categories (< 55 or ≥ 55 years; < 65 or ≥ 65 years), birth year (< 1945, 1945 to 1965, > 1965), geographic region (North America, Europe, or Australia/New Zealand), country, BMI category (< 30 or ≥ 30 kg/m$^2$), and women of childbearing potential (females between the ages of 18 and 55 years, inclusive). Baseline characteristics will include HCV genotype 1 subtype (1a, 1b, or other), IL28B genotype (CC, CT, or TT; CC or non-CC), baseline log$_{10}$ HCV RNA levels (continuous), baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL), type of response to previous pegIFN/RBV treatment (null responder [definition 1 or 2], partial responder, or relapser), baseline IP-10 (continuous), baseline IP-10 (< 600 or ≥ 600 ng/L), baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L$^2$), tobacco (user, ex-user, or non-user) and alcohol (drinker, ex-drinker, or non-drinker) use status, former injection drug user status (yes, no, or unknown), baseline fibrosis stage (equivalent to Metavir F0-F1, F2 or F3 and higher), history of diabetes, history of depression or bipolar disorder, history of bleeding disorders, history of hypertension, and history of cardiovascular disease.

If the IL28B genotype result is not available from a sample collected during the Screening period, then a result available from a sample collected at any time during the study will be used to summarize IL28B genotype.

HOMA-IR is defined as fasting glucose (mmol/L) × fasting insulin (μIU/mL) ÷ 22.5. Subjects who do not have a fasting glucose value and/or a fasting insulin value at Baseline will be excluded from the summary of baseline HOMA-IR. When defining geographic region, sites in Canada, Mexico, Puerto Rico, and USA will be grouped under North America; sites in the Czech Republic, Denmark, France, Germany, Ireland, Italy, the Netherlands, Portugal, Russia, Spain, and the United Kingdom will be grouped under Europe; sites in Australia will be grouped under Australia/New Zealand. Histories of diabetes, depression or bipolar disorder, bleeding disorders, hypertension, and cardiovascular disease will be based on the Medical History (MH) eCRF. History of diabetes is defined as presence of "Metabolic/Diabetes mellitus" on the MH eCRF.
History of depression or bipolar disorder is defined as presence of "Neurologic and Psychiatric System/Depression" or "Neurologic and Psychiatric System/Bipolar Disorder" on the MH eCRF. All medical history terms within "Clotting/bleeding problems" or "Other" under the "Blood" body system on the MH eCRF will be reviewed to identify subjects with a history of bleeding disorders (e.g., hemophilia). History of hypertension is defined as presence of "Cardiovascular/Hypertension" on the MH eCRF. History of cardiovascular disease includes conditions or diagnoses of "Angina," "Myocardial infarction," "Congestive heart failure," and "Coronary artery disease" under the "Cardiovascular" body system. Medical history terms within "Other Body System" or any condition/diagnosis of "Other" may be reviewed for all baseline characteristics determined by the MH eCRF.

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores. If a subject has more than one score recorded, then only one score will be used to categorize the subject. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the Baseline FibroTest result (i.e., last non-missing FibroTest result on or before DB Day 1) will be used to categorize the subject.

Subjects will be categorized as F0-F1, F2, F3 or F4 according to Table 8. For analysis purposes, F3 and F4 will be combined in the ≥ F3 category. Note that any subjects enrolling in the study with a Metavir score greater than 3, Ishak score greater than 4, or FibroScan score of 9.6 kPa or higher will be grouped in the ≥ F3 category though they are not expected to enroll per protocol.
Table 8. Baseline Fibrosis Stage

<table>
<thead>
<tr>
<th>Baseline Fibrosis Stage, Metavir Equivalents</th>
<th>Liver Biopsy Metavir, Batts Ludwig, Knodell, IASL, Scheuer, or Laennec Score</th>
<th>Liver Biopsy Ishak Score</th>
<th>FibroScan (kPa)</th>
<th>FibroTest</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 – F1</td>
<td>0 or 1</td>
<td>0, 1, or 2</td>
<td>&lt; 8.8</td>
<td>≤ 0.48</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>3</td>
<td>≥ 8.8 to &lt; 9.6</td>
<td>0.49 to 0.58</td>
</tr>
<tr>
<td>F3</td>
<td>3</td>
<td>4</td>
<td>≥ 9.6 to &lt; 14.6</td>
<td>0.59 to 0.72</td>
</tr>
<tr>
<td>F4</td>
<td>4</td>
<td>5 or 6</td>
<td>≥ 14.6</td>
<td>≥ 0.73</td>
</tr>
</tbody>
</table>

Double-Blind Treatment Period

Summary statistics (N, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI), and a one-way analysis of variance (ANOVA) with treatment arm as the factor will be used to compare treatment groups (active versus placebo). The number and percentage of subjects will be presented for categorical variables (e.g., gender and race), and treatment groups will be compared using a chi-square test.

Open-Label Treatment Period

The same set of demographics and baseline characteristics will be summarized for all subjects in the OL population. Baseline will be determined by the last non-missing measurement collected before the first dose of DB study drug is received. Summary statistics will be presented for continuous variables and the number and percentage of subjects will be presented for categorical variables.

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting
more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized by treatment group. A prior medication is defined as any medication taken prior to the date of the first dose of double-blind study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of double-blind study drug and continued to be taken after the first dose of double-blind study drug or any medication that started on or after the date of the first dose of (double-blind or open-label) study drug, but not after the date of the last (maximum) dose of study drug. Concomitant medications will be summarized for all subjects in the safety population as one summary for the DB and OL Treatment Periods, combined. The number and percentage of subjects taking prior or concomitant medications will be summarized by generic drug name based on the WH O Drug Dictionary. Note that prior HCV medications (pegIFN and RBV) will be summarized separately from other prior medications.

Medications related to the treatment of HCV will be collected in the PT Period and will be summarized by generic drug name for each treatment arm. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last (maximum) dose of study drug and entered as "Post Treatment HCV medications" on the eCRF.

8.0 Patient Disposition

The number of subjects for each of the following categories will be summarized overall and by investigator for each treatment group and overall.

- Randomized subjects;
- Subjects who took at least one dose of double-blind (active or placebo) study drug;
- Subjects who completed double-blind study drug;
• Subjects who discontinued from double-blind study drug;
• Subjects who took at least one dose of open-label (active) study drug;
• Subjects who completed open-label study drug;
• Subjects who discontinued from open-label study drug;
• Subjects who completed the study;
• Subjects who discontinued from the study;
• Subjects ongoing in the Post-Treatment Period at the time of the primary analysis.

Note that subjects randomized to placebo may prematurely discontinue study drug but upon unblinding at this Premature Discontinuation visit find that they are on placebo and elect to continue on placebo and complete the DB Treatment Period in order to receive open-label, active study drug in the OL Treatment Period. For these placebo subjects, reasons for discontinuation from blinded study drug will be collected on the DB Study Drug Completion 1 eCRF. If a placebo subject chooses to continue the DB Treatment Period in order to enter the OL Treatment Period, but then prematurely discontinues placebo before completing the DB Treatment Period, reasons for discontinuation from placebo will be collected on the DB Study Drug Completion 2 eCRF.

All subjects who prematurely discontinue from double-blind study drug, including all placebo subjects who discontinue from study drug (regardless of whether they elect to continue in the DB Treatment Period or not), will be counted in the disposition table described above. In other words, tabulations of discontinuations from double-blind study drug are based on information collected on the DB Study Drug Completion 1 eCRF only.

The number and percentage of subjects who discontinued study drug will be summarized by reason (all reasons) and by primary reason (per eCRF) for each treatment group and overall, as described below, for all subjects and separately for women of childbearing potential. Similar summaries will be provided for discontinuations from the study and discontinuations from the OL Treatment Period.
The number and percentage of subjects who discontinued study drug and the reasons recorded on the DB Study Drug Completion 1 eCRF will be presented in a table for all subjects who prematurely discontinued from double-blind study drug. The reasons recorded on the DB Study Drug Completion 2 eCRF for the placebo subjects who continued in the DB Treatment Period will be included in the CSR listings and not summarized in tables. A table that lists reasons for discontinuation of study drug will be provided for women of childbearing potential who discontinued during the DB and OL Treatment Periods.

The number and percentage of screened subjects who screen failed and the reasons for screen failure (inclusion/exclusion criteria, withdrew consent, lost to follow-up, and/or other) will be summarized in a table. A CSR listing of reason for screen failure will be provided for all subjects who screen failed.

