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. Original statistical analysis plan (there were no amendments to the plan)
1.0 Title Page

Clinical Study Protocol M13-099

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

Abbott Investigational Product: ABT-450/r/ABT-267, ABT-333

Date: 21 August 2012

Development Phase: 3

Study Design: This is a randomized, open-label combination drug study.

EudraCT Number: 2012-003088-23

Investigator: Multicenter. Investigator information is on file at Abbott.

Sponsor: Abbott Laboratories (Abbott)*

Sponsor/Emergency Contact: Roger Trinh, MD, MPH

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.
## Synopsis

<table>
<thead>
<tr>
<th><strong>Abbott Laboratories</strong></th>
<th><strong>Protocol Number:</strong> M13-099</th>
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<tbody>
<tr>
<td><strong>Name of Study Drug:</strong></td>
<td><strong>Phase of Development:</strong> Phase 3</td>
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<tr>
<td>ABT-450, ritonavir, ABT-267, ABT-333</td>
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<tr>
<td><strong>Name of Active Ingredient:</strong></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,14,15,16a-tetradecahydrocyclopenta[e]pyrrolo[1,2-a][1,4]diazacyclopentadecane-14a(5H)-carboxamide hydrate</td>
<td></td>
</tr>
<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>
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<tr>
<td>ABT-267: Dimethyl [(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diyldi carbamoyl(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>
<tr>
<td><strong>Date of Protocol Synopsis:</strong></td>
<td>21 August 2012</td>
</tr>
<tr>
<td><strong>Protocol Title:</strong></td>
<td>A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)</td>
</tr>
<tr>
<td><strong>Objectives:</strong></td>
<td>The primary objectives of this study are to assess efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR&lt;sub&gt;12&lt;/sub&gt; (HCV ribonucleic acid (RNA) &lt; lower limit of quantification (LLOQ) 12 weeks following treatment) and safety of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with RBV for 12 or 24 weeks in HCV genotype 1-infected adults with compensated cirrhosis. 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 for the 12-week arm or at Week 24 for the 24-week arm) and compare SVR&lt;sub&gt;12&lt;/sub&gt; between the two arms.</td>
</tr>
<tr>
<td>Investigator:</td>
<td></td>
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<td>----</td>
<td></td>
</tr>
<tr>
<td>Multicenter trial: Investigator information is on file at Abbott.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Study Site:</th>
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<tr>
<td>Approximately 75 sites.</td>
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<tr>
<th>Study Population:</th>
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<tbody>
<tr>
<td>Adults age 18 to 70 years of age, inclusive with HCV genotype 1, treatment-naïve and previous pegIFN (pegylated-interferon alfa-2a or alfa-2b)/RBV treatment-experienced adults with compensated cirrhosis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Subjects to be Enrolled:</th>
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<tr>
<td>Approximately 300 subjects.</td>
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<tr>
<th>Methodology:</th>
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</table>
| This is a Phase 3, randomized, open-label, multicenter study evaluating the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin for 12 or 24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. 

The treatment arms are:

- **Arm A:** ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV* for 12 weeks
- **Arm B:** ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 24 weeks

* RBV will be administered weight-based 1000 – 1200 mg divided to twice daily.

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 300 subjects are enrolled at approximately 75 sites. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. Subjects will be stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B (Interleukin 28B) genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapsers) and by HCV subgenotype (1a versus non-1a). No more than 150 treatment-experienced subjects will be allowed to enroll. The combined number of prior relapsers and prior partial responders will limited to no more than 70.

This study will consist of a Treatment Period and a Post-Treatment (PT) Period. All subjects dosed with study drug who complete or prematurely discontinue study drug will be followed for 48 weeks in the Post-Treatment Period, to monitor safety, HCV RNA, the emergence and persistence of viral variants and assessment of PROs.

Visits will occur during the treatment period at Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12 for all subjects and at Weeks 16, 20, and 24 for subjects in the 24-week arm, and Post-Treatment Weeks 2, 4, 8, 12, 24, 36, and 48.

The safety data will be reviewed by the sponsor, as this is an open-label study, and by an independent Data Monitoring Committee (DMC) during the Treatment Period of the study.
Methodology (Continued):

Virologic Failure Criteria

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

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of \( > 1 \log_{10} \text{IU/mL} \) 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 during treatment.

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met for a subject in the Treatment Period, study drug will be discontinued.

All subjects who receive at least one dose of study drug in the Treatment Period will be monitored in the Post-Treatment Period for safety, HCV RNA, the durability of viral response, for the emergence and persistence of resistant viral variants and assessment of Patient Reported Outcomes (PROs) for up to 48 weeks following the last dose of study drug. Resistance monitoring following the end of therapy will take place regardless of whether subjects receive any other anti-viral therapy post-treatment.

The Sponsor will evaluate efficacy throughout the Treatment and Post-Treatment Periods in this open-label study. If excessive rates of virologic failure or virologic relapse are observed, enrollment will be stopped or treatment durations will be extended to 24 weeks. Modifications will be applied to all subjects or for appropriate subgroups depending on the pattern of virologic failure.

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. 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).
3. Screening laboratory result indicating HCV genotype 1-infection.
4. Compensated cirrhosis defined as a Child-Pugh Score of ≤ 6 at Screening
5. Subject has plasma HCV RNA level > 10,000 IU/mL at Screening.
Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

**Main Exclusion:**

1. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).
2. Prior therapy with direct acting antiviral agents for the treatment of HCV, including telaprevir and boceprevir.
3. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation such as ascites (noted on physical exam), esophageal varices, or hepatic encephalopathy.
4. Presence of hepatocellular carcinoma indicated on imaging techniques such as ultrasonography, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or on ultrasound performed at Screening.
5. 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
6. 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 < 2.8 g/dL
   - Prothrombin time/International normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the Abbott Study Designated Physician.
   - Hemoglobin < LLN
   - Platelets < 60,000 cells per mm3
   - Absolute neutrophil count (ANC) < 1500 cells/μL
   - Total bilirubin ≥ 3.0 mg/dL

**Investigational Product:**

- ABT-450/Ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet
- ABT-333 250 mg tablet
- Ribavirin 200 mg tablet
ABT-450/r/ABT-267 and ABT-333  
M13-099 Protocol  
EudraCT 2012-003088-23

| Dose: | • ABT-450/Ritonavir/ABT-267 150/100/25 mg QD  
• ABT-333 250 mg BID  
• Ribavirin weight-based dosing 1000 to 1200 mg divided twice daily |
| Mode of Administration: | Oral |
| Duration of Treatment: | Subjects will receive ABT-450/Ritonavir/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks. |
| Criteria for Evaluation: |  
Efficacy:  
Plasma HCV RNA (IU/mL) will be assessed at each Treatment and Post-Treatment Visit.  
Patient Reported Outcomes (PROs):  
The change in general and disease-specific Health Related Quality of Life (HRQoL) will be assessed using the SF-36v2 (Short Form 36-Version 2) and HCV Patient Reported Outcomes (HCVPRO) instruments, respectively. Health State Utility will be measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L).  
Resistance:  
The resistance endpoints for subjects who experience virologic failure are the variants at each amino acid position by population and/or clonal nucleotide sequencing at the available post-baseline time points compared to baseline and prototypic reference sequences.  
Pharmacokinetic:  
Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be determined at each study visit up to the end of treatment (12 or 24 weeks).  
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 endpoints are the percentage of subjects with SVR\textsubscript{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each of the treatment arms. The secondary efficacy 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 for the 12-week arm or at Week 24 for the 24-week arm) in each of the treatment arms, and the SVR\textsubscript{12} rate in the 24-week arm compared to the 12-week arm. |
Statistical Methods (Continued):
Efficacy (Continued):

Primary
1. SVR_{12} for the 24-week arm
2. SVR_{12} for the 12-week arm

Secondary
1. RVR for the 24-week arm
2. RVR for the 12-week arm
3. EOTR for the 24-week arm
4. EOTR for the 12-week arm
5. SVR_{12} in 24-week arm compared to 12-week arm

For the primary endpoints and first four secondary endpoints the simple percentage of subjects achieving the response within the 12- and 24-week treatment arms will be calculated and a two-sided 95% confidence interval of the percentage will be computed using the normal approximation to the binomial. For each of these endpoints, efficacy will be demonstrated if the lower confidence bound of the 95% confidence interval for each rate is > 38%. For the last secondary endpoint, the percentage of subjects with SVR_{12} following 12 or 24 weeks of treatment will be compared using a logistic regression model with treatment arm, baseline log_{10} HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non-CC), and pegIFN/RBV treatment history (naïve or experienced) as predictors at the alpha = 0.05 significance level. A fixed-sequence testing procedure will be used to control the Type I error rate at 0.05.

The number and percentage of subjects achieving SVR_{12} in each treatment arm for each stratification factor will be presented with two-sided 95% confidence intervals.

Resistance:
The following resistance information will be analyzed for subjects 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 standard 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 within each treatment arm.

Pharmacokinetic:
Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be determined and summarized at each study visit through the end of the Treatment Period (Week 12 or Week 24).
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, and comparisons will be performed using Fisher's exact test. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by severity (mild, moderate, or severe) and relationship to study drug(s).

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized and compared between the arms using ANOVA (analysis of Variance) models. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects within each treatment arm with potentially clinically significant values will be calculated and compared between the treatment arms using Fisher's exact test.

Sample Size:
With a sample size of 150 subjects in each treatment arm, this study has greater than 90% power to achieve a two-sided 95% lower confidence bound greater than 38% if the underlying SVR12 rate is 51% or higher. Subjects who do not have data at Post-Treatment Week 12 (after imputing) count as failures for SVR12 so no adjustment for dropout is applicable.
1.2 List of Abbreviations and Definition of Terms

Abbreviations

AARDEX Advanced Analytical Research on Drug Exposure
Ab Antibody
ABT-450/r/ABT-267 ABT-450 co-formulated with ritonavir and ABT-267
AE Adverse event
ALT Alanine aminotransferase
ANC Absolute neutrophil count
ANCOVA Analysis of covariance
ANOVA Analysis of variance
aPTT Activated partial thromboplastin time
AST Aspartate aminotransferase
AUC Area Under the Concentration Curve
BID Twice Daily
BMI Body mass index
BOC Boceprevir
BUN Blood urea nitrogen
CL/F Apparent Oral Clearance
CR/CL Creatinine clearance
CRF Case report form
CT Computed Tomography
CYP2C8 Cytochrome P450 2C8
CYP3A Cytochrome P450 3A
DAA Direct-acting antiviral agent
D/C Discontinuation
DMC Data Monitoring Committee
DNA Deoxyribonucleic acid
EC Ethics Committee
ECG Electrocardiogram
eCRF Electronic case report form
EDC Electronic data capture
EDTA Edetic acid (ethylenediaminetetraacetic acid)
EOT End of treatment
EOTR  End of treatment response
EU   European Union
EQ-5D-5L  EuroQol 5 Dimensions 5 Levels Health State Instrument
FSH  Follicle stimulating hormone
GAM  Generalized additive method
GCP  Good Clinical Practice
GCSF  granulocyte colony stimulating factor
GGT  Gamma-glutamyl transferase
GT   Genotype
HBsAg  Hepatitis B surface antigen
HBV  Hepatitis B Virus
hCG  Human Chorionic Gonadotropin
HCV  Hepatitis C virus
HCV Ab  Hepatitis C virus antibody
HCVPRO  Hepatitis C Virus Patient Reported Outcomes Instrument
Hemoglobin A1c  Glycated hemoglobin
HIV  Human immunodeficiency virus
HIV Ab  Human immunodeficiency virus antibody
HRQoL  Health Related Quality of Life
ICH  International Conference on Harmonization
IEC  Independent ethics committee
IFN  Interferon
IL28B  Interleukin 28B
IMP  Investigational Medical Product
INR  International normalized ratio
IP-10  Interferon gamma-induced protein 10
IRB  Institutional Review Board
IRT  Interactive Response Technology
ITT  Intent to Treat
IU  International units
IUD  Intrauterine device
LLN  Lower limit of normal
LLOD  Lower limit of detection
LLOQ  Lower limit of quantification
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>MCID</td>
<td>Minimally Clinical Important difference</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental Component Summary</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger Ribonucleic acid</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NONMEM</td>
<td>Non-linear mixed-effect modeling</td>
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<tr>
<td>NS3A</td>
<td>Nonstructural viral protein 3A</td>
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<tr>
<td>NS4A</td>
<td>Nonstructural viral protein 4A</td>
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<tr>
<td>NS5A</td>
<td>Nonstructural viral protein 5A</td>
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<tr>
<td>NS5B</td>
<td>Nonstructural viral protein 5B</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PCS</td>
<td>Physical Component Summary</td>
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<tr>
<td>PegIFN</td>
<td>Pegylated-interferon alfa-2a or alfa-2b</td>
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<td>PK</td>
<td>Pharmacokinetic</td>
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<tr>
<td>POR</td>
<td>Proof of Receipt</td>
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<tr>
<td>PRO</td>
<td>Patient Reported Outcomes</td>
</tr>
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<td>PT</td>
<td>Post-Treatment</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
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<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate</td>
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<td>QTcF</td>
<td>QTc using Fridericia's correction formula</td>
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<td>RBC</td>
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<td>RBV</td>
<td>Ribavirin</td>
</tr>
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<td>RNA</td>
<td>Ribonucleic acid</td>
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<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase PCR</td>
</tr>
<tr>
<td>RVR</td>
<td>Rapid virologic response</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>sAFP</td>
<td>Serum Alpha-Fetoprotein</td>
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<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SF-36 V2</td>
<td>Short Form 36-Version 2</td>
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<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloacetic transaminase</td>
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<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
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**Definition of Terms**

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<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>SVR</td>
<td>Sustained virologic response</td>
</tr>
<tr>
<td>SVR$_{4}$</td>
<td>Sustained virologic response 4 weeks post dosing</td>
</tr>
<tr>
<td>SVR$_{12}$</td>
<td>Sustained virologic response 12 weeks post dosing</td>
</tr>
<tr>
<td>SVR$_{24}$</td>
<td>Sustained virologic response 24 weeks post dosing</td>
</tr>
<tr>
<td>TP</td>
<td>Treatment Period</td>
</tr>
<tr>
<td>TVR</td>
<td>Telaprevir</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>V/F</td>
<td>Apparent Volume of distribution</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
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**Study Drug**  ABT-450/r/ABT-267, ABT-333, RBV  
**Study Day 1**  First day of study drug dosing  
**Treatment Period**  Baseline/Day 1 through last dose of study drug  
**Post-Treatment Period**  Day after the last dose of study drug through Post-Treatment Week 48 or Post-Treatment Discontinuation
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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.\(^1\) Cirrhosis is a common sequelae of HCV infection occurring in approximately 20% of patients.\(^2\) Complications of cirrhosis include hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and hepatocellular carcinoma ensue at a rate of about 3% per year.\(^3-6\) Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.\(^7\) As a result of the high prevalence of HCV infection and resultant complications, HCV is the leading indication for liver transplantation in the United States and the world as a whole.\(^8\)

Patients with compensated cirrhosis who achieve an SVR (sustained virologic response) essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.\(^9-11\)

While the introduction of the protease inhibitors, telaprevir (TVR) or boceprevir (BOC), have increased SVR rates, current treatment is less than optimal as the protease inhibitors must be used in combination with pegIFN/RBV, two agents with considerable treatment limiting toxicities and treatment may extend for up to 48 weeks. Furthermore, regardless of a patient's treatment history, treatment of HCV infected patients with underlying cirrhosis with either telaprevir or boceprevir in combination with pegIFN/RBV results in lower rates of SVR when compared to patients without cirrhosis: treatment-naïve patients treated with TVR (62% versus 79%),\(^12,13\) prior null responders treated with TVR (34% versus 59%),\(^14,15\) prior null responders treated with TVR (14% versus 32%),\(^14,15\) treatment-naïve patients treated with BOC (42% versus 62%),\(^16\) and treatment-experienced patients treated with BOC (35% versus 59%).\(^16\)

Combinations of multiple DAAs (direct-acting antiviral agent) have the potential of further improving HCV treatment by increasing SVR rates, eliminating interferon (IFN) as a component of therapy, increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. Promising short-term
antiviral efficacy results have been reported from IFN-free combinations (either with or without RBV) of a protease inhibitor with a nucleoside polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a nonstructural protein 5A (NS5A) inhibitor. Twelve-week SVR (SVR\textsubscript{12}) rates of 36% (4/11 HCV genotype 1-infected null responders) and 90% (9/10 HCV genotype 1b-infected null responders) have been observed in subjects treated with the combination of a protease inhibitor and NS5A inhibitor (BMS-650032 and BMS-790052) for 24 weeks. Additionally, a recent descriptive sub-analysis from the SOUND-C2 study, a Phase 2b study evaluating IFN-free treatment with Boehringer Ingelheim's investigational DAA compounds BI 201335 and BI 207127 plus RBV, reported SVR\textsubscript{12} rates of 54% (20/37) in genotype 1, treatment-naive patients with compensated liver cirrhosis, regardless of IL-28B allele status.

Together, these safety and efficacy data suggest that interferon-free DAA combinations may address patient's needs and further advance HCV therapy by increasing SVR rates even in difficult-to-treat populations, improving safety and tolerability of treatment, reducing duration, and simplifying treatment.

Abbott currently has a number of DAAs in clinical development: ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor, ABT-267 is a NS5A inhibitor and ABT-333 is a non-nucleoside nonstructural protein 5B (NS5B) polymerase inhibitor. Based on data from a Phase 2b study (Study M11-652), Abbott has identified a DAA combination regimen, ABT-450 with ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with RBV, that appears safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects.

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. The majority of subjects in all 8- and 12-week treatment arms have completed study treatment and are in post-treatment follow-up. Among the treatment naïve subjects, the SVR\textsubscript{4} rates in the 2 groups with 4 drugs (ABT-450/r + ABT-267 + ABT-333 with RBV) for 12 weeks are 100% (39/39) and 98% (39/40). The SVR\textsubscript{4} rates, although still high, are numerically lowest in the 8-week group and the ABT-450/r + ABT-333 +RBV group at 89% (71/80) and 88% (36/41), respectively. The SVR\textsubscript{4} rates in the 12-week groups without ABT-333 or without RBV are 90% to 92%.

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) demonstrates numerically higher SVR\textsubscript{4} rates (SVR\textsubscript{4} 95%) than either the 3 drug regimen (ABT-450/r 200 mg QD + ABT-267 25 mg QD with RBV, SVR\textsubscript{4} 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, SVR\textsubscript{4} 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-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 ALT (alanine aminotransferase) 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 study is intended to examine the safety and efficacy of the combination of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 and 24 weeks in treatment-naïve and pegIFN/RBV treatment-experienced adults with chronic HCV GT1 infection and compensated cirrhosis.

### 3.1 Differences Statement

The combination of ABT-450/r, ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks was explored in treatment-naïve and treatment-experienced subjects without cirrhosis in Study M11-652. This is the first study ABT-450/r/ABT-267 and ABT-333 coadministered with RBV has been evaluated in HCV genotype 1-infected subjects with compensated cirrhosis.

### 3.2 Benefits and Risks

This study consists of two arms in which ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for either 12 or 24 weeks in HCV genotype 1-infected patients with compensated cirrhosis. A combination of an investigational protease inhibitor and a non-nucleoside polymerase inhibitor administered with RBV for 28 or 40 weeks resulted in SVR\textsubscript{12} in 20/37 (54%) in genotype 1, treatment-naïve patients with compensated cirrhosis.
cirrhosis.22 Abbott’s DAA regimen consists of a potent ritonavir boosted protease inhibitor, ABT-450/r, a non-nucleoside polymerase inhibitor, ABT-333, and RBV. Moreover, an additional investigational DAA with a novel mechanism of action, ABT-267, an oral NS5A inhibitor, is included in the Abbott DAA combination regimen and will likely increase the percentage of patients achieving an SVR.

The likelihood of successfully curing HCV in compensated cirrhotics following 12 or 24 weeks of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV is unknown. However, preliminary results from the ongoing Study M11-652 in which ABT-450/r, ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in a treatment-experienced, prior null responder population are promising. In the 12-week treatment arm, 95% of subjects have achieved SVR$_4$. Subjects in the 24-week treatment arm are still on treatment; a similar or improved SVR rate to that seen in the 12-week arm is expected.

ABT-450/r, ABT-267 and ABT-333 coadministered with RBV has been well tolerated in the M11-652 Study. Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the informed consent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data of the DAAs alone and in combination is detailed in the Investigator’s Brochure. In addition, safety of the combination in treatment-naïve and experienced subjects in Study M11-652 is detailed in Section 3.0.

Risks associated with ABT-450/r/ABT-267 and ABT-333 coadministered 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 Objectives

4.1 Primary Objective

The primary objectives of this study are to assess the efficacy and safety (the percentage of subjects achieving a 12-week sustained virologic response, SVR$_{12}$ [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin (RBV) for 12 or 24 weeks in HCV genotype 1-infected adults with compensated cirrhosis.

4.2 Secondary Objective

The secondary objectives of this study are to assess the rapid virologic response rate (RVR) (the percentage of subjects with HCV RNA (ribonucleic acid) < LLOQ at Week 4), the end of treatment response (EOTR) rate (the percentage of subjects with HCV RNA < LLOQ at Week 12 for the 12-week arm or at Week 24 for the 24-week arm) and compare the SVR$_{12}$ rates between the two arms.

Additional objectives of the study include assessments of durability of the antiviral response, emergence and persistence of viral variants and changes in liver fibrosis, inflammation and synthetic function.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis.

The treatment arms are:
Arm A: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks

Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 24 weeks

* RBV will be administered weight-based 1000-1200 mg divided to twice daily.

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 300 subjects are enrolled at approximately 75 sites. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. Subjects will be stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B (Interleukin 28B), genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and by HCV subgenotype (1a versus non-1a). No more than 150 treatment-experienced subjects will be allowed to enroll. The combined number of prior relapsers and prior partial responders will be limited to no more than 70.

**Figure 1: Study Schematic**

This study will consist of a Treatment Period and a Post-Treatment (PT) Period.
During the Treatment Period, subjects will receive treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for either 12 or 24 weeks.

Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects will enter the 48-week Post-Treatment Period.

As this is an open-label study, safety and efficacy evaluations will occur throughout the Treatment and Post-Treatment Periods. If efficacy failure criteria as detailed in Section 5.4.1.2 are met, the findings will be reviewed by the Sponsor and the DMC (refer to Section 5.7). Based on efficacy breakthrough criteria observed during treatment, enrollment in both the 12-week and 24-week arms may be terminated and subjects ongoing in either treatment arm may be offered add-on pegIFN/RBV treatment as detailed in Section 5.4.1.2. In this case, the Abbott regimen will be continued for 12 or 24 weeks as specified while pegIFN at standard doses is added on to continue beyond the end of the Abbott regimen for a total of 48 weeks. The pegIFN/RBV will be provided at no cost to the subject.

In addition, enrollment in the 12-week treatment arm (or in some strata of the 12-week arms) may be terminated based upon virologic relapses post treatment as detailed in Section 5.4.1.2. If the 12-week treatment arm is terminated from further enrollment, subjects randomized to that arm who are in the Treatment Period at the time of the termination may have the duration of their treatment extended to 24 weeks.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 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 Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent
process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

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 300 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 without prior Sponsor approval with the exception of exclusionary HCV genotype, a positive drug screen (without prescription for the positive drug), or a positive HIV, HBV (Hepatitis B Virus) 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, approval is required from the Abbott Study Designated Physician prior to rescreening the subject.

- 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 without approval of the Abbott Study Designated Physician.

Subjects being rescreened must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary (if applicable) at the first screening attempt, (with the exception of HCV genotype, IL28B genotype, FibroScan/liver biopsy and ultrasound of the liver, which do not need to be repeated).
Subjects who meet all eligibility criteria with the exception of their initial non-invasive assessment of liver cirrhosis by FibroScan may undergo rescreening by liver biopsy. Subjects being rescreened because of an exclusionary FibroScan must be rescreened for all laboratory and eligibility criteria with the exception of HCV genotype or IL28B genotype and ultrasound of the liver.