The number and percentage of subjects by treatment group for each Treatment Period, as applicable, will be summarized for:

- Subjects with interruptions of all study drugs for toxicity management;
- Subjects with any RBV (or placebo for RBV) dose modifications;
  - Subjects with RBV (or placebo for RBV) dose modification due to decrease in hemoglobin;
  - Subjects with RBV (or placebo for RBV) dose modification due to decrease in creatinine clearance;
  - Subjects with RBV (or placebo for RBV) dose modification due to other reasons;
- Subjects with any RBV (or placebo for RBV) dose modification to 0 mg (i.e., RBV interruption).

Reasons for study drug interruptions and RBV dose modifications will be presented in the CSR listings.
9.0 Study Drug Exposure and Compliance

9.1 Exposure

Study drug exposure will be summarized separately for the DB and OL Treatment Periods. The duration of exposure to study drug in the DB Treatment Period will be summarized for each treatment group and overall in the safety population and during the OL Treatment Period for the OL population. Duration of exposure is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day as follows:

- Exposure duration for the DB Treatment Period: last dose date of double-blind study drug – first dose date of double-blind study drug + 1 day;
- Exposure duration for the OL Treatment Period: last dose date of open-label study drug – first dose date of open-label study drug + 1 day.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented. Study drug duration also will be summarized with frequencies and percentages using the following categories: 1 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days, 61 to 75 days, and > 75 days.

Exposure duration in the DB Treatment Period for all Arm B subjects will be calculated using the latest end date of study drug regimen for the DB Treatment Period.

9.2 Compliance

At each protocol-specified visit during the DB and OL Treatment Periods, the total number of capsules/tablets dispensed and returned is recorded for each type of study drug. The compliance for each study drug (ABT-450/r/ABT-267 or matching placebo, ABT-333 or matching placebo, and RBV or matching placebo) within the DB Treatment Period will be calculated as the percentage of capsules or tablets taken relative to the total capsules or tablets, respectively, expected to be taken. The total number of capsules/tablets prescribed will be equal to the total number of capsules/tablets that should
have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose – date of first dose + 1). Study drug interruptions due to an adverse event or other planned interruptions recorded on the eCRF will be subtracted from the duration. For compliance to RBV or matching placebo, RBV dose modifications due to adverse events, toxicity management, or weight changes as recorded on the RBV Dose Modifications eCRF will be used to modify the total number of capsules or tablets that should have been taken. A subject is considered to be compliant if the percentage is between 80% and 120%. Compliance will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum by treatment group. In addition, the percentage of compliant subjects will be calculated by treatment group for each study drug. Similar summaries of the compliance for each study drug (ABT-450/r/ABT-267, ABT-333, and RBV) within the OL Treatment Period will be provided.

In addition, RBV (or matching placebo) adherence will be assessed by using the Medication Event Monitoring Systems (MEMSTM, AARDEX Group Ltd., Switzerland) throughout the study. The MEMS data will be downloaded from the vendor's web system, and a report of compliance will be supplied to the Sponsor by AARDEX. The adherence summary statistics per subject provided in the report from AARDEX are those commonly used in the literature: taking adherence, correct adherence, and timing adherence.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

Treatment effects will be evaluated based on a 2-sided significance level of 0.050 (when rounded to three decimal places). Efficacy analyses will be performed on the ITT and OL populations as specified below. The primary (SVR$_{12}$) and secondary efficacy endpoints (excluding ALT normalization) will be performed on Arm A subjects in the
ITT population. The secondary endpoint of ALT normalization will be performed on all subjects (Arms A and B) in the ITT population with ALT > ULN at Baseline.

IL28b rs12979860 will be resulted as C/C, C/T, T/T, or Unable to Assign Genotype by the central laboratory. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT PCR) assay v2.0. For this assay, the lower limit of detection (LLOD) is 15 IU/mL and lower limit of quantification (LLOQ) is 25 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "< 25 IU/mL HCV RNA DETECTED" and those that are undetectable are reported as "HCV RNA NOT DETECTED" in the database.

The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 25 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 25 IU/mL HCV RNA DETECTED." HCV RNA ≥ LLOQ are all quantifiable values of 25 IU/mL or greater.

**Definitions for Efficacy Endpoints**

Note that a confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements ≥ LLOQ. During treatment, a confirmed quantifiable value is defined as any two consecutive HCV RNA values ≥ LLOQ, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement.

**Rebound** = confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 log10 IU/mL above nadir) at any time point during treatment.

**On-treatment virologic failure** = Rebound or failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) with at least 6 weeks (defined as study drug duration ≥ 36 days) of treatment.
**RVR** (rapid virologic response) = HCV RNA < LLOQ in the Week 4 window.

**EOTR** (end of treatment response) = HCV RNA < LLOQ in the Week 12 window.

**SVR\textsubscript{4}** = HCV RNA < LLOQ in the SVR\textsubscript{4} window (4 weeks after the last actual dose of active study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

**SVR\textsubscript{12}** = HCV RNA < LLOQ in the SVR\textsubscript{12} window (12 weeks after the last actual dose of active study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

**SVR\textsubscript{12planned}** = HCV RNA < LLOQ in the SVR\textsubscript{12planned} window (12 weeks after the last planned dose of active study drug [i.e., Week 24]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

**SVR\textsubscript{24}** = HCV RNA < LLOQ in the SVR\textsubscript{24} window (24 weeks after the last actual dose of active study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

**SVR\textsubscript{24planned}** = HCV RNA < LLOQ in the SVR\textsubscript{24planned} window (24 weeks after the last planned dose of active study drug [i.e., Week 36]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

**ALT normalization** = Final ALT ≤ ULN in the Treatment Period for subjects with ALT > ULN at Baseline.

**Relapse\textsubscript{4}** = confirmed HCV RNA ≥ LLOQ between end of treatment and 4 weeks after last actual dose of active study drug (up to and including the SVR\textsubscript{4} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as a study drug duration ≥ 77 days.

**Relapse\textsubscript{12}** = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR\textsubscript{12} assessment
time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as a study drug duration ≥ 77 days.

**Relapse** = confirmed HCV RNA ≥ LLOQ between end of treatment and up to and including the last HCV RNA measurement collected in the PT Period for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as a study drug duration ≥ 77 days.

**Relapse** = confirmed HCV RNA ≥ LLOQ within the SVR window for a subject who achieved SVR and has HCV RNA data available in the SVR window.

**Relapse** = confirmed HCV RNA ≥ LLOQ at any time after the SVR assessment time point for a subject who achieved SVR and has post-SVR HCV RNA data available.

If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation). Relapse analyses will exclude subjects who do not have any post-treatment HCV RNA values.

**Reasons for SVR Non-Response**

Subjects who do not achieve SVR (SVR non-responders) will be categorized as having:

1. On-treatment virologic failure (see **On-treatment virologic failure** definition);
2. Relapse (defined according to the **Relapse** definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR non-responder who prematurely discontinued study drug (duration < 77 days) and did not meet the **On-treatment virologic failure** definition);
4. Missing follow-up data in the SVR\(_{12}\) window [defined as any subject who completed study drug without data in the SVR\(_{12}\) window after applying the imputation rules and not meeting the definitions of (1), (2) or (3)];

5. Other [defined as any SVR\(_{12}\) non-responder not meeting the definitions of (1) – (4), such as a subject with a single quantifiable value within the SVR\(_{12}\) window followed by an undetectable value beyond the SVR\(_{12}\) window.]

**Reasons for SVR\(_{24}\) Non-Response**

Subjects who do not achieve SVR\(_{24}\) (SVR\(_{24}\) non-responders) will be categorized as having:

1. On-treatment virologic failure (see On-treatment virologic failure definition);

2. Relapse (defined according to the Relapse\(_{12}\) definition for subjects who complete treatment);

3. Relapsed after achieving SVR\(_{12}\) (see Relapse\(_{24}\) definition);

4. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR\(_{24}\) non-responder who prematurely discontinued study drug [duration < 77 days] and did not meet the On-treatment virologic failure Relapse\(_{12}\), or Relapse\(_{24}\) definitions);

5. Missing follow-up data in the SVR\(_{24}\) window (defined as any subject who completed study drug without data in the SVR\(_{24}\) window after applying the imputation rules and not meeting the definitions of (1), (2), (3) or (4)];

6. Other [defined as any SVR\(_{24}\) non-responder not meeting the definitions of (1) – (5)].
10.2 Justification of Primary and Secondary Endpoint Success Criteria

The success criteria for the primary and secondary efficacy endpoints were defined in Section 5.6.3 of the protocol and are restated here. Historical SVR rates, as reported in the telaprevir US Prescribing Information (USPI),\(^4\) for telaprevir plus pegIFN and RBV treatment in treatment-experienced subjects without cirrhosis from the REALIZE trial are presented in Table 9. The rates are based on a weighted average of relapsers, partial responders, and null responders, with the weighting reflecting the distribution of subjects expected to enroll in Study M13-098.

SVR rates for treatment-experienced subjects by subgenotype are provided in Table 10. Because data are not available in the package inserts on treatment-experienced subjects without cirrhosis by subgenotype, data from the REALIZE study were used, with an adjustment factor to account for the exclusion of subjects with cirrhosis in Study M13-098. Thus, to establish historical control rates relevant to Study M13-098, SVR rates in Table 10 were increased by 0.5%, 12.0%, and 9.2% for relapsers, partial responders, and null responders, respectively. A weighted average of the corresponding SVR rates was calculated to reflect the population expected to enroll in Study M13-098.

Table 9. Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced Subjects Without Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>REALIZE(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All T12/P48(^a)</td>
</tr>
<tr>
<td>Prior relapsers</td>
<td>198/229 (86)</td>
</tr>
<tr>
<td>Prior partial responders</td>
<td>46/65 (71)</td>
</tr>
<tr>
<td>Prior null responders</td>
<td>40/97 (41)</td>
</tr>
</tbody>
</table>

\(^a\) All GT1 treatment-experienced subjects without cirrhosis in the REALIZE study.
<table>
<thead>
<tr>
<th></th>
<th>REALIZE&lt;sup&gt;3,10&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT&lt;sub&gt;1a&lt;/sub&gt; (Pooled T12/PR48) n/N (%)</td>
<td>With Increase for Excluding Cirrhotics (%)</td>
<td>GT&lt;sub&gt;1b&lt;/sub&gt; (Pooled T12/PR48) n/N (%)</td>
<td>With Increase for Excluding Cirrhotics (%)</td>
</tr>
<tr>
<td>Relapsers</td>
<td>119/142 (83.8)</td>
<td>84.3</td>
<td>123/140 (87.9)</td>
<td>88.4</td>
</tr>
<tr>
<td>Partial responders</td>
<td>26/55 (47.3)</td>
<td>59.3</td>
<td>27/40 (67.5)</td>
<td>79.5</td>
</tr>
<tr>
<td>Null responders</td>
<td>24/88 (27.3)</td>
<td>36.5</td>
<td>22/59 (37.3)</td>
<td>46.5</td>
</tr>
</tbody>
</table>

GT<sub>1a</sub> = genotype 1a; GT<sub>1b</sub> = genotype 1b
For a regimen to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV therapy in pegIFN/RBV treatment-experienced HCV genotype 1-infected subjects without cirrhosis, the lower confidence bound for the SVR rate for that regimen must exceed the upper bound of the 95% confidence interval for telaprevir plus pegIFN and RBV therapy (i.e., 70%). To be considered non-inferior to the historical SVR rate for telaprevir plus pegIFN and RBV, a margin of 10.5% is used. The non-inferiority margin of 10.5% is based on the telaprevir ILLUMINATE study which used the same non-inferiority margin. Thus, non-inferiority to the historical SVR rate for telaprevir based therapy is obtained by showing that the lower confidence bound is greater than 60%. The superiority thresholds in genotype 1a and genotype 1b subjects are 65% and 77%, respectively, as described Table 10.

10.3 Handling of Multiplicity

In order to control the Type I error rate at 0.05, a fixed-sequence testing procedure will be used to proceed through the primary and secondary efficacy endpoints that are numbered and ordered below. That is, only if success has been demonstrated for the primary endpoint of non-inferiority of the SVR rate in Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV (1) will the testing continue to the second primary endpoint of superiority of the SVR rate in Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV (2). Similarly, only if success has been demonstrated for the second primary endpoint (2) will testing continue to the first secondary endpoint of ALT normalization (3). If success has been demonstrated for the first secondary endpoint of ALT normalization (3), then testing will continue to the next secondary endpoint (4). Similarly, testing will continue through the other secondary endpoints only if success was met for the preceding endpoint; otherwise, statistical testing will stop.
10.4 Primary Efficacy Analysis

The primary efficacy endpoints are:

1.  SVR\textsubscript{12}: Non-inferiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; lower confidence bound (LCB) of 95% confidence interval must exceed 60% to achieve non-inferiority.

2.  SVR\textsubscript{12}: Superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV; LCB must exceed 70% to achieve superiority.

The following hypotheses will be tested on subjects in the ITT population who were randomized to active study drug (Arm A). To test the hypothesis that the percentage of pegIFN/RBV treatment-experienced HCV genotype 1-infected subjects treated with ABT-450/r/ABT-267 + ABT-333 with RBV who achieve SVR\textsubscript{12} is non-inferior or superior to the historical SVR rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage and 2-sided 95% CI of subjects with SVR\textsubscript{12} will be calculated using the simple proportion and variance, and the normal approximation to the binomial distribution will be used to estimate the confidence interval. The LCB must be greater than 60% in order for the regimen to be considered non-inferior, and the LCB must be greater than 70% in order for the regimen to be considered superior to the historical SVR rate in pegIFN/RBV treatment-experienced HCV genotype 1-infected subjects without cirrhosis treated with telaprevir plus pegIFN and RBV.

HCV RNA and SVR\textsubscript{12} will be imputed as described in Section 6.3.

10.5 Secondary Efficacy Analyses

The secondary efficacy endpoints included in the fixed-sequence testing procedure are:

3.  ALT normalization rate during treatment in Arm A compared to Arm B.

4.  SVR\textsubscript{12}: In GT1a subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must exceed 65%.
5. **SVR\textsubscript{12}:** In GT1b subjects, for superiority of Arm A to the historical rate for telaprevir plus pegIFN and RBV, the LCB must exceed 77%.

Other secondary endpoints not included in the fixed-sequence testing procedure are:

- The percentage of subjects in Arm A with on-treatment virologic failure during the DB Treatment Period (defined per *On-treatment virologic failure* definition);
- The percentage of subjects in Arm A with post-treatment relapse (defined per *Relapse\textsubscript{12}* definition as confirmed HCV RNA $\geq$ LLOQ between Final DB Treatment Visit and 12 weeks after the last dose of study drug among subjects completing treatment and with HCV RNA $< LLOQ$ at the Final DB Treatment Visit).

ALT normalization (Final ALT $\leq$ ULN in the DB Treatment Period) will be calculated for all subjects in the ITT population with ALT above the upper limit of normal (ULN) at baseline. To test the hypothesis that the percentage of subjects in the active arm with ALT normalization is greater than the percentage of subjects in the placebo arm with ALT normalization at the Final DB Visit, the treatment groups will be compared using Fisher's exact test. If superiority of the active arm is demonstrated with a $P$ value $\leq 0.05$, then the DAA combination regimen is considered a success for this endpoint. To test the hypothesis that the percentage of pegIFN/RBV treatment-experienced HCV genotype 1a subjects treated in Arm A who achieve SVR\textsubscript{12} is superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR\textsubscript{12} will be calculated with a 2-sided 95% CI calculated using the normal approximation to the binomial distribution. The LCB must be greater than 65% in order for the regimen to be a success for this endpoint. To test the hypothesis that the percentage of pegIFN/RBV treatment-experienced HCV genotype 1b subjects treated in Arm A who achieve SVR\textsubscript{12} is superior to the historical SVR rate in the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR\textsubscript{12} will be calculated with a 2-sided 95% CI calculated using the normal approximation.
approximation to the binomial distribution. The LCB must be greater than 77% in order for the regimen to be a success for this endpoint.

The percentage and 2-sided 95% confidence intervals using the normal approximation to the binomial distribution of the subjects with virologic failure during treatment and post-treatment relapse will be calculated with simple proportion and variance and summarized. These endpoints will not be part of the fixed-sequence testing procedure as no hypothesis is being tested.

10.6 Sensitivity Analyses for the Primary Efficacy Endpoint

10.6.1 Imputation Approaches

In addition to presenting the primary efficacy endpoint with HCV RNA and SVR\textsubscript{12} imputed as described in Section 6.3, SVR\textsubscript{12} will be presented using the following other methods to impute missing post-treatment virologic results:

1. Imputing any missing HCV RNA values in the SVR\textsubscript{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR\textsubscript{12} window;
2. Impute as described in Section 6.3 but exclude local laboratory HCV RNA data;
3. Impute as described in Section 6.3 but exclude the subjects who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" and "missing follow-up data in the PT Period."