For subjects who do not meet the study eligibility criteria, the site personnel must contact the IRT and identify the subject as a screen failure.

5.1.2 Treatment Period (TP)

After meeting the eligibility criteria, subjects will be randomized via IRT to either 12 or 24 weeks of treatment. Approximately 300 subjects will be randomized. Subjects will be administered study drugs at the site on Study Day 1. Subjects will receive instructions about the study drugs and the dosing schedule at the Day 1 Visit.

ABT-450/r/ABT-267 will be administered orally once daily and ABT-333 and RBV will be dosed orally twice daily as described in Section 5.5.1. The doses are as follows:

- ABT-450/r/ABT-267 150/100/25 mg QD
- ABT-333 250 mg BID
- 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)

Subjects will be administered the first doses of study drugs at the site on Study Day 1 (ABT-450/r/ABT-267, ABT-333, and RBV). All subjects will have the original caps of the bottles for ABT-450/r/ABT-267, ABT-333, and RBV replaced by a Medication Event Monitoring System (MEMS) monitor (cap), manufactured by Advanced Analytical Research on Drug Exposure Ltd. (AARDEX). The MEMS cap will be used to obtain dosing histories. See Section 5.3.1.1 and Section 5.5.8 for further details regarding the MEMS cap.
Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected on Study Day 1 prior to dose and at 2 hours post dose and at the additional visits detailed in Table 2.

All subjects will continue to return to the site on an outpatient basis up to Week 12 or Week 24 for the study procedures identified in Table 2. Sites should ensure that subjects adhere to the study visits listed in Table 2. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (refer to Table 2 and Table 4). Blood samples for optional pharmacogenetic analysis, and optional messenger RNA will be collected as detailed in Table 2. Patient Reported Outcomes (PROs) will also be assessed at the visits listed in Table 2. Ongoing review of the data is planned in order to determine if subjects meet the virologic failure criteria (Section 5.4.1.1).

Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.1.1. The Sponsor will evaluate efficacy failure criteria throughout the Treatment and Post-Treatment Periods in this open-label study as detailed in Section 5.4.1.2.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Table 2 and as described in Section 5.4.1. Ideally, this should occur on the day of study drug discontinuation, but should be no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy if applicable. Subjects who complete or discontinue treatment will be monitored for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs in the 48-week Post-Treatment Period as detailed in Section 5.1.3.
All subjects who receive at least one dose of DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered alternate treatment as described in Section 5.1.3.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last dose of study drug.

The Post-Treatment Period will begin the day following the last dose of study drug treatment. Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Table 3.

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 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.

5.2 Selection of Study Population

The study population consists of HCV genotype 1-infected adult subjects with compensated cirrhosis who are either treatment-naïve or pegIFN/RBV treatment-experienced. Refer to Section 5.2.3.1 for details regarding required documentation for prior pegIFN/RBV treatment failures.
Subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female between 18 and 70 years of age, inclusive, at time of screening.

2. If female, subject is:
   - postmenopausal for at least 2 years (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 practicing 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 a serum specimen obtained within 35 days prior to initial study drug administration, and
• at Study Day 1 (Baseline, prior to dosing) by a 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 Study Day 1 and for 7 months after the last dose of study drug (or per local RBV label):

• Partner(s) using an IUD (intrauterine device),
• 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 has never received antiviral treatment (including pegIFN/RBV) for hepatitis C infection (treatment-naïve subject), or subject must have documentation that they were adherent to prior pegIFN/RBV therapy and meet one of the following categories (treatment-experienced subject):

• Null-responder: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a $2 \log_{10}$ 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 ($\geq 25$ days); or
• Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ 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 ≥ 18 to < 38 kg/m² 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 Institutional Review Board (IRB)/Independent Ethics Committee (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, documentation of cirrhosis by one of the following methods:
   - Histologic diagnosis on liver biopsy performed within 36 months of Screening or during the Screening Period, e.g., Metavir Score of > 3 (including 3/4), Ishak score of > 4 or,
• FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

Subjects with a non-qualifying Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 36 months prior to or during screening.

12. Compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening.

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

**Rationale for Inclusion Criteria**

(1, 5, 9 – 13) To select the appropriate subject population with sufficient disease severity for evaluation.

(7) For the safety of study subjects.

(2, 3, 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 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/RBV.

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 indicating unable to genotype or co-infection with any other HCV genotype.

7. Prior therapy with DAAs for the treatment of HCV, including telaprevir and boceprevir.

8. Use of any medications listed in Table 1 within 2 weeks prior to study drug administration or 10 half-lives, 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>
<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.
9. Use of known inhibitors or inducers of CYP3A (Cytochrome P450 3A) or inhibitors of CYP2C8 (Cytochrome P450 2C8) within 2 weeks or 10 half-lives of the respective medication/supplement, whichever is longer, prior to study drug administration.

10. 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.

11. 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.

12. 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.

13. Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation such as ascites (noted on physical exam), esophageal varices or hepatic encephalopathy.

14. Serum Alpha-Fetoprotein (sAFP) > 200 ng/mL at Screening.

15. Presence of hepatocellular carcinoma indicated on imaging techniques such as ultrasonography, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to screening or on ultrasound performed at screening.
16. 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

17. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - $\text{ALT} > 5 \times \text{upper limit of normal (ULN)}$
   - Aspartate aminotransferase (AST) $> 5 \times \text{ULN}$
   - Calculated creatinine clearance (using Cockcroft-Gault method) $< 60 \text{mL/min}$
   - Albumin $< 2.8 \text{g/dL}$
   - Prothrombin time/International normalized ratio (INR) $> 2.3$. Subjects with a known inherited blood disorder and INR $> 2.3$ may be enrolled with permission of the Abbott Study Designated Physician
   - Hemoglobin $< \text{LLN}$
   - Platelets $< 60,000 \text{cells per mm}^3$
   - Absolute neutrophil count (ANC) $< 1500 \text{cells/μL}$
   - Total bilirubin $\geq 3.0 \text{mg/dL}$

19. 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 Study Day 1 (Baseline, prior to dosing).

20. 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.

21. 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.

22. Current enrollment in another clinical study, prior enrollment in this study, or previous use of any investigational or commercially available anti-HCV agents (other than pegIFN/RBV for treatment experienced subjects), and previous exposure to ABT-450, ABT-267 or 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 trials may be permitted with approval by the Abbott Study Designated Physician.

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

24. Uncontrolled clinically significant cardiac, respiratory (except mild asthma), hepatic, 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, 9-12, 17, 18, 20, 23, 24) To ensure safety of the subjects throughout the study.

(2, 4, 6, 7, 8, 19, 21, 22) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.
(16) To avoid bias for the evaluation of efficacy and safety.

(5, 13 – 15) To exclude subjects with liver diseases other than HCV and compensated cirrhosis.

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 from the time of signing the consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

During the Post-Treatment Period, all medications will be collected 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

Treatment-naïve subjects must not have prior or current use of any investigational or commercially available anti-HCV agents, including IFN, pegIFN, telaprevir, boceprevir or RBV. Subjects who previously participated in trials of direct acting antiviral agents for treatment of HCV may be enrolled with the approval of the Abbott Study Designated Physician if they can provide documentation that they received placebo.

Treatment-experienced subjects must have previously received only pegIFN/RBV prior to Screening and failed treatment (either on treatment or via relapse). These subjects should have documentation of pegIFN/RBV treatment history, including start and stop dates and
type of response in the source. Subject must have been compliant with the prescribed peg-IFN/RBV treatment, as assessed by the treating physician and/or Principal Investigator.

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, whichever is longer, prior to initial study drug administration and up to 2 weeks following discontinuation of study drugs. 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 safely administered with DAAs (including ritonavir) and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drug.

During the Post-Treatment 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, 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, whichever is longer, prior to the initial dose of study drugs and until the subject has completed active study drug in the Treatment Period.
ABT-450/r/ABT-267 and ABT-333
M13-099 Protocol
EudraCT 2012-003088-23

Refer to the ritonavir and RBV labeling for a list of prohibited medications. Anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study.

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 Abbott, and Abbott 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
Table 2. Study Activities – Treatment Period (TP)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>Day 1 / Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 10</th>
<th>Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Provide RBV Medication Guide&lt;sup&gt;e&lt;/sup&gt; and Partner Risk Fact Sheet</td>
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<td>Physical Exam</td>
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<tr>
<td>Vital Signs, Weight, Height</td>
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<td>ECG</td>
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<tr>
<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
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<tr>
<td>Pregnancy Test [serum (s) urine (u)]&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X (s)</td>
<td>X (u, s)</td>
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<td>Urine Albumin</td>
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<td>FSH (all females), HbA1c</td>
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<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>Total Insulin</td>
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<td>HCV Genotype and Subgenotype</td>
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</table>
Table 2. Study Activities – Treatment Period (TP) (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Treatment Period (TP)</th>
<th>Treatment Visits – All Subjects</th>
<th>Treatment Visits – 24-Week Arm</th>
<th>Premature D/C&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Day1/ Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Wk 1</td>
<td>Wk 2</td>
</tr>
<tr>
<td>IL28B Sample</td>
<td>X</td>
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<tr>
<td>Screening: Liver Biopsy or FibroScan</td>
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<tr>
<td>Longitudinal FibroTest</td>
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<tr>
<td>Child-Pugh Score</td>
<td>X</td>
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<tr>
<td>Clinical Assessment of Hepatic Decompensation</td>
<td>X&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Liver Ultrasound and Alpha Fetoprotein&lt;sup&gt;n&lt;/sup&gt;</td>
<td>X</td>
<td></td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Randomization</td>
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<tr>
<td>Patient Reported Outcomes Instruments (PROs)&lt;sup&gt;o&lt;/sup&gt;</td>
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<td>Adverse Event Assessment</td>
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<td>Study Drugs Dispensed</td>
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<td>MEMS cap dispensed</td>
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</tbody>
</table>

<sup>a</sup> Day 1/Baseline

<sup>b</sup> Premature D/C

<sup>c</sup> End of Treatment (EOT)
## Table 2. Study Activities – Treatment Period (TP) (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Treatment Period (TP)</th>
<th>Treatment Visits – All Subjects</th>
<th>Treatment Visits – 24-Week Arm</th>
<th>Premature D/C&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Day1/ Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Wk 1 Wk 2 Wk 4 Wk 6 Wk 8 Wk 10 Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt; Wk 16 Wk 20 Wk 24 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>MEMS Downloaded/Review Compliance/Collect MEMS Caps&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
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<tr>
<td>HCV RNA Samples</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
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<td>HCV Resistance Sample</td>
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<tr>
<td>Pharmacokinetic Sample</td>
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<td>Archive Plasma Sample</td>
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<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Archive Serum Sample</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Interferon Gamma-induced protein 10 (IP-10) Sample</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Pharmacogenetic Sample (optional)&lt;sup&gt;t&lt;/sup&gt;</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X X X</td>
</tr>
</tbody>
</table>

Wk = Week; EOT = End of treatment; D/C = Discontinuation; MEMS = Medication Event Monitoring System

- **a.** All procedures, including pharmacokinetic sample collection, to be performed prior to first dose with the exception of the 2-hour post-dose pharmacokinetic sample.
- **b.** Treatment visits:
  - Subjects randomized to the 12-week treatment arm will complete the screening through Week 12 study visit procedures. Week 12 will be the final visit in the Treatment Period.
Table 2.  Study Activities – Treatment Period (TP) (Continued)

- Subjects randomized to the 24-week treatment arm will complete the screening through Week 24 study visit procedures. Week 24 will be the final visit in the Treatment Period.
- Subjects who prematurely discontinue the Treatment Period (Week 12 or Week 24 treatment arm) should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Subjects should begin the Post-Treatment Period after the subject completes study drug treatment or prematurely discontinues Treatment Period.

d. Subjects will need to sign an informed consent for the study (prior to performing any screening or study-specific procedures) and the optional Pharmacogenetic sample(s), if applicable.

e. Where applicable/locally available.

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

g. Height will be measured at Screening only.

h. Evaluate the Day 1 ECG prior to dosing to determine eligibility.

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

j. Done at Day 1/Baseline and collected for decrease in Creatinine Clearance as defined in Section 6.7.5.

k. Subjects who have not had a qualifying liver biopsy within 36 months of Screening, but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo either a FibroScan or a liver biopsy.

l. Longitudinal FibroTest measured for exploratory analysis of fibrosis over time. Day 1 results will be blinded to the investigator/site.

m. Clinical assessment of Hepatic encephalopathy and ascites at Day 1 prior to dosing.

n. Liver Ultrasound to be performed at screening for subjects on the 12-week treatment arm and at screening and Week 24 (EOT) for subjects on the 24-week treatment arm. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit.
**Table 2. Study Activities – Treatment Period (TP) (Continued)**

**o.** 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 and in the order listed below.

- **TP Day 1 (Baseline):** SF-36V2, EQ-5D-5L and HCVPRO
- **TP Weeks 4 and 8:** SF-36V2, EQ-5D-5L and HCVPRO
- **TP Week 12:** SF-36V2, EQ-5D-5L and HCVPRO (= EOT for 12-week treatment arm or Treatment Period Week 12 for the 24-week treatment arm)
- **TP Week 24:** SF-36V2, EQ-5D-5L and HCVPRO (= EOT for 24-week treatment arm)
- **TP Premature D/C Visit:** SF-36V2, EQ-5D-5L and HCVPRO

**p.** Study drugs only dispensed at Weeks 12, 16 and 20 for subjects in 24-week arm.

**q.** MEMS caps will be collected upon completion of study drug, EOT (TP Week 12 or TP Week 24) or TP Premature D/C.

**r.** HCV RNA will be collected at 0-hour (immediately prior to the morning dose) and at 2 hours post-dose.

**s.** Blood Sample(s) for pharmacokinetic assay as described in Section 5.3.2 will be collected as follows:

- **Day 1:** 0-hr (immediately prior to the morning dose), and at 2 hours post-dose.
- A single pharmacokinetic sample will be collected at all other Treatment Study Visits without regard to the time of dosing as detailed in Table 2 above.

**t.** If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study.

**u.** To be performed at End of Treatment (EOT), either TP Week 12 or TP Week 24, as appropriate.
### Table 3. 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/Coagulation Panel</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>Monthly Pregnancy Test (females)(^b)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>(Weeks 12, 16, 20, 24, 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal FibroTest</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver Ultrasound and Alpha Fetoprotein(^c)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PRO Instruments(^d)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medication Assessment(^e)</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(^f)</td>
<td>X</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>HCV Resistance Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td></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>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

a. Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.
Table 3. Study Activities – Post-Treatment (PT) Period* (Continued)

b. Urine pregnancy testing is not required after TP 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.

c. Liver ultrasound and alpha fetoprotein to be performed at PT Week 12 and PT Week 36 for subjects randomized to the 12 Week Arm and at PT Week 24 and PT Week 48 for subjects randomized to the 24 Week Arm, or upon Premature Discontinuation.

d. PRO instruments should be administered before any study procedures and in the order listed below.

- **PT Week 4:** SF36V2, EQ-5D-5L and HCVPRO
- **PT Week 12:** SF36V2, EQ-5D-5L and HCVPRO
- **PT Week 24:** SF36V2, EQ-5D-5L and HCVPRO
- **PT Week 48 or D/C:** SF36V2, EQ-5D-5L and HCVPRO

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

f. Only SAEs will be collected after 30 days post-dosing. Subjects that are receiving add-on pegIFN/RBV will continue to collect AEs throughout the study while on pegIFN/RBV therapy and for 30 days following the end of pegIFN/RBV therapy.
5.3.1.1 Study Procedures

The study procedures outlined in Table 2 and Table 3 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 pharmacogenetic analysis (Section 5.3.1.3), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), the monitoring of treatment compliance (Section 5.5.7), the use of MEMS caps (Section 5.5.8) and the collection of adverse event information (Section 6.0). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to the Sponsor electronically from the individual laboratorie(s).

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 use and injection drug use will be taken from each subject during the Screening Visit. The subject's medical history will be updated at the Day 1 Visit (Treatment Period). This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits indicated in Table 2, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.
The physical examination performed on Day 1 of the Treatment Period 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 indicated in Table 2 and Table 3. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Day 1 will serve as the baseline for clinical assessment. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

**12-lead Electrocardiogram**

A 12-lead resting ECG will be obtained at the visits indicated in Table 2 or upon subject discontinuation from the Treatment Period (or as clinically needed). The Day 1 (Treatment Period) reading will serve as the baseline assessment. The ECG should be performed prior to blood collection.

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

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

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.
The QT interval measurement (corrected by Fridericia formula, QTcF) will be documented in the eCRF only if the local reader's assessment is "prolonged QT."

**Clinical Laboratory Tests**

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 4 at the visits indicated in Table 2 and Table 3.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. 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.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Depending on the location of the study site, samples will be sent to one of the following addresses:

Covance  
8211 SciCor Drive  
Indianapolis, IN 46214 USA  
(For sites in Canada, Puerto Rico and USA)

Covance Geneva  
Rue Moïse-Marcinhes 7  
1217 Meyrin/Genève-CH  
(For sites in Belgium, France, Germany, Italy, Spain and UK)
### Table 4.  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&lt;sup&gt;a,b&lt;/sup&gt;</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, if detected</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Alkaline phosphatase</td>
<td>Urobilinogen</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 acceptable)</td>
<td>Inorganic phosphorus</td>
<td>Albumin&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>ANC</td>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Prothrombin Time/INR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
<td>Total protein</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albumin&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma-glutamyl transferase (GGT)&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>Creatinine clearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Cockcroft Gault calculation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimated glomerular filtration rate (calculation)</td>
<td></td>
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<tr>
<td></td>
<td>Modification of Diet in Renal Disease (MDRD) (calculation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha2-macroglobulin&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td></td>
<td>Haptoglobin&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Apolipoprotein A1&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Alpha fetoprotein</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Additional Tests</strong></td>
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</tr>
<tr>
<td>HBsAg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Anti-HCV Ab&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Anti-HIV Ab&lt;sup&gt;c&lt;/sup&gt;</td>
<td>FSH (all females)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Opiates&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Barbiturates&lt;sup&gt;c&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Amphetamines&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Cocaine&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Alcohol&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Phenecyclidine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Methadone&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Urine and Serum</td>
<td></td>
</tr>
<tr>
<td>Methadone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Human Chorionic Gonadotropin (hCG) females&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Total insulin</td>
<td>HCV RNA</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>IP-10</td>
<td></td>
</tr>
<tr>
<td>IL28B&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HCV genotype and subtype&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Pharmacogenetic sample</td>
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<tr>
<td>(optional)</td>
<td>Pharmacogenetic sample</td>
<td></td>
</tr>
<tr>
<td>mRNA (optional)</td>
<td>Pharmacogenetic sample</td>
<td></td>
</tr>
</tbody>
</table>

a. Also a component of the Child-Pugh Assessment.
b. Also a component of FibroTest.
c. Performed only at Screening.
d. Urine pregnancy testing is not required after Day 1 of the Treatment Period 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.
e. Collected for Creatinine Clearance <50 mL/min as defined in Section 6.7.5.
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 drug or requires a subject to receive treatment will be recorded as an adverse event.

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

**Pregnancy Test**

A urine pregnancy test will be performed for all female subjects at all the visits indicated in Table 2 and Table 3. In addition, a serum pregnancy test will be performed at Screening and 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 indicated in Table 2 and Table 3 and monthly for a minimum of 7 months after the discontinuation of RBV, or according to the local RBV label and/or local treatment guidelines for RBV. A positive urine pregnancy test requires a confirmatory serum test. Urine pregnancy tests are not required after Day 1 for female subjects with a documented history of bilateral tubal ligation, 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 for all females.

During post-treatment 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 at home 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 captured in the eCRF, unless serum pregnancy is elected. Serum pregnancy testing will be completed by the central laboratory.

**Hepatitis and HIV Screen**

HBsAg (hepatitis B surface antigen), 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 HBsAg results will 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 4. 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.

**Screening: Liver Biopsy or FibroScan**

At Screening, subjects should meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy if a biopsy showing compensated cirrhosis in the past 36 months is not available.

To be eligible, subjects must have a diagnosis of cirrhosis by one of the following methods, per local standard practice:
- Histologic diagnosis on liver biopsy performed within 36 months of Screening or during the Screening Period, e.g., Metavir Score of > 3 (including 3/4), Ishak score of > 4, or
- FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.
- Subjects with a non-qualifying Fibroscan result may only be enrolled if they have a qualifying liver biopsy performed within 36 months prior to or during screening.

Rescreening procedures for those subjects who do not have a qualifying FibroScan during the Screening Period are outlined in Section 5.1.1.1.

**Longitudinal FibroTest**

In addition to the assessments of cirrhosis performed during the Screening Period, all subjects will have FibroTest performed at baseline (Day 1) and throughout the Post-Treatment Period as indicated in Table 2 and Table 3 for the purpose of assessing changes in liver fibrosis over time. Day 1 results will be blinded to the investigator/site.

**Child-Pugh Score and Category**

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the visits indicated in Table 2.
Table 5.  Child-Pugh Classification of Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Assigned for Observed Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L (mg/dL)</td>
<td>&lt; 34.2</td>
</tr>
<tr>
<td></td>
<td>(&lt; 2)</td>
</tr>
<tr>
<td>Serum albumin, g/L (g/dL)</td>
<td>&gt; 35</td>
</tr>
<tr>
<td></td>
<td>(&gt; 3.5)</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Hepatic encephalopathy*</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since screening.

Liver Ultrasound and Alpha Fetoprotein

In order to monitor for the presence of hepatocellular carcinoma, alpha fetoprotein will be assayed and an ultrasound of the liver will be performed as indicated in Table 2 and Table 3.

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 2.
During the Post-Treatment Period, antiviral therapies related to the treatment of HCV and medications prescribed in association with an SAE will be recorded in the eCRF at the visits indicated in Table 3.

**Randomization and Assignment of Subject Numbers**

All screening activities must be completed and reviewed prior to randomization. Subjects who meet the eligibility criteria will proceed to randomization via the IRT system on Day 1 (Treatment Period).

Screening numbers will be unique 6-digit numbers and will begin with 100101 with the first three digits representing the investigative site, and the last three digits representing the subjects at that site. Randomized subjects will keep their screening number as their subject number. Subjects will be randomized on Day 1 as described in Section 5.5.4 and will receive a separate unique 7-digit 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.

**Patient Reported Outcomes (PRO) Instruments (Questionnaires)**

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days indicated in Table 2 and Table 3. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read or understand any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all 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, followed by the EQ-5D-5L and followed by 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.

**Short Form 36 – Version 2 Health Status Survey**

The SF-36V2 is a general Health Related Quality of Live (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 to complete.

**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) using country-specific based weights, where available. 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. This instrument has been preliminarily validated and further validation is ongoing. 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.
MEMS Caps

At the Day 1 Visit subjects will be assigned 3 MEMS caps. 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 and Section 5.5.8.

To ensure that a dosing event is recorded for the first dose of each study drug administered (at the site) at the Day 1 visit, the site should place the MEMS cap on each study drug bottle before dispensing the first dose. The event recording of the first study drug dosing is important to the Day 1 PK sample collection.

Study Drug Compliance for Kits

Study drug compliance will be recorded per kit (bottle) in the IRT system. Study drugs will be collected at each drug dispensation visit after Day 1, as indicated in Table 2. The number of tablets of ABT-450/r/ABT-267, ABT-333, and of RBV remaining in each bottle will be recorded in the source and transferred to the IRT system along with the date of reconciliation.

HCV Genotype and Subgenotype

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

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Table 2 and Table 3. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0. The lower limit of detection (LLOD) is 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 0-hour (prior to dose) and 2 hours post dose on Day 1 and at the study visits, indicated in Table 2 and Table 3. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, the Sponsor, or its designee.

**Archive Plasma Sample**

Archive plasma samples will be collected at the study visits, indicated in Table 2 and Table 3. Archive plasma 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.

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

**Archive Serum Sample**

Archive serum samples will be collected at the study visits, indicated in Table 2 and Table 3. Archive 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.