For each of these, the simple percentage of subjects with SVR\textsubscript{12} will be presented along with a 2-sided 95% CI.

10.6.2 Assessment of Homogeneity Across Stratification Variables

Heterogeneity across the randomization stratification variables will be examined for the primary efficacy endpoint of SVR\textsubscript{12} in Arm A using the chi-square test of homogeneity. The six strata are: (1) prior null responder and HCV GT 1a, (2) prior partial responder and HCV GT 1a, (3) prior relapser and HCV GT 1a, (4) prior null responder and HCV GT
non-1a, (5) prior partial responder and HCV GT non-1a, (6) prior relapser and HCV GT non-1a.

A confidence interval based on a stratum-weighted variance will be calculated using the equations below. The variance of $p_s$ will be estimated by:

$$\text{Var}(p_s) = \sum_{h=1}^{H} w_h^2 \frac{p_h(1-p_h)}{n_h - 1}$$

and the 2-sided 95% confidence interval will be calculated as $p_s \pm z \sqrt{\text{Var}(p_s)}$, where $z$ is the 1-$\alpha$/2 point of the standard normal distribution. Note that $n$ represents the number of subjects in Arm A within the ITT population, $n_h$ represents the number of subjects in stratum $h$, $w_h$ will be estimated by $n_h/n$, $p_h =$ the proportion of subjects achieving SVR$_{12}$ in stratum $h$, and $p_s =$ the proportion of subjects with SVR$_{12}$ among $n$ subjects which can be defined as:

$$p_s = \sum_{h=1}^{H} W_h p_h$$

In addition, the number and percentage ($p_h$) of subjects achieving SVR$_{12}$ within each of the six stratum will be presented.

### 10.7 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized and analyzed as specified.

**Double-Blind Treatment Period**

The following analyses will be performed on subjects in the ITT population randomized to active study drug using data collected in the DB Treatment Period.
the percentage of subjects with RVR (HCV RNA < LLOQ at Week 4 of the DB Treatment Period);
the percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12 of the DB Treatment Period);
the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the DB Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
the number of subjects with virologic rebound at each protocol-specified visit in the DB Treatment Period;
the percentage of subjects who failed to suppress HCV RNA (never achieving HCV RNA < LLOQ) during the DB Treatment Period and received at least 6 weeks of treatment (active study drug duration ≥ 36 days);
time to suppression of HCV RNA (defined as the study day of the first occurrence of HCV RNA < LLOQ) during the DB Treatment Period.

Open-Label Treatment Period

The following analyses will be performed on the subjects who were randomized to placebo and received at least one dose of active, open-label study drug.

- the percentage of subjects with ALT normalization (Final ALT ≤ ULN in the OL Treatment Period for subjects with ALT > ULN at Baseline);
- the percentage of subjects with RVR (HCV RNA < LLOQ at Open-Label Week 4);
- the percentage of subjects with EOTR (HCV RNA < LLOQ at Open-Label Week 12);
- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the OL Treatment Period (as observed);
- the percentage of subjects with on-treatment virologic failure during the OL Treatment Period (defined per On-treatment virologic failure definition);
- the number of subjects with virologic rebound at each protocol-specified visit in the OL Treatment Period;
● the percentage of subjects who failed to suppress HCV RNA (never achieving HCV RNA < LLOQ) during the OL Treatment Period and received at least 6 weeks of treatment (active study drug duration ≥ 36 days);
● time to suppression of HCV RNA during the OL Treatment Period.

**Post-Treatment Period**

The following analyses will be performed separately on the subjects in the ITT population who were randomized to Arm A and on the subjects who were randomized to placebo (Arm B) and received at least one dose of active, open-label study drug (i.e., the OL Population).

● the percentage of subjects achieving SVR$_4$;
● the percentage of subjects in the OL population achieving SVR$_{12}$;
● the percentage of subjects in the OL population who relapsed, defined per Relapse$_{12}$ definition;
● the percentage of subjects achieving SVR$_{12}^{\text{planned}}$;
● the percentage of subjects achieving SVR$_{24}$;
● the percentage of subjects achieving SVR$_{24}^{\text{planned}}$;
● the percentage of subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit within the DB or OL Treatment Period, who subsequently relapse anytime post-treatment;
● the percentage of subjects who achieved SVR$_{24}$ who subsequently relapsed (Relapse$_{\text{late}}$);
● time to relapse at any time post-treatment (defined in text below with additional relapse analyses).

The percentage of subjects with RVR, EOTR, SVR$_4$, SVR$_{12}$, SVR$_{12}^{\text{planned}}$, SVR$_{24}$, and SVR$_{24}^{\text{planned}}$ will be calculated using the simple binomial proportion and variance where the normal approximation to the binomial distribution will be used to calculate 2-sided 95% confidence intervals; imputations for missing data will be performed as described in Section 6.3 for analyses of SVR, RVR, and EOTR where a missing response will be
imputed as a failure after performing the described imputation. All other endpoints will be presented using data as observed.

The number and percent of subjects who achieve SVR\(_{12}\) will be presented along with the number of subjects who do not achieve SVR\(_{12}\) by reason for non-response (defined in Section 10.1). The non-responders will be presented in a listing. For the final CSR, the number and percent of subjects who achieve SVR\(_{24}\) will be presented along with the number of subjects who do not achieve SVR\(_{24}\) by reason for non-response (defined in Section 10.0). The non-responders will be presented in a listing.

The number and percent of subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (active study drug duration \(\geq 36\) days) will be tabulated along with the subject numbers corresponding to the subjects who failed to suppress.

The number of subjects who rebound at anytime during treatment and within each protocol-specified visit (defined in Table 1 for the DB Treatment Period and in Table 2 for the OL Treatment Period) will be summarized along with a corresponding listing displaying the subject numbers at the first occurrence of rebound.

The number of completers (defined as study drug duration \(\geq 77\) days) with final on treatment HCV RNA < LLOQ who relapse within the SVR\(_4\) window, within the SVR\(_{12}\) window, within the SVR\(_{24}\) window (defined in Table 3), after the SVR\(_{24}\) window (study drug end day > 210), and anytime post-treatment (study drug end day \(\geq 3\)) will be summarized along with a corresponding listing displaying the first occurrence of relapse. A similar table and listing will be provided of Preterm Relapses for subjects who do not complete treatment (defined as study drug duration < 77 days) with HCV RNA < LLOQ at Final Treatment Visit.

From HCV RNA levels, the time to relapse post-treatment will be calculated for each subject treated with active study drug (double-blind or open-label active) and displayed graphically using a Kaplan-Meier (KM) curve. Separate KM curves will be used to display relapse data for subjects in the ITT population randomized to active study drug
and subjects in the OL population. For time to relapse analyses, time to event will be measured as the number of days from the last dose of active study drug to event or censoring time. The time of relapse post-treatment is defined as the first of two consecutive HCV RNA values ≥ LLOQ between the end of the appropriate (DB or OL) treatment period and end of the PT Period amongst subjects who completed study drug with HCV RNA < LLOQ at the Final Treatment Visit. Subjects who do not relapse will be censored at the date corresponding to the last available HCV RNA value within the PT Period. Time to relapse will be performed only for subjects with HCV RNA < LLOQ at Final Treatment Visit who completed study drug, defined as a study drug duration ≥ 77 days.

The time to suppression on treatment will be calculated for each subject treated with active study drug (double-blind or open-label active) and displayed graphically using a KM curve. Separate KM curves will be used to display time to suppression data for subjects in the ITT population randomized to active study drug and subjects in the OL population. For time to suppression analyses, time to event will be measured as the number of days from the first dose of active study drug to event or censoring time. The time of suppression is defined as the first occurrence of an HCV RNA value < LLOQ during a Treatment Period. Subjects who do not suppress will be censored at the date of the last HCV RNA value within a Treatment Period.

RVR, EOTR, and SVR also will be presented using the LLOD instead of LLOQ to define the endpoint; missing data will be imputed as described in Section 6.3, excluding data from the local laboratory. In these summaries, the number and percentage of subjects meeting each endpoint will be tabulated.