Specific instructions for preparation and storage of archive samples will be provided by the central laboratory, the Sponsor, or its designee.
**Interferon Gamma-Induced Protein 10 (IP-10) Levels**

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 2 and Table 3. Specific instructions for preparation and storage of IP-10 samples will be provided by the central laboratory, the Sponsor, or its designee.

**5.3.1.2 Meals and Dietary Requirements**

All study drugs should be administered with food including RBV as recommended per the labeling.

**5.3.1.3 Blood Samples for Pharmacogenetic Analysis**

**IL28B Sample**

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

**Optional Sample for Pharmacogenetic Analysis**

A separate (optional) whole blood sample for DNA isolation will be collected on Day 1 (Treatment Period) from each subject who consents to provide the optional sample for pharmacogenetic analysis. If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

**Optional Samples for 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 throughout the study, as indicated in Table 2 and Table 3.
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.

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

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 and ABT-333 (or drugs for the treatment of HCV) continues but no longer than 20 years.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, as well as ritonavir and RBV will be collected by venipuncture at each study visit indicated in Table 2, including at Day 1, for the 0-hour and 2-hour PK sample collection, the date and time of the first dose of each drug will be recorded in the source documents and the eCRF. 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, RBV and archive plasma samples will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

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

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV will be determined using validated assay methods under the supervision of the Drug Analysis Department at Abbott. Plasma concentrations of
possible 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 Day 1 through 48 weeks after completion of treatment.

5.3.3.1 Primary Variable

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

5.3.3.2 Secondary Variables

The secondary endpoints are:

- The percentage of subjects with RVR (HCV RNA < LLOQ at Week 4) in each treatment arm;
- The percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12 or Week 24) in each treatment arm;
- The comparison of the percentage of subjects with SVR$_{12}$ between the two arms.

5.3.3.3 Resistance Variables

The following resistance endpoints 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 standard sequences.
5.3.4 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.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of ABT-450, ABT-267, ritonavir, 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.

5.3.6 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN/RBV. 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 Treatment Period or the Post-Treatment Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 2 or Table 3. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 48 weeks for safety, HCV RNA, the emergence and persistence of resistant viral variants and PROs.

If a subject is discontinued from study drug (Treatment Period) or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide
follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug (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

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

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log_{10} IU/mL above nadir) at any time point during treatment;
- 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 during treatment.

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 (Section 5.4.1). Subjects should remain on study treatment until the virologic failure has been confirmed.

5.4.1.2 Efficacy Treatment Adjustment Criteria

The Sponsor will evaluate efficacy by reviewing HCV RNA levels throughout the Treatment and Post-Treatment Periods in this open-label study.
If either of the efficacy failure criteria below are met, the findings will be reviewed by the Sponsor and the DMC (Data Monitoring Committee) as detailed in Section 5.7. In addition, if the first criterion (virologic breakthrough) is met, enrollment in the study will be paused while the review of the results are ongoing. If the second criterion (virologic relapse) is met, enrollment may continue during the review of the results. The characteristics of the subjects experiencing failure will be reviewed to determine what changes are needed and whether changes should apply to the entire study population or only to certain subgroups, such as those defined by HCV subgenotype (1a versus 1b), IL28B genotype, or prior treatment-experience and response.

1. Virologic breakthrough: Across both treatment arms, if ≥ 10 of the first 20 subjects enrolled experience virologic breakthrough during treatment, the Sponsor and DMC will review the data to determine whether further enrollment should be terminated. Enrollment may be terminated for the entire study population or for certain subgroups (e.g., GT-1a infected subjects). If enrollment is terminated for an arm in its entirety or for a subgroup, add-on pegIFN treatment will be offered to the corresponding subjects who are in the Treatment Period. If enrollment is terminated for only a subgroup of subjects (e.g., GT-1a infected subjects), enrollment in the study may be resumed for subjects not in that subgroup (e.g., GT-1b infected subjects).

2. Virologic relapse: In the 12-week treatment arm, if ≥ 5 of the first 10 subjects who complete 12 weeks of therapy experience virologic relapse after treatment, then the Sponsor and DMC will review the data to determine whether the treatment should be extended from 12 to 24 weeks for all subjects on treatment or only for a subgroup of subjects. Enrollment into the study may continue during the data review process. For any subgroup of subjects for whom treatment duration is extended to 24 weeks, the remaining subjects in that subgroup will be enrolled in the 24-week arm. For groups of subjects whose treatment is not extended to 24 weeks, enrollment in both treatment arms may continue.
Similar evaluations of virologic breakthrough and virologic relapse will continue throughout the study. Subjects who drop out for reasons other than virologic failure will not be included in these evaluations.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug (ABT-450/r/ABT-267, ABT-333 and RBV) will be dispensed in the form of tablets at the visits listed in Table 2.

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 tablets. RBV has weight-based dosing 1000 to 1200 mg divided twice daily per local label. (For example, subjects weighing less than 75 kg, RBV may be taken orally as 2 tablets in the morning and 3 tablets in the evening which
corresponds to a 1000 mg total daily dose. Or for subjects weighing 75 kg or more, RBV may be taken orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose.)

At 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 or Week 24 of the Treatment Period.

Subjects will be instructed to take study medication at the same time(s) every day. All compounds 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 indicated in Table 2. Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide visit date information and study drug return information for each kit (Section 5.5.9).

All subjects who receive at least one dose of DAA and who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be discontinued from treatment. Resistance monitoring will continue in the Post-Treatment Period regardless of whether subjects opt for alternative post-study treatment.

### 5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 6.
Table 6. 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</td>
<td>Oral</td>
<td>Tablet</td>
<td>75 mg/50 mg/12.5 mg</td>
</tr>
<tr>
<td>ABT-333</td>
<td>Abbott</td>
<td>Oral</td>
<td>Tablet</td>
<td>250 mg</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Roche or Generic Manufacturer</td>
<td>Oral</td>
<td>Tablet</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

5.5.3 Packaging and Labeling

ABT-450/Ritonavir/ABT-267 will be supplied in bottles containing 64 tablets. ABT-333 will be supplied in bottles containing 64 tablets. Ribavirin will be supplied in bottles containing 168 tablets each.

Each bottle will be labeled as required per country requirements.

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

5.5.3.1 Storage and Disposition of Study Drug

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/Ritonavir/ABT-267 bottles</td>
<td>15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia: Store below 25°C</td>
</tr>
<tr>
<td>ABT-333 bottles</td>
<td>15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia: Store below 25°C</td>
</tr>
<tr>
<td>Ribavirin bottles</td>
<td>15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td></td>
<td>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 drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the Sponsor. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.
5.5.4 **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 kit numbers and a unique randomization number. The randomization number will be used only by Abbott 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. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

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

5.5.5 **Selection and Timing of Dose for Each Subject**

Selection of the doses for this study is discussed in Section 5.6.4. Study drug dosing will be initiated at the 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 capsules taken in the morning, and 3 RBV capsules should be taken in the evening.

All compounds should be taken with food.

5.5.6 **Blinding**

This is an open-label study.
5.5.7 Treatment Compliance

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

At the start of the study, each subject should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance. Subjects will be administered study drugs at the site at the Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

The subjects will be instructed to return all bottles of study drug (full, partial or empty) and MEMS caps to the study site at each study visit. Study site personnel will inspect the contents of the bottles and record the status of each one as well as the exact number of remaining tablets ABT-450/r/ABT-267 and ABT-333 or tablets of RBV and the date of reconciliation in the IRT system. Returned study drug should not be re-dispensed to the subject. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

At Day 1, for the 0-hour and 2-hour PK sample collection, the date and time of the first dose of each drug will be recorded in the source documents and the eCRF. The date of last dose of all study drugs will be recorded in the source documents and the appropriate eCRF.

5.5.8 MEMS Caps

All subjects will utilize a MEMS monitor (cap), manufactured by AARDEX (Advanced Analytical Research on Drug Exposure) on the bottles for ABT-450/r/ABT-267, ABT-333, and RBV. The MEMS cap will be used to obtain daily dosing histories for ABT-450/r/ABT-267, ABT-333, and RBV for all subjects. In addition, MEMS data will
be provided to the Investigator to guide treatment compliance and will be the primary data used to assess pharmacokinetic (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 Day 1 Visit (Treatment Period), subjects will be assigned 3 MEMS caps that will be placed on the ABT-450/r/ABT-267, ABT-333 and 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.

Each drug will be assigned a specific color, identified by a color coded label on the drug bottle and a corresponding color coded MEMS cap so that the same MEMS cap is used for only one drug throughout the study. 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 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.

To ensure that a dosing event is recorded for the first dose of each study drug administered (at the site) at the Day 1 visit, the site should place the MEMS cap on each study drug bottle before dispensing the first dose.
The subject should return all study drug bottles (empty bottles along with in-use bottles with the MEMS monitors attached) at each visit. The site staff will download the dosing history data at each visit, for each study drug bottle, and will review the downloaded data for compliance. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

The MEMS cap will be collected from the subject at the completion of study drug 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) and the returned study drug reconciliation data in IRT will be the only data utilized for adherence.

Additional instructions for the subject on the use of the MEMS cap will be provided by Abbott.

A start and stop date of all study drugs will be recorded in the source documents and the eCRF.

5.5.9 Drug Accountability

The Investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the Investigator and will include lot number, POR number, number of tablets dispensed, subject number, initials of person who dispensed study drug and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Abbott monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. 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 bottle, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each 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 study drug bottles (containing unused study drugs) will be returned to the Sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT 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

Based upon the results of three Phase 2 studies, Study M12-267, Study M12-746, and Study M11-652 (discussed in detail in Section 3.0), Abbott plans to evaluate ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in treatment-naïve and pegIFN/RBV treatment-experienced (who are prior null responders, partial responders or relapsers), HCV genotype 1-infected adults with compensated cirrhosis (Child-Pugh score 5 – 6) in this multicenter randomized, open-label, duration ranging, Phase 3 study.
A placebo-controlled trial was not considered to be appropriate in HCV subjects with compensated liver disease because they have a greater risk of progression to decompensated liver disease with treatment delays for a placebo treatment group. An active comparator of the current standard (telaprevir or boceprevir with pegIFN/RBV) is considered infeasible to enroll because of the toxicity associated with the currently approved protease inhibitor/pegIFN/RBV regimens and the perceived imminent availability of a better-tolerated, short course (12- to 24-week), pegIFN-free, DAA combination regimen.

A comparative study with 2 different durations of therapy provides randomization and comparative data supporting selection of treatment duration. Since HCV patients with compensated cirrhosis have been shown to be more difficult to cure, a longer duration may be needed for subjects with cirrhosis even though 12 weeks is an adequate duration for subjects without cirrhosis. This study design will provide data to confirm whether a duration longer than 12 weeks will provide additional benefit with respect to efficacy.

Given the above considerations, the study design will maximize the probability of success in this harder to cure population, and DMC oversight will ensure the high efficacy and safety of all subjects. Also, this study design will maximize the benefit of an IFN-free treatment for all study subjects while avoiding the limitations of study designs employing an active or placebo comparator.

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 and population sequencing methods are experimental. The SF-36V2 and EQ-5D-5L instruments are standard in the literature and thoroughly validated. The HCVPRO is preliminarily validated and has demonstrated excellent responsiveness in patients with HCV.
5.6.3 Suitability of Subject Population

This study plans to enroll both HCV treatment-naïve and treatment-experienced (pegIFN/RBV) subjects with genotype 1 chronic HCV and compensated cirrhosis. Naïve subjects are included to assess the safety and efficacy of the DAA regimen in these subjects with compensated cirrhosis. The optimal treatment duration of a DAA combination regimen in cirrhotic patients remains unclear. Data from other HCV regimens have demonstrated lower efficacy rates in compensated cirrhotics (both treatment-naïve and treatment-experienced) compared to non-cirrhotics. Durations of therapy other than those used in the non-cirrhotic population may improve efficacy rates.

Both the identification of the appropriate treatment duration with the DAA regimen and the characterization of the benefit-risk ratio in patients with compensated cirrhosis that will result from Study M13-099 must be clearly understood before initiating studies of DAA regimens in patients with more advanced liver disease. This study approach protects against the potential complications that may come with initial study in patients with decompensated cirrhosis, including avoidance of potential adverse events through exposure to 24 weeks of DAA therapy without a demonstrated incremental increase in SVR with an additional 12 weeks of treatment.

All 3 categories of treatment-experienced subjects (null-responders, non-responders/partial responders, and relapsers to prior pegIFN/RBV therapy) are included to gain experience with the 3 DAA regimen with RBV in all 3 types of treatment-experienced subjects with compensated cirrhosis. Null-responders are included as they are the most difficult to treat, and if the regimens are efficacious in these subjects they will likely be more efficacious in non-responders/partial responders and relapsers. No more than 70 prior relapsers and partial responders, combined, will be randomized to ensure that adequate numbers of prior null responders are treated. The protocol will also specifically exclude subjects with any prior exposure to DAA HCV inhibitors, since prior DAA therapy may have selected mutations which may alter the antiviral response to the DAAs in this study.
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. This study will restrict enrollment to HCV genotype 1-infected subjects who have evidence of compensated cirrhosis. Unanticipated pharmacokinetic or other adverse effects not observed in prior dosing in healthy volunteers or HCV-infected subjects without compensated cirrhosis will be assessed. 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. The exposure viral load response from subjects treated to date with ABT-450/r, ABT-333 and ABT-267 indicates that changes in exposure due to BMI is not expected to significantly affect response. Moreover, because of the acceptable safety and pharmacokinetic profiles of ABT-450/r, ABT-267 and ABT-333 in Phase 1 studies, this protocol will enroll subjects with a BMI up to 38 kg/m².

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 both as monotherapy in combination with pegIFN/RBV, and in combination with each other and RBV. Doses comparable to, and higher than the DAA doses to be administered in this study have been studied in single- and multiple-dose healthy volunteer studies and administered to HCV-infected subjects without cirrhosis as monotherapy or in combination with pegIFN/RBV and found to be generally safe and well tolerated. The regimen and doses used in this study were administered to approximately 20 HCV subjects without cirrhosis who were prior null-responders to pegIFN/RBV and to 40 HCV subjects without cirrhosis who were treatment-naïve in Study M11-652.

In addition, as described in Section 3.0, the pharmacokinetics of ABT-450, ABT-267, ABT-333 and ritonavir when given in combination to subjects with hepatic impairment were comparable to slightly lower than that in subjects with normal hepatic function. The exposures area under the concentration curve (AUC) of ABT-450, ABT-267 and
ABT-333 were comparable (≤ 30% change) in subjects with mild hepatic impairment compared to healthy controls. The AUC for ritonavir was 34% lower in subjects with mild hepatic impairment. Based on these data, no dose adjustment is required for subjects taking the DAA combination in this study. Additionally, based on the package insert for ribavirin, dose adjustments are not required in subjects with mild hepatic impairment.

**ABT-450/r**

The ABT-450/r doses of 100/100 and 150/100 mg evaluated in the Phase 2 studies using the ABT-450 Spray dried dispersion (SDD) tablet provided high SVR$_4$ rates in treatment-naïve and treatment-experienced subjects when dosed with ABT-333 and ABT-267 ± RBV. The higher ABT-450 dose of 150 mg, administered with 100 mg ritonavir, however, 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 was 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 doses were also associated with higher SVR$_{12}$ rates combined with pegIFN/RBV. Thus based on resistance profile and SVR$_{12}$ data with pegIFN/RBV, higher doses provide better efficacy. However, higher doses (200/100 and 250/100 mg SDD tablet) were associated with a greater incidence of Grade 3 ALT elevations suggesting that doses ≤ 200/100 mg SDD tablet might be optimal to minimize the Grade 3 elevations.

The 150 mg ABT-450 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 ~50% lower than that from the 200/100 mg SDD formulation. The 150 mg ABT-450 dose from the coformulation will hence to reduce the incidences of asymptomatic,
ABT-450/r/ABT-267 and ABT-333  
M13-099 Protocol  
EudraCT 2012-003088-23

transient Grade 3 elevations but still maintain sufficient ABT-450 exposure to at least partially suppress the most fit protease mutant, R155K.

The maximum dose of ABT-450/Ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablets will not exceed 150 mg/100 mg/25 mg per day for 24 weeks.

**ABT-267**

An ABT-267 dose of 25 mg has been selected to advance into Phase 3 studies based on comparable viral load decline following monotherapy and lower potential to decrease ABT-450 exposures as compared to higher ABT-267 doses.

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 no 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 resistance were observed following monotherapy with doses of 5 to 200 mg. On the contrary, higher ABT-267 doses have been associated with decrease in ABT-450 exposures; ABT-267 200 mg dose resulted in ~80% lower ABT-450 exposures (ABT-450 250 mg 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 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 a comparable bioavailability to the 25 mg ABT-267 tablet used in Phase 2 studies. Hence, the ABT-267 dose in the current study is the 25 mg as it provides exposures that maximizes efficacy without compromising ABT-450 exposures.

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.
ABT-333

An ABT-333 dose of 250 mg BID that is expected to have exposures comparable to the 400 mg BID dose used in Phase 2 studies has been selected to advance into Phase 3 studies based on comparable efficacy and better safety profile compared to exposures at higher doses.

Comparable viral load decline following monotherapy (approximately 1 log_{10} IU/mL) were observed at exposures ≥ that achieved with the 400 mg BID doses evaluated in Phase 2 studies. Additionally similar SVR rates (63%) when combined with pegIFN/RBV for 12 weeks followed by 36 weeks of pegIFN/RBV were observed at the 400 and 800 mg BID doses indicating that increasing ABT-333 dose > 400 mg BID did not improve efficacy. Additionally, available data from the Phase 2b study indicates that when 400 mg BID dose of ABT-333 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/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 400 mg BID dose and compared to placebo plus pegIFN/RBV.

The optimized formulation used in the current study has a higher bioavailability and is expected to be comparable 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 to higher ABT-333 doses.

The maximum total daily dose of ABT-333 250 mg tablets administered in this study will not exceed 500 mg per day for 24 weeks.
RBV

The daily dose of RBV 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.

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

5.7 Data Monitoring Committee

An independent DMC will review safety and virologic data from this study and provide recommendations to the Abbott Study Designated Physician as per the DMC charter. The charter also describes DMC member responsibilities and membership, which will include individuals with extensive experience in the management of patients with chronic hepatitis C. The DMC will receive interim summaries of safety and virologic data according to a schedule and in a format specified in the charter. The DMC will be informed if either of the efficacy treatment adjustment criteria in Section 5.4.1.2 are met. After each review, the DMC will communicate its recommendations to Abbott. Abbott will retain sole responsibility for study management, communication with study sites and regulatory authorities.

6.0 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record
any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet 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 Abbott as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

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

**Life-Threatening**
An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

**Hospitalization or Prolongation of Hospitalization**
An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

**Congenital Anomaly**
An anomaly detected at or after birth, or any anomaly that results in fetal loss.

**Persistent or Significant Disability/Incapacity**
An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome

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

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

Assessment of relatedness will be made with respect to the DAAs (ABT-450/r, ABT-267, and ABT-333), with respect to RBV and with respect to pegIFN (due to possible add-on
therapy). The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

<table>
<thead>
<tr>
<th>Reasonable Possibility</th>
<th>An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Reasonable Possibility</td>
<td>An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.</td>
</tr>
</tbody>
</table>

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, Abbott will consider the event associated.

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

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration (including any pegIFN/RBV add-on therapy) 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 until the end of their participation in the study.

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

Roger Trinh, MD, MPH

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

6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with Day 1 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 Abbott within 1 working day of the site becoming aware of the pregnancy. Female subjects who report a positive pregnancy test during the Treatment Period must be discontinued (Section 5.4.1) and notified to stop all study medication. The site must complete and fax to Abbott appropriate pregnancy-specific forms that will require the collection of maternal information and fetal
outcome information. 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 Abbott within 24 hours of the site becoming aware of the event.

6.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. A table of Clinical Toxicity Grades for evaluating laboratory abnormalities is provided in Appendix C. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 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 drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the Investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

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 study drug interruptions and/or RBV dose modifications and consequent required adverse events ensures that the Abbott Safety Team (Study Designated Physician, safety monitor, 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 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.

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. 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 drug; interruption of study drugs 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, all study drugs should be interrupted and the laboratory
parameter followed until it reaches Grade 1. The study drugs can be restarted if the laboratory parameter reaches Grade 1 within 7 days of study drug interruption. If the study drugs are interrupted and restarted and abnormality recurs, then all study drugs should be permanently discontinued. If the abnormality does not improve to Grade 1 or less within 7 days of interruption, the study drug 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. If the laboratory abnormality does not improve within 7 days, then study drugs should be permanently discontinued. 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.

**Severe Adverse Event**

If a subject experiences a severe drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed below in Sections 6.7.3 through 6.7.5) during the study, all study drugs should be interrupted. 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 adverse event (reasonable possibility) 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.

If a subject experiences a non drug-related severe adverse event (no reasonable possibility) study drugs may be continued.

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 adverse event (reasonable possibility) (other than those based on abnormal lab parameters discussed below in Sections 6.7.3 through 6.7.5) during the study, the study assignment should be permanently discontinued. 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 to the study drugs (no reasonable possibility), the 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 Abbott 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. Hemoglobin abnormalities should be managed according to Table 7. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease.

If a subject experiences a hemoglobin decrease (as outlined in Table 7), a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 7 should be followed.

Use of hematologic growth factors such as erythropoietin, filgrastim, or blood transfusions are not recommended; and are permitted only with approval of the Abbott Study Designated Physician. Management of hematologic growth factor therapy is the responsibility of the Investigator, and growth factors will not be provided by Abbott.

Alternate management of hemoglobin decreases requires approval of the Abbott Study Designated Physician.
### Table 7. Management of Hemoglobin Decreases

#### Hemoglobin in Patients with No Cardiac Disease

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.5 g/dL ≤ Hemoglobin &lt; 10.0 g/dL</td>
<td>Study drugs may be continued. Reduce RBV dose and continue to monitor hemoglobin per protocol. If hemoglobin increases to ≥ 10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments towards original dose. If Hb decreases to &lt; 8.5 g/dL see appropriate row below.</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.5 g/dL</td>
<td>Permanently discontinue all study drugs. Manage the subject as medically appropriate. Enter discontinuation into appropriate eCRFs and create corresponding adverse event.</td>
</tr>
<tr>
<td>Hemoglobin decrease of ≥ 4 g/dL between two scheduled study visits but hemoglobin ≥ 10 g/dL</td>
<td>Manage the subject as medically appropriate. Study drugs may be continued.</td>
</tr>
</tbody>
</table>

#### Hemoglobin in Patients with History of Stable Cardiac Disease

| Hemoglobin decrease of ≥ 2 g/dL from baseline during a 4-week treatment period (Hb ≥ 10 g/dL) without symptoms and/or signs of cardiac disease | Study drugs may be continued. Reduce RBV dose. Continue to monitor hemoglobin levels per protocol. 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. If hemoglobin does not increase; investigator may manage the subject as medically appropriate. If hemoglobin decreases to < 10 g/dL see appropriate row below. |
| Hemoglobin decrease of ≥ 2 g/dL from baseline during a 4-week treatment period (Hb ≥ 10 g/dL) with symptoms and/or signs of cardiac disease | If the subject has symptoms consistent with their cardiac disease; manage subject as medically appropriate; Abbott Study Designated Physician may be contacted. Study drugs may be continued. |
| Hemoglobin decrease ≥ 4 g/dL between study visits but hemoglobin ≥ 10 g/dL | Investigator should manage subject as medically appropriate, but study drugs may be continued. |
### Table 7. Management of Hemoglobin Decreases (Continued)

<table>
<thead>
<tr>
<th>Hemoglobin in Patients with History of Stable Cardiac Disease (continued)</th>
<th>Study drugs may be continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.5 g/dL ≤ Hemoglobin &lt; 10.0 g/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 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>
</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></td>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event (AE)</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.

If a subject experiences an ALT level ≥ 5 × ULN that is ≥ 2 × Baseline, a confirmatory test should be performed. If the ALT is confirmed ≥ 5 × ULN, the management guidelines in Table 8 should be followed.

Alternate management of ALT increases requires approval of the Abbott Study Designated Physician.
Table 8. Management of Confirmed ALT Levels $\geq 5 \times ULN$ and $\geq 2 \times$ Baseline

| ALT $\geq 10 \times ULN$ | • Permanently discontinue study drugs.  
| | • 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.  
| | • 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.  
| | • 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.
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 within 2 scheduled study visits (2 CrCl values still < 50 mL/min) then all study drug should be permanently discontinued, with further medical management as appropriate.

If CrCl improves consideration should be given to the readjustment 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 Abbott personnel:

Primary Contact: Theresa Brouillard
Alternate Contact: Sara Gibbs

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all randomized subjects have completed the Treatment Period through Post-Treatment Week 12 of the Post-Treatment Period or prematurely discontinued from the study. SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. The intent-to-treat (ITT) population will consist of all randomized subjects who receive at least one dose of study drug. Efficacy, safety, and demographic analyses will be performed on all subjects in the ITT population. If enrollment to the 12-week arm is discontinued and ongoing subjects in that arm have his/her treatment extended to 24 weeks, then these subjects will be grouped with
the 24-week arm in all efficacy and safety analyses. If the efficacy breakthrough criteria are met and pegIFN/RBV add-on therapy is offered, subjects who chose to add-on pegIFN/RBV treatment will be removed from the analysis of the efficacy and safety endpoints for the 12- and 24-week arms and summarized separately.

No data will be imputed for any efficacy or safety analyses 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. If a respondent answers at least 12 of the 16 items on the HCVPRO, 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 HCVPRO 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., SVR\textsubscript{4}, SVR\textsubscript{12}, SVR\textsubscript{24} [sustained virologic response 24 weeks post dosing]), 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 Day1/baseline characteristics will be summarized for each treatment arm for all subjects in the ITT population. Demographics include age, weight, height, and BMI, and the frequency of gender, race and ethnicity. Baseline characteristics will include HCV genotype 1 subtype (1a, 1b, other), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), pegIFN/RBV treatment history (treatment-naïve or treatment-experienced [null responder, partial responder, or relapser]), 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, or Australia). 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 arms. The number and percentage of subjects will be presented for categorical variables (e.g., gender and race); treatment arms will be compared using a chi-square test.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay version 2.0. 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.
8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are the percentage of subjects with SVR\textsubscript{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the 24-week and 12-week treatment arms. The simple percentage of subjects achieving SVR\textsubscript{12} within each treatment arm will be calculated and a two-sided 95% confidence interval of the percentage will be computed using the normal approximation to the binomial. For each arm, if the lower confidence bound is > 38% (based on a weighted SVR rate for treatment-naïve and treatment-experienced subjects with cirrhosis treated with boceprevir), then the arm will be considered successful. A fixed-sequence testing procedure will be used to control the Type I error rate at 0.05, where the SVR\textsubscript{12} rate for the 24-week arm will be tested first by comparing its lower confidence bound to 38%. The analysis will proceed to test the SVR\textsubscript{12} rate for the 12-week arm only if a lower confidence bound > 38% is achieved for the SVR\textsubscript{12} rate in the 24-week arm.

As a sensitivity analysis, the lower bound of the two-sided confidence interval for SVR\textsubscript{12} in each arm will be compared to 47%, based on the response rate observed for treatment with telaprevir + pegIFN/RBV in treatment-naïve and treatment-experienced subjects with cirrhosis.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

a. The percentage of subjects with RVR (HCV RNA < LLOQ at Week 4) in the 24-week arm;

b. The percentage of subjects with RVR (HCV RNA < LLOQ at Week 4) in the 12-week arm;

c. The percentage of subjects with EOTR (HCV RNA < LLOQ at Week 24) in the 24-week arm;
d. The percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12) in the 12-week arm;
e. The percentage of subjects with SVR<sub>12</sub> in the 24-week arm compared to the 12-week arm.

If success was demonstrated for both of the primary efficacy endpoints, then the fixed-sequence testing procedure will continue in the order listed above though the secondary efficacy endpoints. For secondary endpoints (a – d), the simple percentage of subjects achieving the response (RVR and EOTR) within each treatment arm will be calculated, and a two-sided 95% confidence interval of the percentage will be computed using the normal approximation to the binomial. For each endpoint, if the lower confidence bound is > 38%, then the arm will be considered successful for the endpoint, and testing will continue to the next endpoint; otherwise, testing will stop. If success is demonstrated for secondary endpoints (a – d), then the percentage of subjects with SVR<sub>12</sub> following 12 or 24 weeks of treatment will be compared using a logistic regression model with treatment arm, baseline log<sub>10</sub> HCV RNA level, HCV subtype (1a, non-1a), IL28B genotype (CC, non-CC), and pegIFN/RBV treatment history (naïve or experienced) as predictors.

8.1.2.3 Subgroup Analysis

The percentage (and two-sided confidence intervals) of subjects with SVR<sub>12</sub> for each treatment arm will be presented for the following subgroups:

- Treatment-naïve versus previous pegIFN/RBV treatment- experienced subjects;
  - For treatment-experienced subjects, type of response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser);
  - For subjects who are treatment-naïve, IL28B genotype (CC or non-CC), (CC, CT, or TT);
- HCV genotype 1 subtype (1a, 1b, other);
- Baseline HCV RNA level (≤ 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 ($< 65$ versus $\geq 65$ years);
- Race (Black versus non-black);
- Ethnicity (Hispanic versus none);
- Geographic Region (North America, Europe, or 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);
- Baseline Child-Pugh Score (5 versus 6).

If the lower confidence bound of the two-sided 95% confidence interval for a subgroup is $> 38\%$, then the regimen will be considered efficacious in the subgroup.

### 8.1.2.4 Additional Efficacy Endpoints

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

- The percentage of subjects with HCV RNA $< \text{LLOQ}$ at each post-baseline visit in the 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 on treatment;
The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed post-treatment within 4 weeks after the last actual dose of study drug;

The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed post-treatment within 12 weeks after the last actual dose of study drug;

The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed at anytime post-treatment;

Time to relapse at anytime post-treatment for subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit;

The percentage of subjects with SVR₄ weeks after the last actual dose of study drug (SVR₄);

The percentage of subjects with SVR₁₂ weeks after the last planned dose of study drug (SVR₁₂ planned);

The percentage of subjects with SVR₂₄ weeks after the last actual dose of study drug (SVR₂₄);

The percentage of subjects with SVR₂₄ weeks after the last planned dose of study drug (SVR₂₄ planned);

Mean change from baseline in liver function tests (e.g., PT/INR/Fibrotest) to each applicable post-baseline time point;

Mean change in MELD to each applicable post-baseline time point;

Shift from baseline to each applicable post-baseline time point in FibroTest score (< 0.59, 0.59 – 0.72, 0.73 – 0.74, 0.75 – 1.00).

In the above analyses for SVR, the percentage of subjects with SVR in each treatment arm will be calculated as a simple percentage and two-sided confidence intervals will be calculated using the normal approximation to the binomial. Analyses of mean change from baseline for the liver assessments (i.e., FibroTest score, PT/INR, and albumin) will be compared between treatment arms using an analysis of covariance (ANCOVA) model with treatment arm as a factor and baseline score as a covariate. Shifts from baseline will
be summarized descriptively. From HCV RNA levels, the time to suppression on
treatment and time to relapse post-treatment will be displayed graphically using
Kaplan-Meier curves.

Separate summaries for RVR, EOTR, SVR₄, SVR₁₂, and SVR₂₄ will be provided defined
by HCV RNA < LLOD in addition to the summaries based on HCV RNA < LLOQ.

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 minimally
  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 arm 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 Treatment
Visit and from Baseline to Post-Treatment Week 12 will be compared between treatment
arms 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 arm will be provided with percent change from baseline on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis. These plots will be used to show change from Baseline to Final Treatment Visit and change from Baseline to Post-Treatment Week 12.

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 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 treatment visit in the each of these measures > the appropriate MCID will be compared between treatment arms using a chi-square test (or Fisher's exact test as appropriate).

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

8.1.4 Resistance Analysis

The following resistance variables will be summarized for the subjects who experience virologic failure:

- The variants at each amino acid position (1) by nucleotide population sequencing at baseline compared to the prototypic standard reference sequence, and (2) by nucleotide population and/or clonal sequencing for each post-baseline time point that is analyzed compared to baseline and prototypic standard reference sequences.
a. Two non-failure subjects 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 vs. the group of subjects who did not experience 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 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 each treatment arm and within each subject, respectively. Four additional summaries (and accompanying listings) will be created for all subjects who do not achieve SVR\textsubscript{12} 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 Post-Treatment 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 study drug will be included in the safety analyses.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects in each treatment arm with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between the treatment arms using Fisher's exact tests. The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to study drug will also be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to
study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be performed if useful and appropriate.

8.1.5.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized by treatment arm at each visit. The baseline value will be the last measurement prior to the initial dose of study drug. Mean changes from baseline to each Post-Baseline Visit will be summarized and differences between the treatment arms will be analyzed using contrasts within an ANOVA model with treatment arm as the factor.

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 arm.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values will be summarized by treatment arm. Comparisons will be performed between the treatment arms of the percentage of subjects with Potentially Clinically Significant 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

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit will be summarized descriptively for each treatment arm and will be compared between the treatment arms using contrasts within an ANOVA model with treatment arm as the factor. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically
Significant vital signs values will be summarized. Comparisons of the percentage of subjects experiencing a value meeting the criteria between treatment arms will be performed 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) \text{(WTi-median value)} + \Theta(4) \text{(AGEi – 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 DAA. 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, SVR, SVR, 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 300 subjects in a 1:1 ratio to a 12- or 24-week treatment duration arm with 150 subjects in each arm. The primary efficacy endpoint of SVR will be assessed within each arm. With a sample size of 150 subjects in each arm, this study has greater than 90% power to achieve a two-sided 95% lower confidence bound greater than 38% if the underlying SVR rate is 51% or higher. Subjects who do not have data at Post-Treatment Week 12 (after imputing) count as failures for SVR so no adjustment for dropout is applicable.
8.3 Randomization Methods

Randomization to the 12- and 24-week treatment arms will occur until approximately 300 subjects are enrolled. In the study overall, subjects will be randomized in a 1:1 ratio to each arm. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. This allows more subjects to be enrolled to the 24-week arm at the start of the study which will expose more subjects to a 24-week duration until the adequacy of a 12-week duration has been established in a population of HCV genotype 1 subjects with compensated cirrhosis.

Subjects will be stratified by having received previous pegIFN/RBV treatment versus being treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll in this study. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapsers) and by HCV subgenotype (1a versus non-1a). No more than 150 treatment-experienced subjects will be allowed to enroll. Enrollment of the combined number of prior relapsers and prior partial responders will be limited to no more than 70.

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 International Conference on Harmonization (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 Abbott.

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.

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to Abbott 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 Abbott and will be maintained in the Trial Master File at Abbott.

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). Abbott (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.

### 11.0 Data Quality Assurance

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.

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 Abbott. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and Abbott. 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 Abbott 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 Abbott to arrange alternative archiving options.

Abbott 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, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

Protocol Date: 21 August 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 Abbott 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 Abbott, 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 Abbott 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 Abbott and/or the appropriate regulatory agency, and retaining all study-related documents until notification from Abbott.

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 Abbott.

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>Clinical</td>
</tr>
<tr>
<td>Theresa Brouillard</td>
<td>Clinical Research Management Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Roger Trinh</td>
<td>Associate Medical Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Heidi Wells</td>
<td>Clinical Supply Project Manager</td>
<td>Global Drug Supply Management</td>
</tr>
</tbody>
</table>
## Appendix C. 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 Neutrophil Count Decreased</td>
<td>&lt; LLN (\leq 1500/\text{mm}^3)</td>
<td>(1500 – 1000/\text{mm}^3)</td>
<td>(1000 – 500/\text{mm}^3)</td>
<td>(\leq 500/\text{mm}^3)</td>
</tr>
<tr>
<td>Eosinophil Count Increased</td>
<td>650 – 1500 cells/\text{mm}^3</td>
<td>1501 – 5000 cells/\text{mm}^3</td>
<td>&gt; 5000 cells/\text{mm}^3</td>
<td>Hypereosinophilic</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>&lt; LLN (\leq 10.0\ \text{g/dL})</td>
<td>(10.0 – 8.0\ \text{g/dL})</td>
<td>(8.0 – 6.5\ \text{g/dL})</td>
<td>(\leq 6.5\ \text{g/dL})</td>
</tr>
<tr>
<td>&lt; LLN (\leq 6.2\ \text{mmol/L})</td>
<td>(6.2 – 4.9\ \text{mmol/L})</td>
<td>(4.9 – 4.0\ \text{mmol/L})</td>
<td>(\leq 4.0\ \text{mmol/L})</td>
<td></td>
</tr>
<tr>
<td>&lt; LLN (\leq 100\ \text{g/L})</td>
<td>(100 – 80\ \text{g/L})</td>
<td>(80 – 65\ \text{g/L})</td>
<td>(\leq 65\ \text{g/L})</td>
<td></td>
</tr>
<tr>
<td>International Normalized Ratio (INR), Increased</td>
<td>(&gt; 1 – 1.5 \times \text{ULN})</td>
<td>(1.5 – 2 \times \text{ULN})</td>
<td>(2 \times \text{ULN})</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte Count Decreased</td>
<td>&lt; LLN (\leq 800/\text{mm}^3)</td>
<td>(800 – 500/\text{mm}^3)</td>
<td>(500 – 200/\text{mm}^3)</td>
<td>(\leq 200/\text{mm}^3)</td>
</tr>
<tr>
<td>&lt; LLN (\leq 0.8 – 10^9/\text{L})</td>
<td>(0.8 – 0.5 \times 10^9/\text{L})</td>
<td>(0.5 – 0.2 \times 10^9/\text{L})</td>
<td>(\leq 0.2 \times 10^9/\text{L})</td>
<td></td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>&lt; LLN (\leq 75,000/\text{mm}^3)</td>
<td>(75,000 – 50,000/\text{mm}^3)</td>
<td>(50,000 – 25,000/\text{mm}^3)</td>
<td>(\leq 25,000/\text{mm}^3)</td>
</tr>
<tr>
<td>&lt; LLN (\leq 75.0 \times 10^9/\text{L})</td>
<td>(75.0 – 50.0 \times 10^9/\text{L})</td>
<td>(50.0 – 25.0 \times 10^9/\text{L})</td>
<td>(\leq 25.0 \times 10^9/\text{L})</td>
<td></td>
</tr>
<tr>
<td>FTT</td>
<td>(&gt; 1 – 1.5 \times \text{ULN})</td>
<td>(1.5 – 2 \times \text{ULN})</td>
<td>(2 \times \text{ULN})</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count Decreased</td>
<td>&lt; LLN (\leq 3000/\text{mm}^3)</td>
<td>(3000 – 2000/\text{mm}^3)</td>
<td>(2000 – 1000/\text{mm}^3)</td>
<td>(\leq 1000/\text{mm}^3)</td>
</tr>
<tr>
<td>&lt; LLN (\leq 3.0 \times 10^9/\text{L})</td>
<td>(3.0 – 2.0 \times 10^9/\text{L})</td>
<td>(2.0 – 1.0 \times 10^9/\text{L})</td>
<td>(\leq 1.0 \times 10^9/\text{L})</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count Increased</td>
<td>10,800 – 15,000 cells/\text{mm}^3</td>
<td>&gt; 15,000 – 20,000 cells/\text{mm}^3</td>
<td>&gt; 20,000 – 25,000 cells/\text{mm}^3</td>
<td>&gt; 25,000 cells/\text{mm}^3</td>
</tr>
</tbody>
</table>

### CHEMISTRIES

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin, Serum, Low</td>
<td>&lt; LLN (\leq 3\ \text{g/dL})</td>
<td>(3 – 2\ \text{g/dL})</td>
<td>(2\ \text{g/dL})</td>
<td></td>
</tr>
<tr>
<td>&gt; ULN (\leq 1.5\ \text{ULN})</td>
<td>(1.5 – 3.0\ \text{ULN})</td>
<td>(3.0 – 10.0\ \text{ULN})</td>
<td>(10.0 \times \text{ULN})</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, High</td>
<td>(1.25 – 2.5\ \text{ULN})</td>
<td>(2.5 – 5.0\ \text{ULN})</td>
<td>(5 – 10.0\ \text{ULN})</td>
<td>(10 \times \text{ULN})</td>
</tr>
<tr>
<td>Calcium, Serum, Low</td>
<td>&lt; LLN (\leq 8.0\ \text{mg/dL})</td>
<td>(8.0 – 7.0\ \text{mg/dL})</td>
<td>(7.0 – 6.0\ \text{mg/dL})</td>
<td>(6.0 \text{mg/dL})</td>
</tr>
<tr>
<td>&lt; LLN (\leq 2.0\ \text{mmol/L})</td>
<td>(2.0 – 1.75\ \text{mmol/L})</td>
<td>(1.75 – 1.5\ \text{mmol/L})</td>
<td>(1.5 \text{mmol/L})</td>
<td></td>
</tr>
<tr>
<td>Calcium, Serum, High</td>
<td>&gt; ULN (\leq 11.5\ \text{mg/dL})</td>
<td>(11.5 – 12.5\ \text{mg/dL})</td>
<td>(12.5 – 13.5\ \text{mg/dL})</td>
<td>(13.5\ \text{mg/dL})</td>
</tr>
<tr>
<td>&gt; ULN (\leq 2.9\ \text{mmol/L})</td>
<td>(2.9 – 3.1\ \text{mmol/L})</td>
<td>(3.1 – 3.4\ \text{mmol/L})</td>
<td>(3.4\ \text{mmol/L})</td>
<td></td>
</tr>
</tbody>
</table>
### Clinical Toxicity Grades for HCV Studies

<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>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>
<td>&lt; 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>
<td>&gt; 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>
<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>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>
<td>&gt; 2.5 mg/dL or requires dialysis</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>
<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>GLUCOSE, SERUM, HIGH</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>(Fasting)</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>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>
<td>&lt; 0.7 mg/dL</td>
</tr>
<tr>
<td>MAGNESIUM, SERUM, 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 – 3.0 mmol/L</td>
<td>&gt; 3.0 mmol/L</td>
<td></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>
<td>&lt; 1.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt; LLN – 0.8 mg/dL</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>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>
<td></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>
<td>&gt; 7.0 mmol/L</td>
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<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>
<td></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>
<td>&gt; 160 mmol/L</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitalization may be indicated</td>
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</tr>
<tr>
<td>TRIGLYCERIDES HIGH</td>
<td>150 – 300 mg/dL</td>
<td>&gt; 300 – 500 mg/dL</td>
<td>&gt; 500 – 1000 mg/dL</td>
<td>&gt; 1000 mg/dL</td>
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<tr>
<td>(Fasting)</td>
<td>1.71 – 3.42 mmol/L</td>
<td>&gt; 3.42 – 5.7 mmol/L</td>
<td>&gt; 5.7 – 11.4 mmol/L</td>
<td>&gt; 11.4 mmol/L</td>
</tr>
<tr>
<td>CHEMISTRIES (continued)</td>
<td>GRADE 1 TOXICITY</td>
<td>GRADE 2 TOXICITY</td>
<td>GRADE 3 TOXICITY</td>
<td>GRADE 4 TOXICITY</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>------------------</td>
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</tr>
<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.
Document Approval

Study M13099 - A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis - EudraCT - 2012-003088-23 - 21Aug2012

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Clinical Study Protocol M13-099

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

Incorporating Administrative Changes 1 and 2 and Amendments 1, 2, 3 and 4

AbbVie Investigational Product: ABT-450/r/ABT-267, ABT-333
Date: 07 May 2013
Development Phase: 3
Study Design: This is a randomized, open-label combination drug study.
EudraCT Number: 2012-003088-23
Investigator: Multicenter. Investigator information is on file at AbbVie.
Sponsor: AbbVie*
Sponsor/Emergency Contact: Roger Trinh, MD, MPH

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.

- Update the approximate number of subjects to be enrolled into the study.

  Rationale: *Approximate number of subjects to be enrolled into the study increased from approximately 300 to approximately 380.*

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

<table>
<thead>
<tr>
<th>AbbVie</th>
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<tr>
<td><strong>Name of Study Drug:</strong></td>
<td><strong>Phase of Development:</strong></td>
</tr>
<tr>
<td>ABT-450, ritonavir, ABT-267, ABT-333</td>
<td>Phase 3</td>
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</table>

<table>
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<tr>
<th>Name of Active Ingredient:</th>
<th>Date of Protocol Synopsis: 07 May 2013</th>
</tr>
</thead>
<tbody>
<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-tetradecahydrocyclopenta[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</td>
<td></td>
</tr>
<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-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}bicarbamate 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, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

**Objectives:**
The primary objectives of this study are to assess the safety and to compare the SVR_{12} rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12} (HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment) of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with RBV for 12 or 24 weeks to the historical SVR rate of telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults with compensated cirrhosis. The secondary objectives of this study are to compare SVR_{12} between the 12- and 24-week treatment arms and assess the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.

**Investigator:**
Multicenter trial: Investigator information is on file at AbbVie.
### Study Site:
Approximately 75 sites.

### Study Population:
Adults age 18 to 70 years of age, inclusive with HCV genotype 1, treatment-naïve and previous pegIFN (pegylated-interferon alfa-2a or alfa-2b)/RBV treatment-experienced adults with compensated cirrhosis.

### Number of Subjects to be Enrolled:
Approximately 380 subjects.

### Methodology:
This is a Phase 3, randomized, open-label, multicenter study evaluating the efficacy and safety of ABT-450/r/ABT-267 and ABT-333 coadministered with ribavirin for 12 or 24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis.

The treatment arms are:

- **Arm A:** ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) + RBV* for 12 weeks
- **Arm B:** ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 24 weeks
  
  * RBV will be administered weight-based 1000 – 1200 mg divided to twice daily.

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 380 subjects are enrolled at approximately 75 sites. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. Subjects will be stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B (Interleukin 28B) genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapers) and by HCV subgenotype (1a versus non-1a).

The treatment-experienced subjects are defined as follows:

- **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 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 (≥ 25 days);  

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

- **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.
Methodology (Continued):

The number of null responders according to definition 2 will be limited to approximately 25% of the overall null responder study population to ensure adequate representation of the presumed harder-to-treat population of null responders according to definition 1.

This study will consist of a Treatment Period and a Post-Treatment (PT) Period. All subjects dosed with study drug who complete or prematurely discontinue study drug will be followed for 48 weeks in the Post-Treatment Period, to monitor safety, HCV RNA, the emergence and persistence of viral variants and assessment of patient reported outcomes (PROs).

Visits will occur during the treatment period at Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12 for all subjects and at Weeks 16, 20, and 24 for subjects in the 24-week arm, and Post-Treatment Weeks 2, 4, 8, 12, 24, 36, and 48.

The safety data will be reviewed by the sponsor, as this is an open-label study, and by an independent Data Monitoring Committee (DMC) during the Treatment Period of the study.

Virologic Failure Criteria

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

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log_{10} IU/mL above nadir) at any time point during treatment;
- 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 during treatment.

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met for a subject in the Treatment Period, study drug will be discontinued.

All subjects who receive at least one dose of study drug in the Treatment Period will be monitored in the Post-Treatment Period for safety, HCV RNA, the durability of viral response, for the emergence and persistence of resistant viral variants and assessment of PROs for up to 48 weeks following the last dose of study drug. Resistance monitoring following the end of therapy will take place regardless of whether subjects receive any other anti-viral therapy post-treatment.