The concordance between SVR₄ and SVR₁₂ will be assessed by the agreement between SVR₄ and SVR₁₂ and by the positive predictive value (PPV) and negative predictive value (NPV) of SVR₄ on SVR₁₂. The agreement between SVR₄ and SVR₁₂ is a percentage defined as the number of subjects achieving both SVR₄ and SVR₁₂ and the number of subjects not achieving both SVR₄ and SVR₁₂ out of all subjects in the ITT population. The PPV of SVR₄ on SVR₁₂ is the proportion of subjects who achieve SVR₄ and SVR₁₂.
out of all subjects who achieved SVR$_4$. The NPV of SVR$_4$ on SVR$_{12}$ is the proportion of subjects who do not achieve SVR$_4$ and SVR$_{12}$ out of all subjects who did not achieve SVR$_4$. Similarly, the concordance between SVR$_{12}$ and SVR$_{24}$ will be assessed by the PPV and NPV of SVR$_{12}$ on SVR$_{24}$ and by the agreement between SVR$_{12}$ and SVR$_{24}$ and summarized in the final CSR.

10.8 Resistance Analyses

If possible, subjects treated with active study drug during the DB Treatment Period who do not achieve SVR$_{12}$ will have resistance testing conducted if (1) they have on-treatment rebound; (2) if they have post-treatment relapse, with a study drug duration $\geq$ 77 days; or (3) if they have at least 6 weeks of treatment and fail to suppress by Week 6 (i.e., meet virologic stopping criteria). If possible, subjects treated with active study drug in the OL Treatment Period will have resistance testing conducted if (1) they have on-treatment rebound; or (2) if they have at least 6 weeks of treatment and fail to suppress by Week 6 (i.e., meet virologic stopping criteria). Subjects meeting one of these criteria will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV subgenotype, IL28B genotype, reason for SVR$_{12}$ non-response, time point(s) sequenced as closest to time of VF, and HCV RNA value at the VF time point(s) will be produced for these subjects. In addition, all listings described below will display HCV subgenotype and reason for SVR$_{12}$ non-response in the subject identifier for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA $\leq$ 1000 IU/mL).

Subjects treated with active study drug during the DB Treatment Period who do not achieve SVR$_{12}$ or treated with active drug in the OL Treatment Period who do not meet the above criteria for the PVF population (e.g., those with less than 6 weeks of therapy who failed to suppress), but have a time point with HCV RNA $\geq$ 1000 IU/mL after treatment discontinuation, will have the sample at that time point and the corresponding baseline sample sequenced. For subjects who are lost to follow-up with less than 6 weeks of therapy while not virally suppressed (e.g., HCV RNA never $<$ LLOQ or have increase
in viral load post nadir), the sample at the latest available time point with HCV RNA $\geq 1000\ \text{IU/mL}$ and the corresponding baseline sample will be sequenced. A listing of all subjects not in the PVF population with post-baseline sequencing available will be created that is similar to the listing of subjects in the PVF population with post-baseline sequencing available.

Only samples with an HCV RNA level of $\geq 1000\ \text{IU/mL}$ will undergo sequence or phenotype analysis in order to allow accurate assessment of products of amplification. Therefore if the HCV RNA level at the time of virologic failure (VF) is $< 1000\ \text{IU/mL}$, the sample closest in time after the failure with an HCV RNA level $\geq 1000\ \text{IU/mL}$ will be used if available. Clonal sequencing of a given target will be performed only if no variants are detected at signature resistance-associated amino acid positions by population sequencing in that sample. In addition, clonal sequencing may be performed if there is a complex mixture of amino acids at one or more signature resistance-associated position that cannot be resolved by population sequencing. Neither clonal sequencing nor phenotype analysis will be included in the primary CSR.

Baseline samples will be sequenced by population sequencing as described above. For each subject in the PVF population, at least two SVR$_{12}$-achieving subjects will be matched to the extent possible by HCV subgenotype, baseline HCV RNA level, and IL28B genotype. Baseline samples from these matched SVR$_{12}$-achieving subjects will also be sequenced by population sequencing.

The regions of interest for population sequencing from all evaluated time points in this study are those encoding complete NS3/4A, NS5A, and NS5B, while for clonal sequencing they are those encoding NS3 amino acids 1 – 181, NS5A amino acids 1 – 215, and NS5B amino acids 300 – 591. The regions encoding NS3 1-357, NS5A 1-215, and NS5B 300-591 will be sequenced for analysis of baseline samples from the matched set that will include at least 2 SVR-achieving subjects for every 1 PVF subject. For phenotyping, the regions of interest are those encoding NS3 amino acids 1 – 251, full length NS5A, and full length NS5B. The prototypic reference sequence used for analysis will be H77 for genotype 1a or Con1 for genotype 1b.
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, 56, 155, 156, and 168 in NS3 for genotype 1a; 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. Although resistance-associated amino acid variants have not been identified in NS3 at position 80 for ABT-450, it will be included in the list of signature positions due to the impact of variants at this position on resistance for other NS3 protease inhibitors. In addition, the impact of the T390I and F415Y variants in NS5B will be examined for their impact on treatment outcome in subjects who receive RBV. The final list of amino acid positions where resistance-associated variants have been identified will be included in the CSR.

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant (by population sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A or NS5B).
- Post-baseline variant by population sequencing: an amino acid variant in a post-baseline time point sample that was not detected at baseline in the subject and is detectable by population sequencing.
- Post-baseline variant by clonal sequencing: a variant at a signature resistance-associated amino acid position that was not present in a subject by population sequencing at baseline that is detected in a post-baseline sample from that subject by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).
- Emerged variant by population sequencing: a post-baseline variant that is observed in 2 or more subjects of the same subgenotype by population sequencing.
● Emerged variant by clonal sequencing: a post-baseline variant that is detected by clonal sequencing in \( \geq 20\% \) of the clones in post-baseline samples from 2 or more subjects of the same subgenotype that was not detected at baseline by population sequencing in those subjects.

● Linked variant by population sequencing: 2 or more signature resistance-associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at either position.

● Linked variant by clonal sequencing: at least 2 clones from a given sample containing the same 2 or more signature resistance-associated amino acid variants by clonal sequencing.

The following data will be available in the primary CSR:

For those subjects in the PVF population, 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 NS5B).

In order to assess the effect of baseline variants on treatment response, the number and percentage of subjects with baseline variants at signature resistance-associated amino acid positions for each DAA target will be compared between the group of subjects in the PVF population and the matched group of subjects who achieved SVR\(_{12}\). The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A or NS5B). The number and percentage of subjects with each baseline variant at a signature resistance-associated amino acid position within each target by HCV subgenotype will be calculated by response (PVF population or SVR\(_{12}\)) for each regimen. For each HCV subgenotype and regimen, a comparison of the percentage of subjects with each resistance-associated variant will be made between the PVF population and SVR\(_{12}\) subjects using Fisher's exact test.
The following analyses will be performed on the samples from subjects who are in the PVF population and have post-baseline resistance data available. These data will be available in the primary CSR:

The HCV amino acid sequence as determined by population sequencing at the time of VF or the sample closest in time after VF with an HCV RNA level of ≥ 1000 IU/mL will be compared to the baseline and appropriate prototypic reference amino acid sequences. A listing by subject and time point of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequences will be provided across all DAA targets (NS3, NS5A and NS5B).

The number and percentage of subjects with emerged variants by population sequencing, by amino acid position and variant within a DAA target at the time of VF compared to baseline will be summarized, along with the number of subjects within a DAA target and overall. The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A, or NS5B) and will list the subject numbers of subjects with each variant.

In addition, a listing by subject and time point of all post-baseline variants (by population sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided.

Linkage between emerged or signature variants by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing for each target will be provided.
The following analyses will be performed on the samples from subjects who are in the not in the PVF population but have post-baseline sequence data available. These data will be available in the primary CSR:

The number and percentage of subjects with emerged variants by population sequencing, by amino acid position and variant within a DAA target compared to baseline will be summarized, along with the number of subjects within a DAA target and overall. The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A or NS5B) and will list the subject numbers of subjects with each variant.

The following data will be available in the final CSR:

Similar analyses as those described above will be performed for subjects treated in the DB Treatment period who experience VF after Post-Treatment Week 12, and for subjects treated in the OL Treatment Period who experience VF any time after treatment, and the analyses provided with the primary CSR will be updated. In addition, all clonal sequencing results will be reported in the final CSR.

For the subset of samples for which clonal sequencing is performed, listings by subject of post-baseline variants by clonal sequencing will be provided for each DAA target. Listings of emerged variants by clonal sequencing by subject, amino acid position and variant within a DAA target, and time point will be provided.