The Sponsor will evaluate efficacy throughout the Treatment and Post-Treatment Periods in this open-label study. If excessive rates of virologic failure or virologic relapse are observed, enrollment will be stopped or treatment durations will be extended to 24 weeks. Modifications will be applied to all subjects or for appropriate subgroups depending on the pattern of virologic failure.
<table>
<thead>
<tr>
<th>Diagnosis and Main Criteria for Inclusion/Exclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Inclusion:</strong></td>
</tr>
<tr>
<td>1. Male or female and age is between 18 and 70 years, inclusive, at time of Screening.</td>
</tr>
<tr>
<td>2. Chronic HCV-infection prior to study enrollment. Chronic HCV-infection is defined as one of the following:</td>
</tr>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>3. Screening laboratory result indicating HCV genotype 1-infection.</td>
</tr>
<tr>
<td>4. Compensated cirrhosis defined as a Child-Pugh Score of ( \leq 6 ) at Screening</td>
</tr>
<tr>
<td>5. Subject has plasma HCV RNA level &gt; 10,000 IU/mL at Screening.</td>
</tr>
<tr>
<td><strong>Main Exclusion:</strong></td>
</tr>
<tr>
<td>1. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).</td>
</tr>
<tr>
<td>2. Prior therapy with direct acting antiviral agents for the treatment of HCV, including telaprevir and boceprevir.</td>
</tr>
<tr>
<td>3. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding, or hepatic encephalopathy.</td>
</tr>
<tr>
<td>4. A positive screening ultrasound for hepatocellular carcinoma (HCC) confirmed with a subsequent CT Scan or MRI during the Screening Period.</td>
</tr>
<tr>
<td>5. Any cause of liver disease other than chronic HCV-infection, including but not limited to the following:</td>
</tr>
<tr>
<td>• Hemochromatosis</td>
</tr>
<tr>
<td>• Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td>• Wilson's disease</td>
</tr>
<tr>
<td>• Autoimmune hepatitis</td>
</tr>
<tr>
<td>• Alcoholic liver disease</td>
</tr>
<tr>
<td>• Drug-related liver disease</td>
</tr>
</tbody>
</table>
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.
## Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

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

   - Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) > 7 × ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
   - Albumin < 2.8 g/dL
   - International normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
   - Hemoglobin < LLN
   - Platelets < 60,000 cells per mm\(^3\)
   - Absolute neutrophil count (ANC) < 1500 cells/μL (< 1200 cells/μL for subjects of black/African descent)
   - Total bilirubin ≥ 3.0 mg/dL

## Investigational Product:

- ABT-450/Ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablet
- ABT-333 250 mg tablet
- Ribavirin 200 mg tablet

## Dose:

- ABT-450/Ritonavir/ABT-267 150/100/25 mg QD
- ABT-333 250 mg BID
- Ribavirin weight-based dosing 1000 to 1200 mg divided twice daily

## Mode of Administration:

Oral

## Duration of Treatment:

Subjects will receive ABT-450/Ritonavir/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks.

## Criteria for Evaluation:

### Efficacy:

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

### Patient Reported Outcomes (PROs):

The change in general and disease-specific Health Related Quality of Life (HRQoL) will be assessed using the SF-36v2 (Short Form 36-Version 2) and HCV Patient Reported Outcomes (HCVPRO) instruments, respectively. Health State Utility will be measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L).
Criteria for Evaluation (Continued):

**Resistance:**
For subjects receiving study 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 variants at each amino acid position by population and/or clonal nucleotide sequencing at the available post-baseline time points compared to baseline and the appropriate prototypic reference sequences will be tabulated and summarized.

**Pharmacokinetic:**
Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-267 metabolites ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be determined at each study visit up to the end of treatment (12 or 24 weeks).

**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 efficacy endpoints are the percentage of subjects with SVR\(_{12}\) (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) within each treatment arm. The overall 2-sided significance level of 0.05 will be split between the two arms using a Bonferroni correction of 0.025 for each arm. The percentage of subjects achieving SVR\(_{12}\) within each treatment arm will be calculated and a 2-sided 97.5% confidence interval (CI) of the percentage will be computed using the normal approximation to the binomial distribution. A gatekeeping testing procedure will be used to control the Type I error rate at 0.05 and the primary endpoints within Arm A will be tested separately from Arm B in the following order:

A1. SVR\(_{12}\): Non-inferiority of Arm A to the historical SVR rate for telaprevir plus peglFN and RBV therapy; the lower confidence bound (LCB) of the 97.5% CI for the percentage of subjects with SVR\(_{12}\) in Arm A must exceed 43% to achieve non-inferiority.

A2. SVR\(_{12}\): Superiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\(_{12}\) in Arm A must exceed 54% to achieve superiority.

B1. SVR\(_{12}\): Non-inferiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\(_{12}\) in Arm B must exceed 43% to achieve non-inferiority.

B2. SVR\(_{12}\): Superiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\(_{12}\) in Arm B must exceed 54% to achieve superiority.
Statistical Methods (Continued):

Efficacy (Continued):

Within Arm A, only if success has been demonstrated for non-inferiority of the SVR\(_{12}\) rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A1) will the testing continue to superiority of the SVR\(_{12}\) rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A2). Within Arm B, only if success has been demonstrated for non-inferiority of the SVR\(_{12}\) rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) will the testing continue to superiority of the SVR\(_{12}\) rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B2). Otherwise, statistical testing will stop. If success is achieved for all of the primary endpoints (A1, A2, B1, and B2), then the first secondary endpoint will be tested; otherwise, statistical testing will stop.

To test the hypothesis that the percentage of treatment-naïve and pegIFN/RBV treatment-experienced HCV genotype 1 infected subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 or 24 weeks who achieve SVR\(_{12}\) is non-inferior or superior to the historical SVR\(_{12}\) rate for the corresponding population treated with telaprevir plus pegIFN and RBV, the percentage of subjects with SVR\(_{12}\) will be calculated with a 2-sided 97.5% CI, and the LCB will be compared to the defined thresholds. The LCB of the 97.5% CI must be greater than 43% in order for the regimen to be considered non-inferior, and the LCB of the 97.5% CI of the SVR\(_{12}\) rate must be greater than 54% in order for the regimen to be considered superior.

The secondary efficacy endpoints are:

- The percentage of subjects with SVR\(_{12}\) in the 24-week arm compared to the 12-week arm;
- The percentage of subjects in each arm with on-treatment virologic failure during the 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 each arm 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).

If success was demonstrated for all of the primary efficacy endpoints, then the multiple testing procedure will continue to the first secondary efficacy endpoint to compare the percentage of subjects with SVR\(_{12}\) following 12 or 24 weeks of treatment. To test the hypothesis that the percentages of subjects who achieve SVR\(_{12}\) is different between Arm A and Arm B, the percentages will be compared using a logistic regression model with treatment arm, baseline log\(_{10}\) HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non-CC), and pegIFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.

The percentages (with 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 for each arm. These endpoints will not be part of the multiple testing procedure as no hypothesis is being tested.
Statistical Methods (Continued):

Resistance:
The following resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR and 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 within each treatment arm, and 4) the persistence of viral resistance will be summarized.

Pharmacokinetic:
Plasma concentrations for ABT-450, possible ABT-450 metabolites, ritonavir, ABT-267, ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites and RBV will be determined and summarized at each study visit through the end of the Treatment Period (Week 12 or Week 24).

Safety:
The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment arm, and comparisons will be performed using Fisher's exact test. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by severity (mild, moderate, or severe) and relationship to study drug(s). Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects within each treatment arm with potentially clinically significant values during treatment will be calculated and compared between the treatment arms using Fisher's exact test.

Sample Size:
With a total sample size of about 380 subjects and assuming that 68% of the subjects in each arm will achieve SVR_{12}, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90% power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54%. Subjects who do not have data at Post-Treatment Week 12 (after imputing) count as failures for SVR_{12} so no adjustment for dropout is applicable.
1.3 List of Abbreviations and Definition of Terms

Abbreviations

AARDEX Advanced Analytical Research on Drug Exposure
Ab Antibody
ABT-450/r/ABT-267 ABT-450 co-formulated with ritonavir and ABT-267
AE Adverse event
ALT Alanine aminotransferase
ANC Absolute neutrophil count
ANCOVA Analysis of covariance
ANOVA Analysis of variance
aPTT Activated partial thromboplastin time
AST Aspartate aminotransferase
AUC Area Under the Concentration Curve
BID Twice Daily
BMI Body mass index
BOC Boceprevir
BUN Blood urea nitrogen
CL/F Apparent Oral Clearance
CR/CL Creatinine clearance
CRF Case report form
CT Computed Tomography
CYP2C8 Cytochrome P450 2C8
CYP3A Cytochrome P450 3A
DAA Direct-acting antiviral agent
D/C Discontinuation
DMC Data Monitoring Committee
DNA Deoxyribonucleic acid
EC Ethics Committee
ECG Electrocardiogram
eCRF Electronic case report form
EDC Electronic data capture
EDTA Edetic acid (ethylenediaminetetraacetic acid)
EOT End of treatment
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>EOTR</td>
<td>End of treatment response</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<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>
</tr>
<tr>
<td>GAM</td>
<td>Generalized additive method</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
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<tr>
<td>GT</td>
<td>Genotype</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
</tr>
<tr>
<td>hCG</td>
<td>Human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<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</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HIV Ab</td>
<td>Human immunodeficiency virus antibody</td>
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<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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<td>IFN</td>
<td>Interferon</td>
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<td>IL28B</td>
<td>Interleukin 28B</td>
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<tr>
<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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<tr>
<td>IP-10</td>
<td>Interferon gamma-induced protein 10</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IRT</td>
<td>Interactive Response Technology</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent to Treat</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<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>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental Component Summary</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>MID</td>
<td>Minimally Important Difference</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger Ribonucleic acid</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NONMEM</td>
<td>Non-linear mixed-effect modeling</td>
</tr>
<tr>
<td>NS3A</td>
<td>Nonstructural viral protein 3A</td>
</tr>
<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>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical Component Summary</td>
</tr>
<tr>
<td>PegIFN</td>
<td>Pegylated-interferon alfa-2a or alfa-2b</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>POR</td>
<td>Proof of Receipt</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient Reported Outcomes</td>
</tr>
<tr>
<td>PT</td>
<td>Post-Treatment</td>
</tr>
<tr>
<td>QD</td>
<td>Once daily</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate</td>
</tr>
<tr>
<td>QTcF</td>
<td>QTc using Fridericia's correction formula</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>RBV</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase PCR</td>
</tr>
<tr>
<td>RVR</td>
<td>Rapid virologic response</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>sAFP</td>
<td>Serum Alpha-Fetoprotein</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SF-36 V2</td>
<td>Short Form 36-Version 2</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
</tbody>
</table>
SOC  System Organ Class
SUSAR  Suspected Unexpected Serious Adverse Reaction
SVR  Sustained virologic response
SVR<sub>4</sub>  Sustained virologic response 4 weeks post dosing
SVR<sub>12</sub>  Sustained virologic response 12 weeks post dosing
SVR<sub>24</sub>  Sustained virologic response 24 weeks post dosing
TP  Treatment Period
TVR  Telaprevir
ULN  Upper limit of normal
VAS  Visual analogue scale
V/F  Apparent Volume of distribution
WBC  White blood cells

**Definition of Terms**

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 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).

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

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.

Study Drug  ABT-450/r/ABT-267, ABT-333, RBV
Study Day 1  First day of study drug dosing
Treatment Period  Baseline/Day 1 through last dose of study drug
Post-Treatment Period  Day after the last dose of study drug through Post-Treatment Week 48 or Post-Treatment Discontinuation
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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.\(^1\) Cirrhosis is a common sequelae of HCV infection occurring in approximately 20% of patients.\(^2\) Complications of cirrhosis include hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and hepatocellular carcinoma ensue at a rate of about 3% per year.\(^3\) Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.\(^7\) As a result of the high prevalence of HCV infection and resultant complications, HCV is the leading indication for liver transplantation in the United States and the world as a whole.\(^8\)

Patients with compensated cirrhosis who achieve an SVR (sustained virologic response) essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of hepatocellular carcinoma by two-thirds.\(^9\)\(^-\)\(^11\)

While the introduction of the protease inhibitors, telaprevir (TVR) or boceprevir (BOC), have increased SVR rates, current treatment is less than optimal as the protease inhibitors must be used in combination with pegIFN/RBV, two agents with considerable treatment limiting toxicities and treatment may extend for up to 48 weeks. Furthermore, regardless of a patient's treatment history, treatment of HCV infected patients with underlying cirrhosis with either telaprevir or boceprevir in combination with pegIFN/RBV results in lower rates of SVR when compared to overall response rates: treatment-naïve patients treated with TVR (62% response rate in cirrhotics versus 79% overall response rate in the ADVANCE study),\(^12\)\(^,\)\(^13\) prior partial responders treated with TVR (34% response rate in cirrhotics versus 59% overall response rate in the REALIZE study),\(^14\)\(^,\)\(^15\) prior null responders treated with TVR (14% response rate in cirrhotics versus 32% overall response rate in the REALIZE study),\(^14\)\(^,\)\(^15\) treatment-naïve patients treated with BOC (31% to 42% response rate in cirrhotics versus 62% to 66% overall response in the SPRINT-2 study),\(^16\) and treatment-experienced patients treated with BOC (35% response in cirrhotics versus 59% overall response rate in the RESPOND-2 study).\(^16\)
Combinations of multiple DAAs (direct-acting antiviral agent) have the potential of further improving HCV treatment by increasing SVR rates, eliminating interferon (IFN) as a component of therapy, increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. Promising short-term antiviral efficacy results have been reported from IFN-free combinations (either with or without RBV) of a protease inhibitor with a nucleoside polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a nonstructural protein 5A (NS5A) inhibitor. Twelve-week SVR (SVR12) rates of 36% (4/11 HCV genotype 1-infected null responders) and 90% (9/10 HCV genotype 1b-infected null responders) have been observed in subjects treated with the combination of a protease inhibitor and NS5A inhibitor (BMS-650032 and BMS-790052) for 24 weeks. Additionally, a recent descriptive sub-analysis from the SOUND-C2 study, a Phase 2b study evaluating IFN-free treatment with Boehringer Ingelheim's investigational DAA compounds BI 201335 and BI 207127 plus RBV, reported SVR12 rates of 54% (20/37) in genotype 1, treatment-naive patients with compensated liver cirrhosis, regardless of IL-28B allele status.

Together, these safety and efficacy data suggest that interferon-free DAA combinations may address patient's needs and further advance HCV therapy by increasing SVR rates even in difficult-to-treat populations, improving safety and tolerability of treatment, reducing duration, and simplifying treatment.

AbbVie currently has a number of DAAs in clinical development: ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor, ABT-267 is a NS5A inhibitor and ABT-333 is a non-nucleoside nonstructural protein 5B (NS5B) polymerase inhibitor. Based on data from a Phase 2b study (Study M11-652), AbbVie has identified a DAA combination regimen, ABT-450 with ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with RBV, that appears safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects.

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. The majority of subjects in all 8- and 12-week treatment arms have completed study treatment and are in post-treatment follow-up. Among the treatment-naïve subjects, the intent-to-treat (ITT) SVR\textsubscript{12} rate in those treated with 4 drugs (ABT-450/r + ABT-267 + ABT-333 with RBV) for 12 weeks is 97.5% (77/79). The ITT SVR\textsubscript{12} rates were numerically lowest in the 8-week treatment group and the ABT-450/r + ABT-333 +RBV group at 88% (70/80) and 85% (35/41), respectively. The ITT SVR\textsubscript{12} rates in the 12-week groups without ABT-333 and without RBV are 90% and 87%, respectively.

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 SVR\textsubscript{12} rates. Numerically higher SVR\textsubscript{12} results (21/22 subjects, 96%) were observed as 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%). For this reason, the regimen of ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD and ABT-333 250 mg BID coadministered with RBV is being assessed in this 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 study is intended to examine the safety and efficacy of the combination of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in treatment-naïve and pegIFN/RBV treatment-experienced adults with chronic HCV GT1 infection and compensated cirrhosis.

3.1 Differences Statement

The combination of ABT-450/r, ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks was explored in treatment-naïve and treatment-experienced subjects without cirrhosis in Study M11-652. This is the first study to evaluate ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in HCV genotype 1-infected subjects with compensated cirrhosis.
3.2 Benefits and Risks

This study consists of two arms in which ABT-450/r/ABT-267 and ABT-333 is coadministered with RBV for either 12 or 24 weeks in HCV genotype 1-infected patients with compensated cirrhosis. A combination of an investigational protease inhibitor and a non-nucleoside polymerase inhibitor administered with RBV for 28 or 40 weeks resulted in SVR12 in 20/37 (54%) in genotype 1, treatment-naive patients with compensated cirrhosis.\textsuperscript{22} AbbVie's DAA regimen consists of a potent ritonavir boosted protease inhibitor, ABT-450/r, a non-nucleoside polymerase inhibitor, ABT-333, and RBV. Moreover, an additional investigational DAA with a novel mechanism of action, ABT-267, an oral NS5A inhibitor, is included in the AbbVie DAA combination regimen and will likely increase the percentage of patients achieving an SVR.

The likelihood of successfully curing HCV in compensated cirrhotics following 12 or 24 weeks of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV is unknown. However, preliminary results from the ongoing Study M11-652 in which ABT-450/r, ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in a treatment-experienced, prior null responder population are promising. Based on data from Study M11-652, the SVR\textsubscript{12} rate of 12 weeks of ABT-450/r, ABT-333, ABT-267 coadministered with RBV in a null responder population is 91% and 96% with the lower dose of ABT-450/r (100/100 mg) and the higher dose of ABT-450/r (150/100 mg), respectively. In the 24-week treatment arms, 98% of subjects have achieved SVR\textsubscript{4} and a similar SVR\textsubscript{12} rate to that seen in the 12-week arm is expected. Partial responders and relapsers have had higher SVR rates than null responders in multiple regimens by other sponsors.

ABT-450/r, ABT-267 and ABT-333 coadministered with RBV has been well tolerated in the M11-652 Study. Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the informed consent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures. Additional safety data of the DAAs alone and in combination is
detailed in the Investigator's Brochure. In addition, safety of the combination in
treatment-naïve and experienced subjects in Study M11-652 is detailed in Section 3.0.

Risks associated with ABT-450/r/ABT-267 and ABT-333 coadministered 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 Objectives

4.1 Primary Objective

The primary objectives of this study are to assess the safety and to compare the SVR_{12}
rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR_{12}
[HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following
treatment]) of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and
ABT-333 coadministered with ribavirin (RBV) for 12 or 24 weeks to the historical SVR
rate of telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults with
compensated cirrhosis.

4.2 Secondary Objective

The secondary objectives of this study are to compare the SVR_{12} rates between the
12- and 24-week treatment arms and assess the percentage of subjects with virologic
failure during treatment and the percentage of subjects with relapse post-treatment.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and
efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or
24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV
treatment-experienced adults with compensated cirrhosis.

The treatment arms are:

Arm A: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID +
RBV* for 12 weeks

Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID +
RBV* for 24 weeks

* RBV will be administered weight-based 1000 – 1200 mg divided twice daily.

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week
treatment arms until approximately 380 subjects are enrolled at approximately 75 sites.
At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the
12- and 24-week arms. After the first 200 subjects are enrolled, the remaining subjects
will be randomized in a 3:1 ratio to the 12- and 24-week arms. Subjects will be stratified
by having received previous pegIFN/RBV treatment (treatment-experienced) versus being
treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll.
The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a)
and by IL28B (Interleukin 28B), genotype (CC versus non-CC). The
treatment-experienced subjects will be stratified by type of non-response to previous
pegIFN/RBV treatment (null responder, partial responder, or relapser) and by HCV
subgenotype (1a versus non-1a). 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 approximately 25% of the total null responder
study population to ensure adequate representation of the presumed harder-to-treat
population of null responders according to definition 1.
This study will consist of a Treatment Period and a Post-Treatment (PT) Period.

During the Treatment Period, subjects will receive treatment with ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for either 12 or 24 weeks.

Upon completing the Treatment Period or premature discontinuation of the Treatment Period, subjects will enter the 48-week Post-Treatment Period.

As this is an open-label study, safety and efficacy evaluations will occur throughout the Treatment and Post-Treatment Periods. If efficacy failure criteria as detailed in Section 5.4.1.2 are met, the findings will be reviewed by the Sponsor and the DMC (refer to Section 5.7). Based on efficacy breakthrough criteria observed during treatment, enrollment in both the 12-week and 24-week arms may be terminated and subjects ongoing in either treatment arm may be offered add-on pegIFN/RBV treatment as detailed in Section 5.4.1.2. In this case, the AbbVie regimen will be continued for 12 or 24 weeks as specified while pegIFN at standard doses is added on to continue beyond the end of the AbbVie regimen for a total of 48 weeks. The pegIFN/RBV will be provided at no cost to the subject.

In addition, enrollment in the 12-week treatment arm (or in some strata of the 12-week arms) may be terminated based upon virologic relapses post-treatment as detailed in Section 5.4.1.2. If the 12-week treatment arm is terminated from further enrollment, subjects randomized to that arm who are in the Treatment Period at the time of the termination may have the duration of their treatment extended to 24 weeks.
The primary analysis will occur after all randomized subjects have completed the Treatment Period through Post-Treatment Week 12 of the Post-Treatment Period or prematurely discontinued from the study.

5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via the Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 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 Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 35 days following the Screening Visit to enroll into the study.

Subjects who meet all eligibility criteria with the exception of their initial non-invasive assessment of liver cirrhosis by FibroScan may undergo a liver biopsy.

Liver biopsy should only be performed during the Screening Period if all inclusion criteria and none of the exclusion criteria are met (see Section 5.3.1.1 for exception regarding FibroScan).

The study is designed to enroll approximately 380 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

5.1.1.1 Rescreening

Subjects who test positive at Screening for any of the following parameters are not eligible to rescreen:
- Exclusionary HCV genotype,
- Positive drug screen (without prescription for the positive drug, or positive for alcohol),
- Positive HIV, HBV (Hepatitis B Virus),
- Positive pregnancy test.

Subjects may be rescreened only once as follows:

- Subjects who meet all eligibility criteria with the exception of one exclusionary laboratory parameter may rescreen without prior Sponsor approval.
- Subjects who otherwise meet all eligibility criteria, but have a positive urine alcohol screen, may have only the urine alcohol screen repeated. If the repeat urine alcohol screen is negative the subject may be considered eligible.
- Subjects who have multiple exclusionary laboratory results, approval is required from the AbbVie Study Designated Physician prior to rescreening the subject.
- 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 without approval of the AbbVie Study Designated Physician.
- Subjects that screen failed due to eligibility criteria that were subsequently amended may rescreen once under the amended protocol with approval of the AbbVie Study Designated Physician.
- Subjects may rescreen once for any other reason with approval of the AbbVie Study Designated Physician.

Subjects being rescreened must be rescreened for all laboratory and eligibility criteria, not just those that were exclusionary (unless otherwise noted in Section 5.1.1.1 above) at the first screening attempt, (with the exception of HCV genotype, IL28B genotype, FibroScan/liver biopsy and ultrasound of the liver, which do not need to be repeated).
For subjects who rescreen or subjects that do not meet the study eligibility criteria, the site personnel must contact the IRT and identify the subject as a screen failure.

### 5.1.2 Treatment Period (TP)

After meeting the eligibility criteria, subjects will be randomized via IRT to either 12 or 24 weeks of treatment. Approximately 380 subjects will be randomized. Subjects will be administered study drugs at the site on Study Day 1. Subjects will receive instructions about the study drugs and the dosing schedule at the Day 1 Visit.

ABT-450/r/ABT-267 will be administered orally once daily and ABT-333 and RBV will be dosed orally twice daily as described in Section 5.5.1. The doses are as follows:

- ABT-450/r/ABT-267 150/100/25 mg QD
- ABT-333 250 mg BID
- 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)

Subjects will be administered the first doses of study drugs at the site on Study Day 1 (ABT-450/r/ABT-267, ABT-333, and RBV). All subjects will have the original caps of the bottles for ABT-450/r/ABT-267, ABT-333, and RBV replaced by a Medication Event Monitoring System (MEMS) monitor (cap), manufactured by Advanced Analytical Research on Drug Exposure Ltd. (AARDEX). The MEMS cap will be used to obtain dosing histories. See Section 5.3.1.1 and Section 5.5.8 for further details regarding the MEMS cap.

Plasma samples for pharmacokinetic analysis and HCV RNA analysis will be collected on Study Day 1 prior to dose and at 2 hours post dose and at the additional visits detailed in Table 2.
All subjects will continue to return to the site on an outpatient basis up to Week 12 or Week 24 for the study procedures identified in Table 2. Sites should ensure that subjects adhere to the study visits listed in Table 2. Subjects who cannot complete their study visit per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Some of the Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, 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.

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (refer to Table 2 and Table 4). Blood samples for optional pharmacogenetic analysis, and optional messenger RNA will be collected as detailed in Table 2. Patient Reported Outcomes (PROs) will also be assessed at the visits listed in Table 2. Ongoing review of the data is planned in order to determine if subjects meet the virologic failure criteria (Section 5.4.1.1).

Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.1.1. The Sponsor will evaluate efficacy failure criteria throughout the Treatment and Post-Treatment Periods in this open-label study as detailed in Section 5.4.1.2.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Table 2 and as described in Section 5.4.1. Ideally, this should occur on the day of study drug discontinuation, but should be no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy if applicable. Subjects who complete or discontinue treatment will be monitored for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs in the 48-week Post-Treatment Period as detailed in Section 5.1.3.
All subjects who receive at least one dose of DAA and who do not achieve and maintain virologic suppression (HCV RNA < LLOQ), or who relapse post DAA therapy, may be offered alternate treatment as described in Section 5.1.3.

5.1.3 Post-Treatment (PT) Period

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last dose of study drug.

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

Subjects who prematurely discontinue the Post-Treatment Period should return to the site for a Post-Treatment discontinuation visit as outlined in Table 3.

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 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.

5.2 Selection of Study Population

The study population consists of HCV genotype 1-infected adult subjects with compensated cirrhosis who are either treatment-naïve or pegIFN/RBV treatment-experienced. Refer to Section 5.2.3.1 for details regarding required documentation for prior pegIFN/RBV treatment failures.

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

5.2.1 Inclusion Criteria

1. Male or female between 18 and 70 years of age, 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 using two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent
form or other subject information documents), starting with Study Day 1 and for 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 study drug treatment.)

3. Females must have negative results (unless otherwise noted below) for pregnancy tests performed:
   - at Screening by a serum specimen obtained within 35 days prior to initial study drug administration, and
   - at Study Day 1 (Baseline, prior to dosing) by a urine specimen.
Female subjects with a borderline hCG 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 two effective forms of birth control (as outlined in the subject informed consent or other subject information documents) throughout the course of the study, starting with 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 study drug treatment.)

5. Subject has never received antiviral treatment (including pegIFN/RBV) for hepatitis C infection (treatment-naïve subject), or subject must have documentation that they were adherent to prior pegIFN/RBV therapy and meet one of the following categories (treatment-experienced subject):
• 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 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 $\geq 2 \log_{10}$ 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.

HCV RNA levels that serve as documentation to support the type of prior non-response should have been 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 $\geq 18$ to $< 38 \text{ kg/m}^2$ 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 Institutional Review Board (IRB)/Independent Ethics Committee (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, documentation of cirrhosis by one of the following methods:

- Previous histologic diagnosis on liver biopsy, e.g., Metavir Score of > 3 (including 3/4 or 3–4), Ishak score of > 4 or,
- FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.

Subjects with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy performed during screening.

12. Compensated cirrhosis defined as Child-Pugh score of ≤ 6 at Screening.

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

14. Absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) performed within 3 months prior to Screening or a negative ultrasound at Screening.
Rationale for Inclusion Criteria

(1, 5, 9 – 14) To select the appropriate subject population with sufficient disease severity for evaluation.

(7) For the safety of study subjects.

(2, 3, 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 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/RBV.

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 indicating unable to genotype or co-infection with any other HCV genotype.

7. Prior therapy with DAAs for the treatment of HCV, including telaprevir and boceprevir.
8. Use of any medications listed in Table 1 within 2 weeks prior to study drug administration, including but not limited to:

Table 1. Medications Contraindicated for Use with the Study Drug Regimen

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

* Use of hormonal contraceptives requires SDP approval.

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.

9. Use of known strong inhibitors or inducers of CYP3A (Cytochrome P450 3A) or inhibitors of CYP2C8 (Cytochrome P450 2C8) within 2 weeks prior to study drug administration.
10. 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. Single positive results on urine screen for alcohol are discussed in Section 5.1.1.1, Rescreening.

11. 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.

12. 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.

13. Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.

14. Serum Alpha-Fetoprotein (sAFP) > 100 ng/mL at Screening.

15. A positive screening ultrasound for hepatocellular carcinoma (HCC) confirmed with a subsequent CT Scan or MRI during the screening period.

16. 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.

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

- ALT > 7 × upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 7 × ULN
- Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
- Albumin < 2.8 g/dL
- International normalized ratio (INR) > 2.3. Subjects with a known inherited blood disorder and INR > 2.3 may be enrolled with permission of the AbbVie Study Designated Physician
- Hemoglobin < LLN
- Platelets < 60,000 cells per mm³
- Absolute neutrophil count (ANC) < 1500 cells/µL (< 1200 cells/µL for subjects of black race or subjects of African descent who are black)
- Total bilirubin ≥ 3.0 mg/dL


19. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 470 msec at Screening or Study Day 1 (Baseline, prior to dosing).

20. 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.
21. 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.

22. Current enrollment in another clinical study, prior enrollment in this study, or previous use of any investigational or commercially available anti-HCV agents (other than commercially available interferon and/or pegIFN/RBV for treatment experienced subjects) and previous exposure to ABT-450, ABT-267 or 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 trials may be permitted with approval by the AbbVie Study Designated Physician.

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

24. Uncontrolled clinically significant cardiac, respiratory (except mild asthma), hepatic, 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, 9 – 12, 17, 18, 20, 23, 24) To ensure safety of the subjects throughout the study.

(2, 4, 6, 7, 8, 19, 21, 22) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.

(16) To avoid bias for the evaluation of efficacy and safety.

(5, 13 – 15) To exclude subjects with liver diseases other than HCV and compensated cirrhosis.
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 from the time of signing the consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential interactions.

During the Post-Treatment Period, all medications will be collected 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

Treatment-naïve subjects must not have prior or current use of any investigational or commercially available anti-HCV agents, including IFN, pegIFN, telaprevir, boceprevir or RBV. Subjects who previously participated in trials of direct acting antiviral agents for treatment of HCV may be enrolled with the approval of the AbbVie Study Designated Physician if they can provide documentation that they received placebo.

Treatment-experienced 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 prior to initial study drug administration and through 2 weeks following discontinuation of study drugs. Subjects must be consented prior to discontinuing any prohibited medications or herbals supplements for the purpose of meeting study inclusion criteria.

Investigator should confirm that concomitant medication can be safely administered with DAAs (including ritonavir) and RBV. Some medications may require dose adjustments due to potential for drug-drug interactions. Subjects should be on a stable dose of concomitant medications for at least 2 weeks prior to initiation of study drug.

During the Post-Treatment 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, use of known strong inhibitors or inducers of CYP3A or inhibitors of CYP2C8 is prohibited within 2 weeks prior to the initial dose of study drugs and through the first 2 weeks after the subject has completed active study drugs in the Treatment Period.

Refer to the ritonavir and RBV labeling for a list of prohibited medications. anti-HCV medications other than those specified in the protocol will not be allowed during the Treatment Period of the study.
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.

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

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

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart
## Table 2. Study Activities – Treatment Period (TP)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening</th>
<th>Day1/ Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 10</th>
<th>Wk 12 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24 (EOT)&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Premature D/C&lt;sup&gt;b,c&lt;/sup&gt;</th>
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<tr>
<td>Provide RBV Medication Guide&lt;sup&gt;e&lt;/sup&gt; and Partner Risk Fact Sheet</td>
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<td>Pregnancy Test [serum (s) urine (u)]&lt;sup&gt;i&lt;/sup&gt;</td>
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<td>X (u, s)</td>
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<td>FSH (all females), HbA1c</td>
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<td></td>
</tr>
<tr>
<td>HBsAg, Anti-HCV Ab, Anti-HIV Ab</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Drug/Alcohol Screen</td>
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<td></td>
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<tr>
<td>Total Insulin</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>HCV Genotype and Subgenotype</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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### Table 2. Study Activities – Treatment Period (TP) (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Treatment Period (TP)</th>
<th>Treatment Visits – All Subjects</th>
<th>Treatment Visits – 24-Week Arm</th>
<th>Premature D/C&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>Day1/ Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Wk 1</td>
<td>Wk 2</td>
</tr>
<tr>
<td>IL28B Sample</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening: Liver Biopsy or FibroScan&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal FibroTest</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Score</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment of Hepatic Decompensation</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound and Alpha Fetoprotein&lt;sup&gt;n&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medication Assessment</td>
<td>X X X X X X X X X X X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Reported Outcomes Instruments (PROs)&lt;sup,o&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
<td>X         X X X X X X X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drugs Dispensed</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MEMS cap dispensed</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>Screening</td>
<td>Day1/ Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Wk 1</td>
<td>Wk 2</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------</td>
<td>----------------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>MEMS Downloaded/Review Compliance/Collect MEMS Caps&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td>X</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV Resistance Sample</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic Sample</td>
<td>X&lt;sup&gt;s&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Archive Serum Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Interferon Gamma-induced protein 10 (IP-10) Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic Sample (optional)&lt;sup&gt;t&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Wk = Week; EOT = End of treatment; D/C = Discontinuation; MEMS = Medication Event Monitoring System
Table 2. Study Activities – Treatment Period (TP) (Continued)

a. All procedures, including pharmacokinetic sample collection, to be performed prior to first dose with the exception of the 2-hour post-dose pharmacokinetic sample.

b. Treatment visits:
   - Subjects randomized to the 12-week treatment arm will complete the screening through Week 12 study visit procedures. Week 12 will be the final visit in the Treatment Period.
   - Subjects randomized to the 24-week treatment arm will complete the screening through Week 24 study visit procedures. Week 24 will be the final visit in the Treatment Period.
   - Subjects who prematurely discontinue the Treatment Period (Week 12 or Week 24 treatment arm) should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).

c. Subjects should begin the Post-Treatment Period after the subject completes study drug treatment or prematurely discontinues Treatment Period.

d. Subjects will need to sign an informed consent for the study (prior to performing any screening or study-specific procedures) and the optional Pharmacogenetic sample(s), if applicable.

e. Where applicable/locally available.

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

g. Height will be measured at Screening only.

h. Evaluate the Day 1 ECG prior to dosing to determine eligibility.

i. Urine pregnancy testing is not required after the Day 1 Visit for female subjects with a documented history of bilateral tubal ligation, bilateral oophorectomy or hysterectomy or who are confirmed to be post-menopausal. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.)

j. Done at Day 1/Baseline and collected for decrease in Creatinine Clearance as defined in Section 6.7.5.

k. Subjects who do not have a qualifying historical liver biopsy, but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo either a FibroScan or a liver biopsy.

l. Longitudinal FibroTest measured for exploratory analysis of fibrosis over time. Day 1 results will be blinded to the investigator/site.

m. Clinical assessment of Hepatic encephalopathy and ascites at Day 1 prior to dosing.
Table 2. Study Activities – Treatment Period (TP) (Continued)

n. Liver Ultrasound and alpha fetoprotein to be performed at screening for subjects on the 12-week treatment arm and at screening and Week 24 (EOT) for subjects on the 24-week treatment arm. Subjects with a historical negative Liver Ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening Ultrasound performed. If additional Liver Ultrasound testing is required it should be completed as an unscheduled visit. A positive Ultrasound result suspicious for HCC will be confirmed with CT scan or MRI.

o. 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 and in the order listed below.
   - **TP Day 1 (Baseline):** SF-36v2, EQ-5D-5L and HCVPRO
   - **TP Weeks 4 and 8:** SF-36v2, EQ-5D-5L and HCVPRO
   - **TP Week 12:** SF-36v2, EQ-5D-5L and HCVPRO (= EOT for 12-week treatment arm or Treatment Period Week 12 for the 24-week treatment arm)
   - **TP Week 24:** SF-36v2, EQ-5D-5L and HCVPRO (= EOT for 24-week treatment arm)
   - **TP Premature D/C Visit:** SF-36v2, EQ-5D-5L and HCVPRO

p. Study drugs only dispensed at Weeks 12, 16 and 20 for subjects in 24-week arm.

q. MEMS caps will be collected upon completion of study drug, EOT (TP Week 12 or TP Week 24) or TP Premature D/C.

r. HCV RNA will be collected at 0-hour (immediately prior to the morning dose) and at 2 hours post-dose.

s. Blood Sample(s) for pharmacokinetic assay as described in Section 5.3.2 will be collected as follows:
   - Day 1: 0-hr (immediately prior to the morning dose), and at 2 hours post-dose.
   - A single pharmacokinetic sample will be collected at all other Treatment Study Visits without regard to the time of dosing as detailed in Table 2 above.

T. If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study.

u. To be performed at End of Treatment (EOT), either TP Week 12 or TP Week 24, as appropriate.
<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&lt;sup&gt;a&lt;/sup&gt;</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/Coagulation Panel</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>Monthly Pregnancy Test (females)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>(Weeks 12, 16, 20, 24, 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Longitudinal FibroTest</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>Child-Pugh Score</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound and Alpha Fetoprotein&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>PRO Instruments&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Concomitant Medication Assessment&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Adverse Event Assessment&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA&lt;sup&gt;g&lt;/sup&gt;</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>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Archive Serum Sample</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>IP-10 Sample</td>
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<tr>
<td>mRNA Sample (optional)</td>
<td>X</td>
<td></td>
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</tbody>
</table>

Wk = Week; PT D/C = Post-Treatment Discontinuation
Table 3. Study Activities – Post-Treatment (PT) Period* (Continued)

* Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.

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

b. Urine pregnancy testing is not required after TP 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.

c. Liver ultrasound and alpha fetoprotein to be performed at PT Week 12 and PT Week 36 for subjects randomized to the 12 Week Arm and at PT Week 24 and PT Week 48 for subjects randomized to the 24 Week Arm. A positive Ultrasound result suspicious for HCC will be confirmed with CT scan or MRI.

d. PRO instruments should be administered before any study procedures and in the order listed below.

- **PT Week 4:** SF-36v2, EQ-5D-5L and HCVPRO
- **PT Week 12:** SF-36v2, EQ-5D-5L and HCVPRO
- **PT Week 24:** SF-36v2, EQ-5D-5L and HCVPRO
- **PT Week 48 or D/C:** SF-36v2, EQ-5D-5L and HCVPRO

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

f. Only SAEs will be collected after 30 days post-dosing. Subjects that are receiving add-on pegIFN/RBV will continue to collect AEs throughout the study while on pegIFN/RBV therapy and for 30 days following the end of pegIFN/RBV therapy.

g. Confirmation of an HCV RNA ≥ LLOQ in the post-treatment period should be completed as soon as possible per Section 5.1.3.
5.3.1.1 Study Procedures

The study procedures outlined in Table 2 and Table 3 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 pharmacogenetic analysis (Section 5.3.1.3), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), the monitoring of treatment compliance (Section 5.5.7), the use of MEMS caps (Section 5.5.8) and the collection of adverse event information (Section 6.0). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to the Sponsor electronically from the individual laboratorie(s).

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 use and injection drug use will be taken from each subject during the Screening Visit. The subject's medical history will be updated at the Day 1 Visit (Treatment Period). This updated medical history will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits indicated in Table 2, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.
The physical examination performed on Day 1 of the Treatment Period will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

**Vital Signs, Weight, Height**

Body temperature (oral or tympanic), blood pressure, pulse and body weight will be measured at the visits indicated in Table 2 and Table 3. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Day 1 will serve as the baseline for clinical assessment. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

**12-lead Electrocardiogram**

A 12-lead resting ECG will be obtained at the visits indicated in Table 2 or upon subject discontinuation from the Treatment Period (or as clinically needed). The Day 1 (Treatment Period) reading will serve as the baseline assessment. The ECG should be performed prior to blood collection.

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

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

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.
The QT interval measurement (corrected by Fridericia formula, QTcF) will be documented in the eCRF only if the local reader's assessment is "prolonged QT."

**Clinical Laboratory Tests**

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 4 at the visits indicated in Table 2 and Table 3.

Blood samples for serum chemistry tests should be collected following a minimum 8-hour fast (with the exception of the Screening Visit, which may be non-fasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight. Subjects whose visits occur following the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Day 1 study visit, a fasting blood sample is to be collected prior to the first dose of study drug which is administered at the Day 1 study visit. Subjects should be reminded to eat prior to their first dose of study drug (e.g. suggest they bring a light snack). 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.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is Covance. Depending on the location of the study site, samples will be sent to one of the following addresses:
Covance
8211 SciCor Drive
Indianapolis, IN  46214 USA
(For sites in Canada, Puerto Rico and USA)

Covance Geneva
Rue Moïse-Marcinhes 7
1217 Meyrin/Genève-CH
(For sites in Belgium, France, Germany, Italy, Spain and UK)
Table 4. **Clinical Laboratory Tests**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Additional Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood Urea Nitrogen (BUN)</td>
<td>HBsAg&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Creatinine</td>
<td>Anti-HCV Ab&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Red Blood Cell (RBC) count</td>
<td>Total bilirubin&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Anti-HIV Ab&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>White Blood Cell (WBC) count</td>
<td>Direct and indirect bilirubin</td>
<td>FSH (all females)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Opiates&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bands, if detected</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Barbiturates&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Alkaline phosphatase</td>
<td>Amphetamines&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Sodium</td>
<td>Cocaine&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Basophils</td>
<td>Potassium</td>
<td>Benzodiazepines&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Calcium</td>
<td>Alcohol&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Platelet count (estimate not acceptable)</td>
<td>Inorganic phosphorus</td>
<td>Phencyclidine&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ANC</td>
<td>Uric acid</td>
<td>Propoxyphene&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prothrombin Time/INR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Total protein</td>
<td>Methadone&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
<td>Glucose</td>
<td>Urine and Serum</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>Triglycerides</td>
<td>Human Chorionic</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>Albumin</td>
<td>Gonadotropin (hCG) females&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Cholesterol</td>
<td>Total insulin</td>
</tr>
<tr>
<td>Ketones</td>
<td>Total protein</td>
<td>HCV RNA</td>
</tr>
<tr>
<td>pH</td>
<td>Glucose</td>
<td>Hepatitis B Panel&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein</td>
<td>Triglycerides</td>
<td>Hepatitis A Antibody, Total&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood</td>
<td>Albumin</td>
<td>Hepatitis E Virus IgG&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucose</td>
<td>Chloride</td>
<td>Hepatitis E Virus IgM&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>Bicarbonate</td>
<td>Hemoglobin A1C&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Magnesium</td>
<td>IP-10</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>Gamma-glutamyl transferase (GGT)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IL28B&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microscopic (reflex)</td>
<td>Creatinine clearance (Cockcroft Gault calculation)</td>
<td>HCV genotype and subtype&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Albumin&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Alpha2-macroglobulin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pharmacogenetic sample (optional)</td>
</tr>
<tr>
<td>Urine Archive Specimen&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Haptoglobin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>mRNA (optional)</td>
</tr>
</tbody>
</table>

a. Also a component of the Child-Pugh Assessment.
b. Also a component of FibroTest.
c. Performed only at Screening.
d. Urine pregnancy testing is not required after Day 1 of the Treatment Period 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.
e. Collected for Creatinine Clearance <50 mL/min as defined in Section 6.7.5.
f. 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 drug or requires a subject to receive treatment will be recorded as an adverse event.

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

**Pregnancy Test**

A urine pregnancy test will be performed for all female subjects at all the visits indicated in Table 2 and Table 3. In addition, a serum pregnancy test will be performed at Screening and 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 indicated in Table 2 and Table 3 and monthly for a minimum of 7 months after the discontinuation of RBV, or according to the local RBV label and/or local treatment guidelines for RBV. A positive urine pregnancy test requires a confirmatory serum test. Urine pregnancy tests are not required after Day 1 for female subjects with a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy, or for subjects who are confirmed to be postmenopausal. Confirmation of postmenopausal status will be determined during the Screening period, based on the subject's history and on the FSH level.

During post-treatment 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 at home 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 captured in the eCRF, unless serum pregnancy is elected. Serum pregnancy testing will be completed by the central laboratory.

**Hepatitis and HIV Screen**

HBsAg (hepatitis B surface antigen), 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 HBsAg results will 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 4. 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 alcohol screen repeated as described in Section 5.1.1.1. If the repeat urine screen is negative, and all other eligibility criteria have been met, the subject may be considered eligible for study participation.

These analyses will be performed by the certified central laboratory chosen for the study.
Screening: Liver Biopsy or FibroScan

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

To be eligible, subjects must have a diagnosis of cirrhosis by one of the following methods, per local standard practice:

- Previous histologic diagnosis on liver biopsy, e.g., Metavir Score of > 3 (including 3/4), Ishak score of > 4, or
- FibroScan score ≥ 14.6 kPa within 6 months of Screening or during the Screening Period.
- Subjects with a non-qualifying FibroScan result may only be enrolled if they have a qualifying liver biopsy performed during screening.

Procedures for those subjects who do not have a qualifying FibroScan during the Screening Period are outlined in Section 5.1.1.

Longitudinal FibroTest

In addition to the assessments of cirrhosis performed during the Screening Period, all subjects will have FibroTest performed at baseline (Day 1) and throughout the Post-Treatment Period as indicated in Table 2 and Table 3 for the purpose of assessing changes in liver fibrosis over time. Day 1 results will be blinded to the investigator/site.

Child-Pugh Score and Category

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the visits indicated in Table 2.
Table 5.  
**Child-Pugh Classification of Severity of Cirrhosis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Assigned for Observed Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>&lt; 34.2 (&lt; 2)</td>
<td></td>
</tr>
<tr>
<td>34.2 – 51.3 (2 – 3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 51.3 (&gt; 3)</td>
<td></td>
</tr>
<tr>
<td>Serum albumin, g/L (g/dL)</td>
<td></td>
</tr>
<tr>
<td>&gt; 35 (&gt; 3.5)</td>
<td></td>
</tr>
<tr>
<td>28 – 35 (2.8 – 3.5)</td>
<td></td>
</tr>
<tr>
<td>&lt; 28 (&lt; 2.8)</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.7</td>
<td></td>
</tr>
<tr>
<td>1.7 – 2.3</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.3</td>
<td></td>
</tr>
<tr>
<td>Ascites*</td>
<td>None</td>
</tr>
<tr>
<td>Hepatic encephalopathy**</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* None.

Slight ascites = Ascites detectable only by ultrasound examination.

Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.

Severe ascites = Large or gross ascites with marked abdominal distension.

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

**Clinical Assessment of Hepatic Decompensation**

A clinical assessment of hepatic encephalopathy and ascites will be performed at Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since screening.

**Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein**

In order to monitor for the presence of hepatocellular carcinoma (HCC), alpha fetoprotein will be assayed and an ultrasound of the liver will be performed as indicated in Table 2 and Table 3.
A positive Ultrasound result suspicious for HCC at screening will be confirmed with CT scan or MRI during the screening period. Suspicious ultrasound lesions confirmed by CT or MRI are exclusionary.

A positive Ultrasound result suspicious for HCC during the treatment or post-treatment period will be confirmed with CT scan or MRI. Confirmatory results should be discussed with the AbbVie Study Designated Physician as appropriate.

**Concomitant Medication Assessment**

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements) from the time of signing the consent through 30 days after last dose of study drug will be recorded in the eCRF at each study visit indicated in Table 2.

During the Post-Treatment Period, antiviral therapies related to the treatment of HCV and medications prescribed in association with an SAE will be recorded in the eCRF at the visits indicated in Table 3.

**Randomization and Assignment of Subject Numbers**

All screening activities must be completed and reviewed prior to randomization. Subjects who meet the eligibility criteria will proceed to randomization via the IRT system on Day 1 (Treatment Period).

Screening numbers will be unique 6-digit numbers and will begin with 100101 with the first three digits representing the investigative site, and the last three digits representing the subjects at that site. Randomized subjects will keep their screening number as their subject number. Subjects will be randomized on Day 1 as described in Section 5.5.4 and will receive a separate unique 7-digit 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.
Patient Reported Outcomes (PRO) Instruments (Questionnaires)

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days indicated in Table 2 and Table 3. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read or understand any of the instruments may have site personnel read the questionnaires to them. Site personnel will encourage completion of each instrument at all 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, followed by the EQ-5D-5L and followed by the HCVPRO. PRO instruments should be completed prior to drug administration (on Day 1) and prior to any discussion of adverse events or any review of laboratory findings, including HCV RNA levels.