The number and percentage of subjects with emerged variants by clonal sequencing, by amino acid position and variant within a DAA target will be summarized, along with the number of subjects within a DAA target and overall. The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A or NS5B) and will list the subject numbers of subjects with each variant. Furthermore, listings of linked variants by clonal sequencing by subject, DAA target, and time point will be provided.
For all subjects who experience VF, the persistence of resistance-associated substitutions that emerged for each target (NS3, NS5A, and NS5B) will be assessed by population sequencing (with clonal sequencing performed if no resistance-associated variants are detected by population sequencing) at Post-Treatment Weeks 24 and 48. Listings by subject and time point of all post-baseline variants relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A and NS5B).

Additionally, the number and percentage of subjects in whom an emerged variant persisted at Post-Treatment Week 24 or 48 out of the total number of subjects with that emerged variant at the VF time point and at Post-Treatment Week 24 and/or Post-Treatment Week 48 will be summarized by HCV subgenotype, DAA target, and variant.

If resistance-associated variants are not detected by either population or clonal sequencing in a given target for a subject either at the time of failure or in a post-treatment sample, then that target will not be sequenced in subsequent samples from that subject.

If at the time of VF, no variants at known resistance-associated amino acid positions are detected by population or clonal sequencing, the target gene(s) from that sample as well as from the corresponding baseline sample will be introduced into the appropriate 1a or 1b reference strain replicon and assessed for phenotypic resistance. Thus, in the subset of subjects who have EC$_{50}$ levels at baseline and at least one post-baseline time point, the fold change in EC$_{50}$ level to both baseline and the appropriate prototypic standard will be calculated and provided in a listing of these subjects.

Resistance datasets will be submitted to the Agency according to the revised template supplied on 25 February 2013 (courtesy copy of Draft Guidance, "Attachment to Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency; Guidance for Submitting HCV Resistance Data").
10.9 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): HCVPRO, EQ-5D-5L, and SF-36 version 2 (SF-36v2). PROs will be collected at protocol-specified visits in the DB Treatment Period for all randomized subjects and in the PT Period for subjects randomized to active drug (Arm A). The HCVPRO, EQ-5D-5L, and SF-36v2 will be collected at Baseline, Weeks 4, 8 and 12, and Post-Treatment Weeks 4, 12, 24 and 48, or upon premature discontinuation of the Treatment or Post-Treatment Periods. Missing data for each instrument will be handled as described in Section 6.3.

The following exploratory analyses of PROs will be performed:

- mean change from baseline in HCVPRO total score to each applicable post-baseline time point;
- mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;
- mean change from baseline to each applicable post-baseline time point in the SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) measures;
- continuous plots of the percent change from Baseline to Final DB Treatment Visit in the SF-36v2 PCS and MCS, HCVPRO total score, EQ-5D-5L health index score and VAS on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis;
- percentage of subjects without a decrease from Baseline to Final DB Treatment Visit in the SF-36v2 PCS and MCS that is greater than or equal to the minimally important difference (MID) of five points;
- percentage of subjects without a decrease from Baseline to Final DB Treatment Visit in the EQ-5D-5L health index score that is greater than or equal to its study-defined MID;
- percentage of subjects without a decrease from Baseline to Final DB Treatment Visit in the HCVPRO total score that is greater than or equal to its study-defined MID.
The HCVPRO consists of 16 items with 5 response choices (1, 2, 3, 4, or 5) that are recoded to 0, 1, 2, 3, or 4, respectively, when deriving the total score. The total score is the sum of all 16 items and is converted to a score between 0 and 100 by

\[
    \text{Scaled Score} = \frac{\text{Sum} \times 100}{64}
\]

Subject's responses to the self-administered HCVPRO instrument will be assessed for the total score. Subject's responses to the EQ-5D-5L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-5L states will be converted into a single preference-weighted health utility index score by applying country-specific weights (if available) or US weights (if not available).\(^1\)\(^2\) The VAS score will be measured separately. The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (MCS) and physical (PCS) health status. The score for each of the 8 domains ranges from 0 to 100 and will be normalized according to the user manual.\(^3\) The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a SD of 10. The two summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, score for any item with multiple responses will be set to "missing." Missing item responses will be handled as described in Section 6.3. Subject's responses to the SF-36v2 will be summarized for the PCS and MCS measures.

Summary statistics (n, mean, SD, median, minimum and maximum) for the mean change from baseline to each applicable visit by treatment group will be provided for the HCVPRO total score, EQ-5D-5L index and VAS scores, and the SF-36v2 PCS and MCS scores.

For HCVPRO total score, SF-36v2 PCS and MCS scores, and EQ-5D-5L health index and VAS scores, the following ANCOVA analyses will be performed. An ANCOVA analysis will be performed on the change from baseline to Final DB Treatment Visit with treatment group as a factor and baseline score as a covariate. The between group mean change from baseline with the 95% confidence interval, standard error, and \(P\) value will be presented.
An MID of $-5$ will be used for the change from Baseline to Final DB Treatment Visit in the SF-36v2 PCS and MCS. The percentage of subjects in each treatment group with a change from Baseline to Final DB Treatment Visit $>-5$ will be presented along with 95% confidence intervals and compared between treatment groups using Fisher's exact test.

To calculate the MID for HCVPRO and EQ-5D-5L, a receiver operating characteristics (ROC) analysis will be performed from PROC LOGISTIC with each of the following anchors for the change from Baseline to Final DB Treatment Visit in the HCVPRO total score and in the EQ-5D-5L health index score:

- Change from Baseline to Final DB Treatment Visit in SF-36 PCS $>-5$ (yes/no);
- Change from Baseline to Final DB Treatment Visit in SF-36 MCS $>-5$ (yes/no).

Change from Baseline to Final is defined as the Final Score – Baseline Score within the DB Treatment Period for all subjects in the ITT population. The point on the ROC curve that is closest to the upper left-hand corner $(0,1)$ yields the optimal sensitivity and specificity. This point will be determined by minimizing $(1 – sensitivity)^2 + (1 – specificity)^2$. The cutoff point corresponding to the sensitivity and specificity values closest to $(0,1)$ for each anchor will be averaged and used as the MID. The MID determined for the HCVPRO total score will be used for the change from baseline to Final DB Treatment Visit in HCVPRO total score. The MID determined for the EQ-5D-5L health index score will be used for the change from baseline to Final DB Treatment Visit in EQ-5D-5L health index score. The percentage of subjects in each treatment group with a change from Baseline to Final DB Treatment Visit $>$ MID will be presented along with 95% confidence intervals and compared between treatment groups using Fisher's exact test. If, for example, the MID is determined to be $-10$ for the HCVPRO total score, then the responders are subjects with an improvement from baseline and subjects with decreases between zero and 10 points in the change from Baseline to Final DB Treatment Visit in HCVPRO total score.
10.10 Efficacy Subgroup Analysis

To evaluate the impact of various characteristics on treatment effect, analyses will be performed for the primary efficacy variable of SVR$_{12}$ using the following subgroups:

- HCV genotype 1 subtype (1a, 1b, or other);
- Type of response to previous pegIFN/RBV treatment (null responder [definition 1 or 2], partial responder, or relapser);
- IL28B genotype (CC or non-CC) and (CC, CT or TT);
- Sex (male or female);
- Age (< 55 or ≥ 55 years) and (< 65 or ≥ 65 years);
- Birth year (< 1945, 1945 to 1965, > 1965);
- Race (Black or non-black);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Geographic Region (North America, Europe, or Australia) and Country (as appropriate);
- BMI (< 30 or ≥ 30 kg/m$^2$);
- Baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL);
- Baseline IP-10 (< 600 or ≥ 600 ng/L);
- Baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L$^2$);
- Baseline fibrosis stage (F0 – F1, F2, or ≥ F3);
- History of Diabetes (yes/no);
- History of Depression or Bipolar Disorder (yes/no);
- History of Bleeding Disorders (yes/no);
- Former injection drug user (yes/no);
- RBV dose modifications (yes/no).

The number and percentage of subjects achieving SVR$_{12}$ within each subgroup will be provided for all subgroups. If there are 10 or more subjects within the subgroup level (e.g., for sex, 10 or more females and 10 or more males), then 2-sided 95% confidence intervals will be presented and calculated using the normal approximation to the binomial
distribution. For each subgroup with a confidence interval, the lower confidence bound will be compared to 60%.

A logistic regression model will be used to explore the associations between each of the subgroup variables and SVR\textsubscript{12} by fitting a logistic regression model on all subjects in the ITT population randomized to active study drug. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR\textsubscript{12}, with \( P \) values of 0.10 to enter and remain in the model.

The number and percent of subjects who relapse or experience on-treatment virologic failure will be summarized by type of response to previous pegIFN/RBV treatment.

11.0 Safety Analysis

11.1 General Considerations

All subjects who receive at least one dose of double-blind study drug will be included in the safety analyses. For safety analyses, data from the active and placebo treatment arms during the DB Treatment Period will be summarized, and comparisons between Arms A and B will be performed. The data from the OL Treatment Period and PT Period will also be summarized, but no comparisons will be performed.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study drug as defined in Section 11.2.1.1. Events where the onset date is the same as the study drug start date are assumed to be treatment emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment emergent, unless there is other evidence that confirms that the event was not treatment emergent (e.g., the event end date was prior to the study drug start date).
11.2.1.1 Definitions of Treatment-Emergent Adverse Events

Double-Blind Treatment Period

For the active arm (Arm A), treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of active study drug through 30 days after the last dose of active study drug. For the placebo arm (Arm B), treatment-emergent events are defined as any event that begins or worsens in severity after initiation of placebo through 30 days after the last dose of placebo and prior to OL Day 1 (if applicable).

Open-Label Treatment Period

For subjects in the OL Population, treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of open-label study drug through 30 days after the last dose of open-label study drug.

11.2.1.2 Tabulations of Treatment-Emergent Adverse Events

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

Adverse events will be presented for the following treatment groups: (1) double-blind active (Arm A), (2) double-blind placebo (Arm B), and (3) open-label active (Arm B). Treatment group comparisons refer to comparisons of events between double-blind active and double-blind placebo during the DB Treatment Period of the study.
Adverse Event Overview

An overview of adverse events will be presented for each treatment group consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
- Severe treatment-emergent adverse events;
- Serious treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events leading to RBV dose modifications;
- Treatment-emergent adverse events leading to death;
- Deaths.

For each adverse event presented in the overview, comparisons of the percentage of subjects experiencing an adverse event between the active and placebo arms (DB Treatment Period) will be performed using Fisher's exact tests. Only $P$ values $≤ 0.100$ when rounded to three digits will be presented. Separate AE overviews will be provided for the DB and OL Treatment Periods.

Adverse Event by SOC and PT

The following summaries of adverse events will be generated:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
● Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
● Serious treatment-emergent adverse events;
● Moderate or severe treatment-emergent adverse events;
● Severe treatment-emergent adverse events;
● Grade 3 or 4 (see definition below) treatment-emergent adverse events;
● Treatment-emergent adverse events leading to discontinuation of study drug;
● Treatment-emergent adverse events leading to interruption of study drug;
● Treatment-emergent adverse events leading to RBV dose modifications;
● Treatment-emergent adverse events leading to death;
● Treatment-emergent adverse events leading to concomitant medication use (events with other action taken of "concomitant medication prescribed").

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each treatment group. Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one adverse event will be counted only once in the overall total.

The percentage of subjects experiencing treatment-emergent adverse events, treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (DAA or RBV), moderate or severe treatment-emergent adverse events, and severe treatment-emergent adverse events will be compared between the active and placebo arms (DB Treatment Period) using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

A listing by treatment group of treatment-emergent adverse events grouped by body system and preferred term with subject numbers will be created.
Adverse Event by PT

The number and percentage of subject experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency in the active treatment group. Similar summaries will be provided for moderate to severe treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs. Percentages will be compared between the active and placebo arms (DB Treatment Period) using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

Adverse Events of Special Interest

Specific treatment-emergent adverse events of special interest, which may be searched using Standardized or Company MedDRA Queries, will be summarized and include hepatic-related events, bilirubin-related events, rash-related events, and anemia. The search criteria for each of the adverse events of interest are as follows:

- Hepatic-related events
  SMQ "Drug related hepatic disorders – severe events only" (broad search)
- Bilirubin-related events
  SMQ "Cholestasis and jaundice of hepatic origin" (broad search)
- Drug Induced Rashes
  CMQ "Drug induced rash" (Version 16.0.2 or later)
- Severe Cutaneous Reactions
  SMQ "Severe cutaneous adverse reactions" (narrow search)
- Anemia
  SMQ "Haematopoietic erythropenia" (broad search) plus the following preferred terms:
    - Haemolytic anaemia,
    - Coombs negative haemolytic anaemia,
    - Coombs positive haemolytic anaemia.
For each adverse event of interest (hepatic, bilirubin, drug induced rash, severe cutaneous reaction, and anemia), the number and percentage of subjects experiencing at least one treatment-emergent adverse event in the search for the event of interest will be presented for each treatment arm overall and by SOC and PT.

A listing of treatment-emergent adverse events for subjects meeting the search criterion will be provided for each adverse event of special interest.

**Adverse Events by Maximum Severity**

Treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs will be summarized by maximum severity of each preferred term. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

**Adverse Events by Maximum Severity Grade Level**

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each preferred term will be assigned a grade level based on severity and seriousness, adapted from the Division of AIDS (DAIDS) table for grading severity of adverse events. All serious adverse events will be categorized as Grade 4. Nonserious adverse events categorized by the investigators as mild, moderate, or severe will be categorized as Grade 1, Grade 2, or Grade 3, respectively. If a subject has a nonserious adverse event with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Grade 3" category. Similarly, if a subject has an adverse event with unknown seriousness, then the subject will be counted in the
severity grade level category of "unknown" unless the subject has another occurrence of the same adverse event that is marked serious. In this case, the subject will be counted under the "Grade 4" category.

**Adverse Events by Maximum Relationship**

Treatment-emergent adverse events also will be summarized by maximum relationship of each preferred term to DAAs or RBV, as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

**11.2.2 Listing of Adverse Events**

Listings of all serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study), treatment-emergent serious adverse events, treatment-emergent adverse events leading to death, treatment-emergent adverse events leading to discontinuation of study drug, treatment-emergent adverse events leading to RBV dose modifications, treatment-emergent adverse events leading to study drug interruptions, and treatment-emergent adverse events of special interest will be provided.

**11.3 Analysis of Laboratory Data**

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

**11.3.1 Variables and Criteria Defining Abnormality**

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands, lymphocytes, monocytes, basophils,
eosinophils, platelet count, absolute neutrophil count (ANC), reticulocyte count, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, gamma glutamyl transferase (GGT), and creatinine clearance (Cockcroft-Gault calculation), calculation of estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation as defined below.

Urinalysis variables include: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen, bilirubin, leukocyte esterase, albumin, and microscopic (reflexly performed if other variables are abnormal).

Additional variables include: total insulin and IP-10.

The following calculation is used by the central lab for eGFR by MDRD, where serum creatinine is measured in mg/dL and age is measured in years:

\[
GFR \ (mL/min/1.73 \text{ m}^2) = 175 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times 1.212 \times 0.742 \ (\text{if Female})
\]

The Criteria for Potentially Clinically Significant (PCS) Laboratory Findings are described in Table 11 and Table 12.
### Table 11. Criteria for Potentially Clinically Significant Hematology Values

<table>
<thead>
<tr>
<th>Test/units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 4.9</td>
<td></td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&lt; 8.0</td>
<td></td>
</tr>
<tr>
<td>(g/L)</td>
<td>&lt; 80</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td>&lt; 50,000</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 50 × 10$^9$</td>
<td></td>
</tr>
<tr>
<td><strong>White Blood Cell Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td>&lt; 2000</td>
<td>&gt; 20,000</td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 2.0 × 10$^9$</td>
<td>&gt; 20 × 10$^9$</td>
</tr>
<tr>
<td><strong>Absolute Neutrophil Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td>&lt; 1000</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 1 × 10$^9$</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphocyte Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td>&lt; 500</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 0.5 × 10$^9$</td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophil Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm$^3$)</td>
<td>&gt; 5000</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&gt; 5 × 10$^9$</td>
<td></td>
</tr>
<tr>
<td><strong>aPTT</strong></td>
<td>&gt; 2 × ULN</td>
<td></td>
</tr>
<tr>
<td><strong>International Normalized Ratio</strong></td>
<td></td>
<td>&gt; 2 × ULN</td>
</tr>
</tbody>
</table>

Note: A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.
<table>
<thead>
<tr>
<th>Test/units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td></td>
<td>&gt; 5 × ULN and ≥ 2 × baseline</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td></td>
<td>&gt; 5 × ULN and ≥ 2 × baseline</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td></td>
<td>&gt; 1.5 × ULN</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dL)</td>
<td></td>
<td>≥ 2.0 × ULN</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mcmol/L)</td>
<td></td>
<td>≥ 132.605</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>&lt; 50</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td>&gt; 5 × ULN</td>
</tr>
<tr>
<td>Uric Acid</td>
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<td></td>
</tr>
<tr>
<td>(mcmol/L)</td>
<td></td>
<td>&gt; 713.817</td>
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<tr>
<td>(mg/dL)</td>
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<td>&gt; 12.0</td>
</tr>
<tr>
<td>Phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 0.6</td>
<td></td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt; 2.0</td>
<td></td>
</tr>
<tr>
<td>Calcium, Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 1.75</td>
<td>&gt; 3.1</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt; 7.0</td>
<td>&gt; 12.5</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>&lt; 130</td>
<td>&gt; 155</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>&lt; 3.0</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 0.4</td>
<td>&gt; 1.23</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt; 0.9</td>
<td>&gt; 3.0</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 2.2</td>
<td>&gt; 13.9</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt; 40</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g/L)</td>
<td>&lt; 20</td>
<td></td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&lt; 2</td>
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</table>
Table 12. Criteria for Potentially Clinically Significant Chemistry Values (Continued)

<table>
<thead>
<tr>
<th>Test/units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g/L)</td>
<td>&lt; 50</td>
<td>--</td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&lt; 5.0</td>
<td>--</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>--</td>
<td>&gt; 10.34</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>--</td>
<td>&gt; 400</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>--</td>
<td>&gt; 5.7</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>--</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

Note: A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.