Short Form 36 – Version 2 Health Status Survey

The SF-36v2 is a general Health Related Quality of Live (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 to complete.

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) using country-specific based weights, where available. 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. This instrument has been preliminarily validated and further validation is ongoing. 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.

**MEMS Caps**

At the Day 1 Visit subjects will be assigned 3 MEMS caps. 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 and Section 5.5.8.

To ensure that a dosing event is recorded for the first dose of each study drug administered (at the site) at the Day 1 visit, the site should place the MEMS cap on each study drug bottle before dispensing the first dose. The event recording of the first study drug dosing is important to the Day 1 PK sample collection.

**Study Drug Compliance for Kits**

Study drug compliance will be recorded per kit (bottle) in the IRT system. Study drugs will be collected at each drug dispensation visit after Day 1, as indicated in Table 2. The number of tablets of ABT-450/r/ABT-267, ABT-333, and of RBV remaining in each
bottle will be recorded in the source and transferred to the IRT system along with the date of reconciliation.

**HCV Genotype and Subgenotype**

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

**HCV RNA Levels**

Plasma samples for HCV RNA levels will be collected as indicated in Table 2 and Table 3. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0. The lower limit of detection (LLOD) is 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 0-hour (prior to dose) and 2 hours post dose on Day 1 and at the study visits, indicated in Table 2 and Table 3. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, the Sponsor, or its designee.

**Archive Plasma Sample**

Archive plasma samples will be collected at the study visits, indicated in Table 2 and Table 3. Archive plasma 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.
Specific instructions for preparation and storage of archive samples will be provided by the central laboratory, the Sponsor, or its designee.

**Archive Serum Sample**

Archive serum samples will be collected at the study visits, indicated in Table 2 and Table 3. Archive 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.

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

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

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 2 and Table 3. Specific instructions for preparation and storage of IP-10 samples will be provided by the central laboratory, the Sponsor, or its designee.

**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.

**5.3.1.3 Blood Samples for Pharmacogenetic Analysis**

**IL28B Sample**

One (required) whole blood sample for DNA isolation will be collected from each subject at Screening for Interleuken 28B (IL28B) pharmacogenetic analysis. This sample will not be used for any testing other than IL28B genotypes.
Optional Sample for Pharmacogenetic Analysis

A separate (optional) whole blood sample for DNA isolation will be collected on Day 1 (Treatment Period) from each subject who consents to provide the optional sample for pharmacogenetic analysis. If the optional pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Optional Samples for 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 throughout the study, as indicated in Table 2 and Table 3.

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.

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

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 and ABT-333 (or drugs for the treatment of HCV) continues but no longer than 20 years.
5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of ABT-450, possible ABT-450 metabolites, ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, as well as ritonavir and RBV will be collected by venipuncture at each study visit indicated in Table 2, including at Day 1, for the 0-hour and 2-hour PK sample collection. The date and time of the first dose of each drug will be recorded in the source documents and the eCRF. 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, RBV and archive plasma samples will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

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

5.3.2.4 Measurement Methods

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of 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 Day 1 through 48 weeks after completion of treatment.

5.3.3.1 Primary Variable

The primary endpoint is the percentage of subjects with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in each treatment arm.
5.3.3.2 Secondary Variables

The secondary endpoints are:

- The comparison of the percentage of subjects with SVR$_{12}$ between the 12- and 24-week arms;
- The percentage of subjects with virologic failure during treatment;
- The percentage of subjects with post-treatment relapse.

5.3.3.3 Resistance Variables

The following resistance analyses will be performed for subjects receiving study drugs 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 standard sequences.

5.3.4 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.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of ABT-450, ABT-267, ritonavir, 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.

5.3.6 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN/RBV. 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 Treatment Period or the Post-Treatment Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 2 or Table 3. Ideally this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC (electronic data capture) system. The subject should then begin the Post-Treatment Period where the subject will be monitored for 48 weeks for safety, HCV RNA, the emergence and persistence of resistant viral variants and PROs.

If a subject is discontinued from study drug (Treatment Period) or the Post-Treatment Period with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

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

### 5.4.1.1 Virologic Failure Criteria

The following criteria will be considered evidence of virologic failure. Subjects demonstrating any of the following will be discontinued from study drug:
● Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements of > 1 log_{10} IU/mL above nadir) at any time point during treatment;

● 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 during treatment.

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

If any of the above criteria are met for subjects on DAA therapy, 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 per Section 5.1.3.

5.4.1.2 Efficacy Treatment Adjustment Criteria

The Sponsor will evaluate efficacy by reviewing HCV RNA levels throughout the Treatment and Post-Treatment Periods in this open-label study.

If either of the efficacy failure criteria below is met, the findings will be reviewed by the Sponsor and the DMC (Data Monitoring Committee) as detailed in Section 5.7. In addition, if the first criterion (virologic breakthrough) is met, enrollment in the study will be paused while the review of the results is ongoing. If the second criterion (virologic relapse) is met, enrollment may continue during the review of the results. The characteristics of the subjects experiencing failure will be reviewed to determine what changes are needed and whether changes should apply to the entire study population or only to certain subgroups, such as those defined by HCV subgenotype (1a versus 1b),
IL28B genotype, or previous HCV treatment experience (treatment-naïve or treatment-experience) and/or type of non–response to previous pegIFN/RBV treatment.

Virologic breakthrough is defined as confirmed HCV RNA ≥ LLOQ (two consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during the Treatment Period. Virologic relapse is defined as confirmed HCV RNA ≥ LLOQ after completing treatment for a subject with HCV RNA < LLOQ at the end of treatment.

1. Virologic breakthrough: Across both treatment arms, if ≥ 10 of the first 20 subjects enrolled experience virologic breakthrough during treatment, the Sponsor and DMC will review the data to determine whether further enrollment should be terminated. Enrollment may be terminated for the entire study population or for certain subgroups (e.g., GT-1a infected subjects). If enrollment is terminated for an arm in its entirety or for a subgroup, add-on pegIFN treatment will be offered to the corresponding subjects who are in the Treatment Period. If enrollment is terminated for only a subgroup of subjects (e.g., GT-1a infected subjects), enrollment in the study may be resumed for subjects not in that subgroup (e.g., GT-1b infected subjects).

2. Virologic relapse: In the 12-week treatment arm, if ≥ 5 of the first 10 subjects who complete 12 weeks of therapy experience virologic relapse after treatment, then the Sponsor and DMC will review the data to determine whether the treatment should be extended from 12 to 24 weeks for all subjects on treatment or only for a subgroup of subjects. Enrollment into the study may continue during the data review process. For any subgroup of subjects for whom treatment duration is extended to 24 weeks, the remaining subjects in that subgroup will be enrolled in the 24-week arm. For groups of subjects whose treatment is not extended to 24 weeks, enrollment in both treatment arms may continue.
Similar evaluations of virologic breakthrough and virologic relapse will continue throughout the study. Subjects who drop out for reasons other than virologic failure will not be included in these evaluations.

An additional assessment of relapse will be performed once data through Post-Treatment Week 4 is obtained for 50 subjects completing treatment in the 12-week treatment arm. If the relapse rate in these 50 subjects is greater than 20%, then the Sponsor and DMC will review the results to determine whether treatment duration should be extended to 24 weeks for a subgroup of ongoing subjects (e.g., if the relapses are concentrated in a difficult-to-treat population such as null responders) or for all ongoing subjects in the 12-week treatment arm (if the relapses occur broadly across all subgroups). Similar assessments to extend the 12-week treatment arm may be performed at other timepoints based on ongoing monitoring of relapse rates.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

Each dose of study drug (ABT-450/r/ABT-267, ABT-333 and RBV) will be dispensed in the form of tablets at the visits listed in Table 2.
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 tablets. RBV has weight-based dosing 1000 to 1200 mg divided twice daily per local label. (For example, subjects weighing less than 75 kg, RBV may be taken orally as 2 tablets in the morning and 3 tablets in the evening which corresponds to a 1000 mg total daily dose. Or for subjects weighing 75 kg or more, RBV may be taken orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose.)

At 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 or Week 24 of the Treatment Period.

Subjects will be instructed to take study medication at the same time(s) every day. All compounds 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 indicated in Table 2. Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C Visit from the Treatment Period, the site will contact the IRT system to provide visit date information and study drug return information for each kit (Section 5.5.9).

All subjects who receive at least one dose of DAA and who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be
discontinued from treatment. Resistance monitoring will continue in the Post-Treatment Period regardless of whether subjects opt for alternative post-study treatment.

5.5.2 Identity of Investigational Product

Information about the study drugs to be used in this study is presented in Table 6.

Table 6. 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/AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>75 mg/50 mg/12.5 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>Ribavirin</td>
<td>Roche or Generic Manufacturer</td>
<td>Oral</td>
<td>Tablet</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

5.5.3 Packaging and Labeling

ABT-450/Ritonavir/ABT-267 will be supplied in bottles containing 64 tablets. ABT-333 will be supplied in bottles containing 64 tablets. Ribavirin will be supplied in bottles containing 168 tablets each.

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.
5.5.3.1 Storage and Disposition of Study Drug

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450/Ritonavir/ABT-267 bottles</td>
<td>15°C to 25°C (59°F to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia: Store below 25°C</td>
</tr>
<tr>
<td>ABT-333 bottles</td>
<td>15°C to 25°C (59°F to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia: Store below 25°C</td>
</tr>
<tr>
<td>Ribavirin bottles</td>
<td>15°C to 25°C (59°F to 77°F)</td>
</tr>
<tr>
<td></td>
<td>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 drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the Sponsor. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.5.4 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 kit numbers and a unique randomization number. The randomization number will be used only by AbbVie 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. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.
Subjects meeting the eligibility criteria will be randomized to Arm A or Arm B as described in Section 8.3. Subjects will be stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and by HCV subgenotype (1a versus non-1a).

5.5.5 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.5. Study drug dosing will be initiated at the Study 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 capsules taken in the morning, and 3 RBV 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 together and with food.

5.5.6 Blinding

This is an open-label study.

5.5.7 Treatment Compliance

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

At the start of the study, each subject should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance. Subjects will be administered study drugs at the site at the Day 1 Visit. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs.

Subjects will be instructed to bring all bottles of study drug (full, partial or empty) and MEMS caps to the study site at each study visit. At every study visit, during the Treatment Period, study site personnel will inspect the contents of the 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 tablets of RBV in IRT at the dispensing visits and in the source at all other Treatment Period visits (Weeks 1, 2, 6, and 10). Study drugs may be re-dispensed at Treatment Period Weeks 1, 2, 6 and 10 therefore, Reconciliation in IRT should occur only when the bottles are returned to the site at the dispensation visits during the Treatment Period in Table 2. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

At Day 1, for the 0-hour and 2-hour PK sample collection, the date and time of the first dose of each drug will be recorded in the source documents and the eCRF. The date of last dose of all study drugs will be recorded in the source documents and the appropriate eCRF.

5.5.8 MEMS Caps

All subjects will utilize a MEMS monitor (cap) (where available), manufactured by AARDEX (Advanced Analytical Research on Drug Exposure) on the bottles for ABT-450/r/ABT-267, ABT-333, and RBV. The MEMS cap will be used to obtain daily dosing histories for ABT-450/r/ABT-267, ABT-333, and RBV for all subjects. In
addition, MEMS data will be provided to the Investigator to guide treatment compliance and will be the primary data used to assess pharmacokinetic (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 Day 1 Visit (Treatment Period), subjects will be assigned 3 MEMS caps that will be placed on the ABT-450/r/ABT-267, ABT-333 and 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.

Each drug will be assigned a specific color, identified by a color coded label on the drug bottle and a corresponding color coded MEMS cap so that the same MEMS cap is used for only one drug throughout the study. 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 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.

To ensure that a dosing event is recorded for the first dose of each study drug administered (at the site) at the Day 1 visit, the site should place the MEMS cap on each study drug bottle before dispensing the first dose.
The subject should return all study drug bottles (empty bottles along with in-use bottles with the MEMS monitors attached) at each visit. The site staff will download the dosing history data at each visit, for each study drug bottle, and will review the downloaded data for compliance. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

The MEMS cap will be collected from the subject at the completion of study drug 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) and the returned study drug reconciliation data in IRT will be the only data utilized for adherence.

Additional instructions for the subject on the use of the MEMS cap will be provided by AbbVie.

A start and stop date of all study drugs will be recorded in the source documents and the eCRF.

**5.5.9 Drug Accountability**

The Investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the Investigator and will include lot number, POR number, number of tablets dispensed, subject number, initials of person who dispensed study drug and date dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.
During the study, should an enrolled subject misplace or damage a study drug bottle, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the bottle is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the IRT system. Study drug start dates for each drug and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each bottle, number of tablets remaining in each 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 study drug bottles (containing unused study drugs) will be returned to the Sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each bottle will be noted in the IRT 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

Based upon the results of three Phase 2 studies, Study M12-267, Study M12-746, and Study M11-652 (discussed in detail in Section 3.0), AbbVie plans to evaluate ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in treatment-naïve and pegIFN/RBV treatment-experienced (who are prior null responders, partial responders or relapers), HCV genotype 1-infected adults with compensated cirrhosis (Child-Pugh score 5 – 6) in this multicenter randomized, open-label, duration ranging, Phase 3 study.
A placebo-controlled trial was not considered to be appropriate in HCV subjects with compensated liver disease because they have a greater risk of progression to decompensated liver disease with treatment delays for a placebo treatment group. An active comparator of the current standard (telaprevir or boceprevir with pegIFN/RBV) is considered infeasible to enroll because of the toxicity associated with the currently approved protease inhibitor/pegIFN/RBV regimens and the perceived imminent availability of a better-tolerated, short course (12- to 24-week), pegIFN-free, DAA combination regimen.

A comparative study with 2 different durations of therapy provides randomization and comparative data supporting selection of treatment duration. Since HCV patients with compensated cirrhosis have been shown to be more difficult to cure, a longer duration may be needed for subjects with cirrhosis even though 12 weeks is an adequate duration for subjects without cirrhosis. This study design will provide data to confirm whether a duration longer than 12 weeks will provide additional benefit with respect to efficacy.

Given the above considerations, the study design will maximize the probability of success in this harder to cure population, and DMC oversight will ensure the high efficacy and safety of all subjects. Also, this study design will maximize the benefit of an IFN-free treatment for all study subjects while avoiding the limitations of study designs employing an active or placebo comparator.

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 and population sequencing methods are experimental. The SF-36v2 and EQ-5D-5L instruments are standard in the literature and thoroughly validated. The HCVPRO is preliminarily validated and has demonstrated excellent responsiveness in patients with HCV.
5.6.3 Justification of Primary Endpoint Success Criteria

Historical SVR_{24} rates, as reported in the telaprevir US Prescribing Information (USPI), for telaprevir plus pegIFN and RBV therapies in HCV genotype 1, treatment-naïve or treatment-experienced subjects with cirrhosis from the ADVANCE, ILLUMINATE, and REALIZE trials are presented in Table 7 and Table 8, respectively. A fixed-effect meta-analysis was used to calculate the estimated SVR rate and 95% confidence interval in the treatment-naïve population (Table 7). A weighted average of the corresponding SVR rates among treatment-naïve and treatment-experienced (prior null responders, partial responders, and relapsers) subjects was calculated to reflect the population expected to enroll in Study M13-099 (Table 8).

For a regimen to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower confidence bound of the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for telaprevir plus pegIFN and RBV presented in Table 8 (i.e., 54%). To be considered non-inferior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower confidence bound of the SVR rate must exceed 43%. The value of 43% used for the non-inferiority comparison represents the 54% historical SVR rate adjusted for a non-inferiority margin of 10.5%. The non-inferiority margin of 10.5% used for comparisons to the historical SVR rate for telaprevir plus pegIFN and RBV is based on the telaprevir ILLUMINATE study which used the same non-inferiority margin.

Table 7. SVR Rates for Telaprevir plus PegIFN and RBV in Treatment-Naïve Subjects

<table>
<thead>
<tr>
<th>Telaprevir Studies</th>
<th>ADVANCE T12/PR n/N (%)</th>
<th>ILLUMINATE T12/PR n/N (%)</th>
<th>Meta Analysis T12/PR % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve subjects with cirrhosis</td>
<td>15/21 (71)</td>
<td>31/61 (51)</td>
<td>56 [45, 67]</td>
</tr>
</tbody>
</table>

GT1a = genotype 1a; GT1b = genotype 1b
Table 8. Estimated SVR Rates for Telaprevir plus PegIFN and RBV in Cirrhotic Subjects

<table>
<thead>
<tr>
<th>REALIZE²⁴</th>
<th>Telaprevir-Treated Subjects with Cirrhosis n/N (%)</th>
<th>Projected Enrollment in Study M13-099 (%)</th>
<th>Population-Based Weighted Average % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve Subjects</td>
<td>(56)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>REALIZE Study²⁴</td>
<td>Prior relapsers 48/57 (84)</td>
<td>12</td>
<td>47 [41, 54]</td>
</tr>
<tr>
<td>Prior partial responders</td>
<td>11/32 (34)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Prior null responders</td>
<td>7/50 (14)</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

5.6.4 Suitability of Subject Population

This study plans to enroll both HCV treatment-naïve and treatment-experienced (pegIFN/RBV) subjects with genotype 1 chronic HCV and compensated cirrhosis.

Naïve subjects are included to assess the safety and efficacy of the DAA regimen in these subjects with compensated cirrhosis. The optimal treatment duration of a DAA combination regimen in cirrhotic patients remains unclear. Data from other HCV regimens have demonstrated lower efficacy rates in compensated cirrhotics (both treatment-naïve and treatment-experienced) compared to non-cirrhotics. Durations of therapy other than those used in the non-cirrhotic population may improve efficacy rates.

Both the identification of the appropriate treatment duration with the DAA regimen and the characterization of the benefit-risk ratio in patients with compensated cirrhosis that will result from Study M13-099 must be clearly understood before initiating studies of DAA regimens in patients with more advanced liver disease. This study approach protects against the potential complications that may come with initial study in patients with decompensated cirrhosis, including avoidance of potential adverse events through exposure to 24 weeks of DAA therapy without a demonstrated incremental increase in SVR with an additional 12 weeks of treatment.
All 3 categories of treatment-experienced subjects (null-responders, non-responders/partial responders, and relapsers to prior pegIFN/RBV therapy) are included to gain experience with the 3 DAA regimen with RBV in all 3 types of treatment-experienced subjects with compensated cirrhosis. Null-responders are included as they are the most difficult to treat, and if the regimens are efficacious in these subjects they will likely be more efficacious in non-responders/partial responders and relapsers.

No more than 70 prior relapsers and partial responders, combined, will be randomized to ensure that adequate numbers of prior null responders are treated. The protocol will also specifically exclude subjects with any prior exposure to DAA HCV inhibitors, since prior DAA therapy may have selected mutations which may alter the antiviral response to the DAAs in this study.

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. This study will restrict enrollment to HCV genotype 1-infected subjects who have evidence of compensated cirrhosis. Unanticipated pharmacokinetic or other adverse effects not observed in prior dosing in healthy volunteers or HCV-infected subjects without compensated cirrhosis will be assessed. 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. The exposure viral load response from subjects treated to date with ABT-450/r, ABT-333 and ABT-267 indicates that changes in exposure due to BMI is not expected to significantly affect response. Moreover, because of the acceptable safety and pharmacokinetic profiles of ABT-450/r, ABT-267 and ABT-333 in Phase 1 studies, this protocol will enroll subjects with a BMI up to 38 kg/m².

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 both as monotherapy in combination with pegIFN/RBV, and in combination with each
other and RBV. Doses comparable to, and higher than the DAA doses to be administered in this study have been studied in single- and multiple-dose healthy volunteer studies and administered to HCV-infected subjects without cirrhosis as monotherapy or in combination with pegIFN/RBV and found to be generally safe and well tolerated. The regimen and doses used in this study were administered to approximately 20 HCV subjects without cirrhosis who were prior null-responders to pegIFN/RBV and to 40 HCV subjects without cirrhosis who were treatment-naïve in Study M11-652.

In addition, as described in Section 3.0, the pharmacokinetics of ABT-450, ABT-267, ABT-333 and ritonavir when given in combination to subjects with hepatic impairment were comparable to slightly lower than that in subjects with normal hepatic function. The exposures area under the concentration curve (AUC) of ABT-450, ABT-267 and ABT-333 were comparable (≤30% change) in subjects with mild hepatic impairment compared to healthy controls. The AUC for ritonavir was 34% lower in subjects with mild hepatic impairment. Based on these data, no dose adjustment is required for subjects taking the DAA combination in this study. Additionally, based on the package insert for ribavirin, dose adjustments are not required in subjects with mild hepatic impairment.

**ABT-450/r**

The ABT-450/r doses of 100/100 and 150/100 mg evaluated in the Phase 2 studies using the ABT-450 Spray dried dispersion (SDD) tablet provided high ITT SVR₁₂ 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, however, 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 was 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 doses were also associated with higher SVR_{12} rates combined with pegIFN/RBV. Thus based on resistance profile and SVR_{12} data with pegIFN/RBV, higher doses provide better efficacy. However, higher doses (200/100 and 250/100 mg SDD tablet) were associated with a greater incidence of Grade 3 ALT elevations suggesting that doses ≤ 200/100 mg SDD tablet might be optimal to minimize the Grade 3 elevations.

The 150 mg ABT-450 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 ~50% lower than that from the 200/100 mg SDD formulation. The 150 mg ABT-450 dose from the coformulation will hence to reduce the incidences of asymptomatic, transient Grade 3 elevations but still maintain sufficient ABT-450 exposure to at least partially suppress the most fit protease mutant, R155K.

The maximum dose of ABT-450/Ritonavir/ABT-267 75 mg/50 mg/12.5 mg tablets will not exceed 150 mg/100 mg/25 mg per day for 24 weeks.

**ABT-267**

An ABT-267 dose of 25 mg has been selected to advance into Phase 3 studies based on comparable viral load decline following monotherapy and lower potential to decrease ABT-450 exposures as compared to higher ABT-267 doses.

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 no 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 resistance were observed following monotherapy with doses of 5 to 200 mg. On the contrary, higher ABT-267 doses have been associated with decrease in ABT-450 exposures; ABT-267 200 mg dose resulted in ~80% lower ABT-450 exposures (ABT-450 250 mg 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 25 mg QD dose of ABT-267 is combined with ABT-450 and ABT-333 + RBV for 12 weeks, very high SVR\textsubscript{12} 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 a comparable bioavailability to the 25 mg ABT-267 tablet used in Phase 2 studies. Hence, the ABT-267 dose in the current study is the 25 mg as it provides exposures that maximizes efficacy without compromising ABT-450 exposures.

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.

**ABT-333**

An ABT-333 dose of 250 mg BID that is expected to have exposures comparable to the 400 mg BID dose used in Phase 2 studies has been selected to advance into Phase 3 studies based on comparable efficacy and better safety profile compared to exposures at higher doses.

Comparable viral load decline following monotherapy (approximately 1 $\log_{10}$ IU/mL) were observed at exposures ≥ that achieved with the 400 mg BID doses evaluated in Phase 2 studies. Additionally similar SVR rates (63%) when combined with pegIFN/RBV for 12 weeks followed by 36 weeks of pegIFN/RBV were observed at the 400 and 800 mg BID doses indicating that increasing ABT-333 dose > 400 mg BID did not improve efficacy. Additionally, available data from the Phase 2b study indicates that when 400 mg BID dose of ABT-333 is combined with ABT-450 and ABT-267 + RBV for 12 weeks, very high SVR\textsubscript{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/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 400 mg BID dose and compared to placebo plus pegIFN/RBV.

The optimized formulation used in the current study has a higher bioavailability and is expected to be comparable 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 to higher ABT-333 doses.

The maximum total daily dose of ABT-333 250 mg tablets administered in this study will not exceed 500 mg per day for 24 weeks.