11.3.2 Statistical Methods

Clinical laboratory tests will be summarized by treatment group at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of double-blind study drug. This same baseline value will be used for all change from baseline tables in the DB, OL, and Post-Treatment Periods.

Mean changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized for each protocol-specified laboratory parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, and median. The differences between the active and placebo arms in the DB Treatment Period will be analyzed using an ANOVA model with treatment group as the factor. The between group mean change from baseline with the 95% confidence interval, standard error, and $P$ value will be presented. Separate tables will be used to present the mean change from baseline to DB Treatment Period visits (Arms A and B), OL Treatment Period visits (Arm B), and Post-Treatment Period visits (Arms A and B).
During the DB and OL Treatment periods, laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline to minimum value, maximum value, and final values during the DB and OL Treatment periods will be created. The shift tables will cross tabulate the frequency of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

The number and percentage of subjects with post-baseline values during the Treatment Periods meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 11 and Table 12) will be summarized by treatment group. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. This will be performed separately for the DB and OL Treatment Periods. Comparisons will be performed between the active and placebo arms in the DB Treatment Period of the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented. A separate listing will be provided that presents all of the lab values for the subjects meeting PCS criteria during treatment.

For hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin, the number and percentage of subjects in each treatment group with a maximum CTCAE Grade of 1, 2, 3, or 4 (see definitions in Table 13) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. This will be performed separately for the DB and OL Treatment Periods. All LFT tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of subjects with at least a Grade 2 laboratory abnormality. Comparisons of the percentage of subjects experiencing a value meeting at least Grade 2 and at least Grade 3 (as reported in the summary row[s]) between the active and placebo arms in the DB Treatment Period will be performed using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented. Accompanying listings of all ALT, AST, total, indirect and
direct bilirubin, and alkaline phosphatase will be created for any subject who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A listing of hematology results will be provided for subjects with hemoglobin abnormalities.

Table 13. Definitions of CTCAE Grades 1, 2, 3, and 4

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
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<tr>
<td>AST/SGOT</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>&gt; ULN – 2.5 × ULN</td>
<td>&gt; 2.5 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3 × ULN</td>
<td>&gt; 3 – 10 × ULN</td>
<td>&gt; 10 × ULN</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>&lt; LLN – 100 g/L</td>
<td>&lt; 100 – 80 g/L</td>
<td>&lt; 80 – 65 g/L</td>
<td>&lt; 65 g/L</td>
</tr>
</tbody>
</table>

The number and percentage of subjects in each treatment group meeting the following criteria will be summarized for each treatment period:

- ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN;
- ALT ≥ 3 × ULN and total bilirubin value < 2 × ULN;
- ALT > 5 × ULN (equivalent to Grade 3 or higher) and total bilirubin value < 2 × ULN;
- ALT < 3 × ULN and total bilirubin ≥ 2 × ULN.

A subject or event will be counted if the post-baseline laboratory values meet the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value). The maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above. For subjects meeting the ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN criterion during the Treatment Periods, a corresponding listing of all ALT, AST, alkaline phosphatase, and total, direct, and indirect bilirubin values will be provided.
11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

Vital sign variables are body temperature (oral), sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, and body weight.

The Criteria for Potentially Clinically Significant Vital Sign Findings are presented in Table 14.

Table 14. Criteria for Potentially Clinically Significant Vital Sign Values

<table>
<thead>
<tr>
<th>Test/Measurement</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline</td>
<td>≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline</td>
<td>≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline</td>
<td>≥ 120 bpm AND An increase of ≥ 15 bpm from baseline</td>
</tr>
<tr>
<td>Weight</td>
<td>A decrease of ≥ 15% from baseline</td>
<td>An increase of ≥ 15% from baseline</td>
</tr>
<tr>
<td>Temperature</td>
<td>--</td>
<td>&gt; 38.3°C AND An increase of ≥ 1.1°C from baseline</td>
</tr>
</tbody>
</table>

11.4.2 Statistical Methods

Vital signs will be summarized by treatment group (DB active and DB placebo) at each visit during the DB Treatment Period and separately for subjects treated in the OL Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of DB study drug. This same baseline value will be used for all change from baseline tables in the DB, OL, and Post-Treatment Periods.

Mean changes from baseline to each post-baseline visit, including applicable Post-Treatment visits, will be summarized for each vital sign parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, and median. The differences between the active and placebo arms in the DB Treatment Period will be analyzed using an ANOVA model with treatment group as the factor. The between group
mean change from baseline with the 95% confidence interval, standard error, and \( P \) value will be presented. Separate tables will be used to present the mean change from baseline to DB Treatment Period visits (Arms A and B), OL Treatment Period visits (Arm B), and Post-Treatment Period visits (Arms A and B).

The number and percentage of subjects with post-baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant Vital Signs values (Table 14) will be summarized by treatment group. A post-baseline value must be more extreme than the baseline value to be considered as a PCS finding. This will be performed separately for the DB and OL Treatment Periods. Comparisons of the percentage of subjects experiencing a value meeting the criteria between the active and placebo arms in the DB Treatment Period will be performed using Fisher's exact tests. Only \( P \) values \( \leq 0.100 \) when rounded to three digits will be presented. A separate listing will be provided that presents all of the vital sign values for the subjects meeting the PCS vital sign criteria during treatment.

### 12.0 Summary of Changes

The following summarizes the changes between the latest version of the protocol (Section 8.1 of Study M13-098 Protocol Amendment 3) and this SAP.

- **Definition of on-treatment virologic failure**
  - The definition in the protocol was "confirmed HCV RNA \( \geq \) LLOQ after HCV RNA \(<\) LLOQ during treatment or confirmed HCV RNA \( \geq \) LLOQ at the end of treatment." The definition in the SAP has been modified to "confirmed HCV RNA \( \geq \) LLOQ after HCV RNA \(<\) LLOQ during treatment, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements \( > 1 \log_{10} \text{IU/mL} \) above nadir) at any time point during treatment, or failure to suppress during treatment (all on-treatment values of HCV RNA \( \geq \) LLOQ) with at least 6 weeks (defined as study drug duration \( \geq 36 \) days) of treatment." Clarified the definition of "on-treatment virologic failure" to indicate that subjects who never demonstrate HCV RNA below the LLOQ and receive at least 6 weeks of treatment will be
included in the on-treatment virologic failure category, in addition to those with HCV RNA rebound. Subjects who never demonstrate HCV RNA < LLOQ but prematurely discontinue study drug after less than 6 weeks of treatment will not be considered virologic failures. The reason for the change is to ensure that the "on-treatment virologic failure" category does not capture patients whose duration of treatment was not sufficient to allow them to achieve HCV RNA < LLOQ.

- The resistance analysis section of the SAP has been updated to more accurately describe the analyses of the sequencing data.
- Definition of treatment-emergent adverse events for Arm B during the Double-Blind Treatment Period
  - The definition in the protocol was "any event that begins or worsens in severity after initiation of placebo through the last dose of placebo." The definition in the SAP has been modified to "any event that begins or worsens in severity after initiation of placebo through 30 days after the last dose of placebo and prior to OL Day 1 (if applicable)." Events that may occur prior to starting open-label active study drug but within 30 days of the last dose of placebo are now included in the summary of treatment-emergent adverse events.

13.0 References


## Document Approval

Study M13098 - Statistical Analysis Plan Version 1 30Sep2013 (E3 16.1.9)

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