**RBV**

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

**5.7 Data Monitoring Committee**

An independent DMC will review safety and virologic data from this study and provide recommendations to the AbbVie Study Designated Physician as per the DMC charter. The charter also describes DMC member responsibilities and membership, which will include individuals with extensive experience in the management of patients with chronic hepatitis C. The DMC will receive interim summaries of safety and virologic data.
according to a schedule and in a format specified in the charter. The DMC will be informed if either of the efficacy treatment adjustment criteria in Section 5.4.1.2 are met. After each review, the DMC will communicate its recommendations to AbbVie. AbbVie will retain sole responsibility for study management, communication with study sites and regulatory authorities.

6.0 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.
Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 6.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

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

### 6.1.2 Serious Adverse Events

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

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

- **Life-Threatening**
  An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

- **Hospitalization or Prolongation of Hospitalization**
  An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

- **Congenital Anomaly**
  An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity

An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

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

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

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

6.2 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

Assessment of relatedness will be made with respect to the DAAs (ABT-450/r, ABT-267, and ABT-333), with respect to RBV and with respect to pegIFN (due to possible add-on therapy). The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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

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

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the 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 (including any pegIFN/RBV add-on therapy) 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 until the end of their participation in the study.

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

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

Antiviral Safety Team  
Dept. R477, Bldg. AP30-3  
1 North Waukegan Road  
North Chicago, IL 60064
For any subject safety concerns, please contact the physician listed below:

Primary Study-Designated Physician:

Roger Trinh, MD, MPH

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

6.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with Day 1 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 AbbVie within 1 working day of the site becoming aware of the pregnancy. Female subjects who report a positive pregnancy test during the Treatment Period must be notified to stop all study medication (Section 5.4.1). Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. The site must complete and fax to AbbVie appropriate pregnancy-specific
forms that will require the collection of maternal information and fetal outcome information. 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 AbbVie within 24 hours of the site becoming aware of the event.

6.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. A table of Clinical Toxicity Grades for evaluating laboratory abnormalities is provided in Appendix C. This table should be used in determination of the appropriate toxicity management as discussed in Section 6.7.1 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 drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the Investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

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 AbbVie Study Designated Physician should be contacted.

During the study, timeliness of EDC data entry to reflect study drug interruptions and/or RBV dose modifications and consequent required adverse events ensures that the AbbVie Safety Team (Study Designated Physician, safety monitor, 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 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.

### 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. 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 drug; interruption of study drugs 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, all study drugs should be interrupted and the laboratory
parameter followed until it reaches Grade 1. The study drugs can be restarted if the laboratory parameter reaches Grade 1 within 7 days of study drug interruption. If the study drugs are interrupted and restarted and abnormality recurs, then all study drugs should be permanently discontinued. If the abnormality does not improve to Grade 1 or less within 7 days of interruption, the study drug 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. If the laboratory abnormality does not improve within 7 days, then study drugs should be permanently discontinued. 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.

Severe Adverse Event

If a subject experiences a severe drug-related (reasonable possibility) adverse event (other than those based on abnormal lab parameters discussed below in Sections 6.7.3 through 6.7.5) during the study, all study drugs should be interrupted. 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 adverse event (reasonable possibility) 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.

If a subject experiences a non drug-related severe adverse event (no reasonable possibility) study drugs may be continued.

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 adverse event (reasonable possibility) (other than those based on abnormal lab parameters discussed below in Sections 6.7.3 through 6.7.5) during the study, the study assignment should be permanently discontinued. 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 to the study drugs (no reasonable possibility), the 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 AbbVie 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. Hemoglobin abnormalities should be managed according to Table 9. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease.

If a subject experiences a hemoglobin decrease (as outlined in Table 9), a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 9 should be followed.

Use of hematologic growth factors such as erythropoietin, filgrastim, or blood transfusions are not recommended; and are permitted only with approval of the AbbVie Study Designated Physician. Management of hematologic growth factor therapy is the responsibility of the Investigator, and growth factors will not be provided by AbbVie.

Alternate management of hemoglobin decreases outside of these criteria requires approval of the AbbVie Study Designated Physician.
### Table 9. 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 ≥ 8.5 g/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>Hemoglobin &lt; 8.5 g/dL</td>
<td>Permanently discontinue all study drugs</td>
</tr>
<tr>
<td></td>
<td>Manage the subject as medically appropriate</td>
</tr>
<tr>
<td>Hemoglobin decrease of ≥ 4 g/dL between two scheduled study visits but hemoglobin ≥ 10 g/dL</td>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event</td>
</tr>
<tr>
<td></td>
<td>Manage the subject as medically appropriate</td>
</tr>
<tr>
<td></td>
<td>Study drugs may be continued</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin in Patients with History of Stable Cardiac Disease</th>
<th>Study drugs may be continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hb ≥ 10 g/dL) without symptoms and/or signs of cardiac disease</td>
<td>Reduce RBV dose</td>
</tr>
<tr>
<td></td>
<td>Continue to monitor hemoglobin levels per protocol</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td>Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hb ≥ 10 g/dL) with symptoms and/or signs of cardiac disease</td>
<td>If the subject has symptoms consistent with their cardiac disease; manage subject as medically appropriate; AbbVie Study Designated Physician may be contacted</td>
</tr>
<tr>
<td></td>
<td>Study drugs may be continued, consider management as for those without cardiac signs and symptoms in the rows above</td>
</tr>
<tr>
<td>Hemoglobin decrease ≥ 4 g/dL between study visits but hemoglobin ≥ 10 g/dL</td>
<td>Investigator should manage subject as medically appropriate, but study drugs may be continued</td>
</tr>
</tbody>
</table>
Table 9. 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 &lt; 10.0 g/dL, but ≥ 8.5 g/dL</td>
<td>Study drugs may be continued</td>
</tr>
<tr>
<td></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 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>
</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></td>
<td>Enter discontinuation into appropriate eCRFs and create corresponding adverse event (AE)</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.

If a subject experiences an ALT level ≥ 5 × ULN that is ≥ 2 × Baseline or ≥ 10 × ULN, a confirmatory test should be performed. If, the ALT is confirmed ≥ 5 × ULN and ≥ 2 × Baseline or ≥ 10 × ULN the management guidelines in Table 10 should be followed.

Alternate management of ALT increases requires approval of the AbbVie Study Designated Physician.
Table 10. Management of Confirmed ALT Elevations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Actions</th>
</tr>
</thead>
</table>
| ALT ≥ 10 × ULN or ALT ≥ 5 × ULN and ≥ 2 × Baseline but < 10 × ULN with symptoms and signs of hepatitis present | • Permanently discontinue study drugs. For subjects with Baseline ALT ≥ 5 × ULN alternate management of ALT increases requires approval of the AbbVie Study Designated Physician  
• 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 and ≥ 2 × Baseline 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.  
• 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.
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 within 2 scheduled study visits (2 CrCl values still < 50 mL/min) then all study drug should be permanently discontinued, with further medical management as appropriate.

If CrCl improves consideration should be given to the readjustment 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: Theresa Brouillard
Alternate Contact: Leticia Canizaro

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will occur after all randomized subjects have completed the Treatment Period through Post-Treatment Week 12 of the Post-Treatment Period or prematurely discontinued from the study. SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. The intent-to-treat (ITT) population will consist of all randomized subjects who receive at least one dose of study drug. If enrollment to the 12-week arm is discontinued and ongoing subjects in that arm have his/her treatment extended to 24 weeks, then these subjects will be grouped with the
24-week arm in all efficacy and safety analyses. If the efficacy breakthrough criteria are met and pegIFN/RBV add-on therapy is offered, subjects who chose to add-on pegIFN/RBV treatment will be removed from the analysis of the efficacy and safety endpoints for the 12- and 24-week arms and summarized separately.

No data will be imputed for any efficacy or safety analyses 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. If a respondent answers at least 12 of the 16 items on the HCVPRO, 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 HCVPRO 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 after performing the flanking imputation 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 arm for all subjects in the ITT population. Demographics include age, weight, and BMI, and the frequency of gender, race, ethnicity, age category [(< 55 years or ≥ 55 years) and (< 65 or ≥ 65 years)] and BMI category (< 30 kg/m$^2$ or ≥ 30 kg/m$^2$). Baseline characteristics will include HCV genotype 1 subtype (1a, 1b, other), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), pegIFN/RBV treatment history (treatment-naïve or treatment-experienced [null responder (definition 1 or 2), partial responder, or relapser]), 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/L$^2$ or ≥ 3 mU × 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, unknown), history of bleeding disorders (yes, no), history of diabetes (yes, no), history of depression or bipolar disorder (yes, no), and geographic region (North America, Europe, or Australia). 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 arms. The number and percentage of subjects will be presented for categorical variables (e.g., gender and race); treatment arms will be compared using a chi-square test.

8.1.2 Efficacy

All efficacy analyses will be performed on the ITT population.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay version 2.0. 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.
8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are the percentage of subjects with SVR\textsubscript{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) within each treatment arm. The overall 2-sided significance level of 0.05 will be split between the two arms using a Bonferroni correction of 0.025 for each arm. The percentage of subjects achieving SVR\textsubscript{12} within each treatment arm will be calculated and a 2-sided 97.5% confidence interval (CI) of the percentage will be computed using the normal approximation to the binomial distribution.

A gatekeeping testing procedure will be used to control the Type I error rate at 0.05 and the primary endpoints within Arm A will be tested separately from Arm B in the following order:

A1. SVR\textsubscript{12}: Non-inferiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the lower confidence bound (LCB) of the 97.5% CI for the percentage of subjects with SVR\textsubscript{12} in Arm A must exceed 43% to achieve non-inferiority.

A2. SVR\textsubscript{12}: Superiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\textsubscript{12} in Arm A must exceed 54% to achieve superiority.

B1. SVR\textsubscript{12}: Non-inferiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\textsubscript{12} in Arm B must exceed 43% to achieve non-inferiority.

B2. SVR\textsubscript{12}: Superiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR\textsubscript{12} in Arm B must exceed 54% to achieve superiority.

Within Arm A, only if success has been demonstrated for non-inferiority of the SVR\textsubscript{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A1) will
the testing continue to superiority of the SVR\textsubscript{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A2). Within Arm B, only if success has been demonstrated for non-inferiority of the SVR\textsubscript{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) will the testing continue to superiority of the SVR\textsubscript{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B2). Otherwise, statistical testing will stop. If success is achieved for all of the primary endpoints (A1, A2, B1, and B2), then the first secondary endpoint will be tested; otherwise, statistical testing will stop.

To test the hypothesis that the percentage of treatment-naïve and pegIFN/RBV treatment-experienced HCV genotype 1 infected subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 or 24 weeks 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 97.5% CI, and the LCB will be compared to the defined thresholds. The LCB of the 97.5% CI must be greater than 43% in order for the regimen to be considered non-inferior, and the LCB of the 97.5% CI of the SVR\textsubscript{12} rate must be greater than 54% in order for the regimen to be considered superior.

The value of 54% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN and RBV represents the upper confidence bound of the 2-sided 95% confidence interval of the combined SVR rate as described in Section 5.6.3. The value of 43% used for the non-inferiority comparison represents the historical SVR rate (54%) adjusted for a non-inferiority margin of 10.5%.

8.1.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The percentage of subjects with SVR\textsubscript{12} in the 24-week arm compared to the 12-week arm;
● The percentage of subjects in each arm with on-treatment virologic failure during the 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 each arm 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).

If success was demonstrated for all of the primary efficacy endpoints, then the multiple testing procedure will continue to the first secondary efficacy endpoint to compare the percentage of subjects with SVR\textsubscript{12} following 12 or 24 weeks of treatment. To test the hypothesis that the percentages of subjects who achieve SVR\textsubscript{12} is different between Arm A and Arm B, the percentages will be compared using a logistic regression model with treatment arm, baseline log\textsubscript{10} HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non CC), and pegIFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.

The percentages (with 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 for each arm. These endpoints will not be part of the multiple testing procedure as no hypothesis is being tested.

8.1.2.3 Subgroup Analysis

The percentage (with 2-sided 95% confidence intervals) of subjects with SVR\textsubscript{12} for each treatment arm will be presented for the following subgroups:

● Treatment-naïve versus previous pegIFN/RBV treatment-experienced subjects;
  ○ For treatment-experienced subjects, type of response to previous pegIFN/RBV treatment (null responder (definition 1 or 2), partial responder, or relapser);
• HCV genotype 1 subtype (1a, 1b, other);
• IL28B genotype (CC or non-CC), (CC, CT, or TT);
• Baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL);
• Baseline IP-10 (< 600 pg/mL or ≥ 600 pg/mL);
• Baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L²);
• Sex (male versus female);
• Age (< 55 versus ≥ 55 years), (< 65 versus ≥ 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 ≥ 30 kg/m²);
• 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 Child-Pugh Score (5 versus 6).

Each subgroup analysis will be performed if there are an adequate number of subjects within each subgroup. For each subgroup, the lower confidence bound of the 2-sided 95% confidence interval will be compared to 43%.
8.1.2.4 Additional EfficacyEndpoints

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

- The percentage of subjects with rapid virologic response (RVR) (HCV RNA < LLOQ at Week 4);
- The percentage of subjects with end of treatment response (EOTR) (HCV RNA < LLOQ at Week 12 for Arm A or at Week 24 for Arm B);
- The percentage of subjects with HCV RNA < LLOQ at each post-baseline visit in the Treatment Period (using only subjects with data in each visit window, i.e., no imputation for missing data);
- The number of subjects with virologic rebound (defined as confirmed increase > 1 log 10 IU/mL from nadir in HCV RNA during treatment or confirmed HCV RNA ≥ LLOQ during treatment after HCV RNA < LLOQ) at each post-baseline visit in the Treatment Period;
- The percentage of subjects who failed to have confirmed suppression of HCV RNA (never achieving two consecutive HCV RNA < LLOQ) during the Treatment Period;
- Time to suppression of HCV RNA (defined as the study day of the first of two successive HCV RNA < LLOQ) during the Treatment Period;
- The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed post-treatment within 4 weeks after the last actual dose of study drug;
- The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed at anytime post-treatment;
- The percentage of subjects who achieved SVR_{12} who subsequently relapsed;
- Time to relapse at anytime post-treatment for subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit;
- The percentage of subjects with SVR_{4} weeks after the last actual dose of study drug (SVR_{4});
• The percentage of subjects with SVR_{12} weeks after the last planned dose of study drug (SVR_{12\,\text{planned}});
• The percentage of subjects with SVR_{24} weeks after the last actual dose of study drug (SVR_{24});
• The percentage of subjects with SVR_{24} weeks after the last planned dose of study drug (SVR_{24\,\text{planned}});
• Mean change from baseline in liver function tests (e.g., PT/INR, Fibrotest) to each applicable post-baseline time point.

In the above analyses for RVR, EOTR, and SVR, the percentage of responders in each treatment arm and two-sided 95% confidence intervals will be calculated using the normal approximation to the binomial distribution. Analyses of mean change from baseline to end of treatment for the liver assessments will be compared between treatment arms using an analysis of covariance (ANCOVA) model with treatment arm as a factor and baseline score as a covariate. From HCV RNA levels, the time to suppression on treatment and time to relapse post-treatment will be displayed graphically using Kaplan-Meier curves.

### 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 final treatment visit in SF-36v2 MCS and PCS greater than or equal to the minimal clinically important difference (MID).

The percentage of subjects in each treatment arm without a decrease from baseline to final 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 final 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 arm 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 Treatment Visit and from Baseline to Post-Treatment Week 12 will be compared between treatment arms 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 arm will be provided with percent change from baseline on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis. These plots will be used to show change from Baseline to Final Treatment Visit and change from Baseline to Post-Treatment Week 12.

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 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 treatment visit in each of these measures greater than the appropriate MID will be compared between treatment arms using a chi-square test (or Fisher's exact test as appropriate).
Additional analyses of PROs will be performed as useful and appropriate.

### 8.1.4 Resistance Analyses

The genes of interest for both population and clonal sequencing in this study are those encoding NS3 amino acids 1 to 181, NS5A amino acids 1 to 215, and NS5B amino acids 300 to 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 study drugs who do 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 standard 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 the appropriate prototypic standard reference sequences.

\(^a\) At least two non-failure subjects will be matched for every subject experiencing virologic failure to the extent possible by HCV subgenotype, treatment-naïve or 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 vs. 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 appropriate prototypic reference amino acid sequence for each DAA target. A listing by subject of all variants at baseline at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequence will be provided for each DAA
target (NS3, NS5A, and NS5B). 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 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 Post-Treatment 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 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 study drug will be included in the safety analyses.

8.1.5.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects in each treatment arm with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between the treatment arms using Fisher's exact tests. The tabulation of the number of
subjects with treatment-emergent adverse events by severity rating and relationship to study drug will also be provided. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident for the severity rating table and the most related for the relationship to study drug table. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional analyses will be performed if useful and appropriate.

8.1.5.2 Clinical Laboratory Data

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

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

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values during treatment will be summarized by treatment arm. Comparisons will be performed between the treatment arms of the percentage of subjects with Potentially Clinically Significant 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

Mean changes in temperature, systolic and diastolic blood pressure, pulse, and weight from baseline to each Post-Baseline Visit will be summarized descriptively for each treatment arm. Frequencies and percentages of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized. Comparisons of the percentage of subjects experiencing a value meeting the criteria between treatment arms will be performed 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:

$$TVCL_i = + \Theta(2) (\text{Comedication } [1,2,\ldots]) + \Theta(3) (\text{WT}_i - \text{median value}) + \Theta(4) (\text{AGE}_i - \text{median value}).$$

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, SVR$_4$, SVR$_{12}$, 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 about 380 subjects to a 12- or 24-week treatment duration arm. The primary efficacy endpoint of SVR$_{12}$ will be assessed within each arm. With a total sample size of about 380 subjects and assuming that 68% of the subjects in each arm will achieve
SVR\textsubscript{12}, this study has greater than 90\% power to demonstrate non-inferiority with a 2-sided 97.5\% lower confidence bound greater than 43\% and 90\% power to demonstrate superiority with a 2-sided 97.5\% lower confidence bound greater than 54\% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).\textsuperscript{25-27} 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\textsubscript{12}.

For the comparison of SVR\textsubscript{12} between Arms A and B, a total sample size of approximately 380 subjects provides 80\% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 13\% assuming underlying SVR\textsubscript{12} rates of 68\% and 81\% in Arms A and B, respectively. If the SVR\textsubscript{12} rates are higher, then there is 80\% power to detect a difference of approximately 10.5\% with SVR\textsubscript{12} rates of 80.5\% and 91\% in Arms A and B, respectively.

8.3 Randomization Methods

Randomization to the 12- and 24-week treatment arms will occur until approximately 380 subjects are enrolled. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. This allows more subjects to be enrolled to the 24-week arm at the start of the study which will expose more subjects to a 24-week duration until the adequacy of a 12-week duration has been established in a population of HCV genotype 1 subjects with compensated cirrhosis.

Subjects will be stratified by having received previous pegIFN/RBV treatment versus being treatment-naïve. No more than 180 treatment-naïve subjects will be allowed to enroll in this study. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapsers) and by
HCV subgenotype (1a versus non-1a). 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 approximately 25% of the total null responder study population to ensure adequate representation of the presumed harder-to-treat population of null responders according to definition 1.

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 International Conference on Harmonization (ICH) GCP.

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

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

9.3 Subject Information and Consent

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

The optional pharmacogenetic and mRNA analyses will only be performed if the subject has voluntarily signed and dated the IRB/IEC approved pharmacogenetic and mRNA informed consent, after the nature of the testing has been explained and the subject has had an 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 testing, it will not impact the subject's participation in the study.
10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

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

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

11.0 Data Quality Assurance

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.

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

12.0 Use of Information

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

13.0 Completion of the Study

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

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

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

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

1. I have received and reviewed the Investigator's Brochure for 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, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

Protocol Date: 07 May 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 AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.

2. Personally conducting or supervising the described investigation(s).

3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.

4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.

5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).

6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.

8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

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

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.
### Appendix B. List of Protocol Signatories

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theresa Brouillard</td>
<td>Clinical Research Management Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Project Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Roger Trinh</td>
<td>Associate Medical Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Heidi Wells</td>
<td>Clinical Supply Project Manager</td>
<td>Global Drug Supply Management</td>
</tr>
</tbody>
</table>
## Appendix C. Clinical Toxicity Grades

### Clinical Toxicity Grades for HCV Studies

<table>
<thead>
<tr>
<th>Hematology</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 – 1,500/mm³</td>
<td>&lt; 1,500 – 1,000/mm³</td>
<td>&lt; 1,000 – 500/mm³</td>
<td>&lt; 500/mm³</td>
</tr>
<tr>
<td><strong>Eosinophil Count Increased</strong></td>
<td>6 ≤ 1500 cells/mm³</td>
<td>1501 – 6000 cells/mm³</td>
<td>&gt; 6000 cells/mm³</td>
<td>Hyper eosinophilia</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 x ULN</td>
<td>&gt; 1.5 – 2 x ULN</td>
<td>&gt; 2 x 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>
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<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>
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<tr>
<td><strong>PTT</strong></td>
<td>&gt; 1 – 1.5 x ULN</td>
<td>&gt; 1.5 – 2 x ULN</td>
<td>&gt; 2 x ULN</td>
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<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>
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<tr>
<td><strong>White Blood Cell Count Increased</strong></td>
<td>10,000 – 15,000 cells/mm³</td>
<td>&gt; 15,000 – 20,000 cells/mm³</td>
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### Chemistry

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<tr>
<th>Albumin, Serum, Low</th>
<th>Grade 1 Toxicity</th>
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<td>&lt; LLN – 3 g/dL</td>
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<td>&lt; 2 g/dL</td>
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<td>&lt; LLN – 30 g/L</td>
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<td>Bilirubin, High</td>
<td>&gt; ULN – 1.5 x ULN</td>
<td>&gt; 1.5 – 3.0 x ULN</td>
<td>&gt; 3.0 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
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<tr>
<td>BUN</td>
<td>1.25 – 2.5 x ULN</td>
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<td>&gt; 5 – 10.0 x ULN</td>
<td>&gt; 10 x ULN</td>
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<td>Calcium, Serum Low</td>
<td>&lt; LLN – 9.0 mg/dL</td>
<td>&lt; 9.0 – 7.0 mg/dL</td>
<td>&lt; 7.0 – 6.0 mg/dL</td>
<td>&lt; 6.0 mg/dL</td>
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<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>
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<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>
<td>&lt; 0.8 mmol/L</td>
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<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>
<td>&gt; 1.8 mmol/L</td>
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Clinical Toxicity Grades for HCV Studies
v1.1, 08 May 2009

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<tr>
<th>Measure</th>
<th>Grade 1 Toxicity</th>
<th>Grade 2 Toxicity</th>
<th>Grade 3 Toxicity</th>
<th>Grade 4 Toxicity</th>
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<td>&gt;900 mg/dL</td>
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<td>&gt;ULN - 7.75 mEq/L</td>
<td>&gt;7.75 - 10.34 mEq/L</td>
<td>&gt;10.34 - 12.92 mEq/L</td>
<td>&gt;12.92 mEq/L</td>
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<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>
<td>&gt;2.5 mg/dL or require dialysis</td>
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<tr>
<td>Glucose, Serum, Low</td>
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<td>&lt;55 - 65 mg/dL</td>
<td>&lt;65 - 80 mg/dL</td>
<td>&lt;80 mg/dL</td>
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<tr>
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<td>&lt;ULN - 2.2 mmol/L</td>
<td>&lt;2.2 - 3.0 mmol/L</td>
<td>&lt;3.0 - 5.0 mmol/L</td>
<td>&lt;5.0 mmol/L</td>
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<tr>
<td>Glucose, Serum, High</td>
<td>&gt;ULN - 140 mg/dL</td>
<td>&gt;140 - 160 mg/dL</td>
<td>&gt;160 - 200 mg/dL</td>
<td>&gt;200 mg/dL</td>
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<tr>
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<td>&gt;ULN - 15.9 mmol/L</td>
<td>&gt;15.9 - 19.9 mmol/L</td>
<td>&gt;19.9 - 23.8 mmol/L</td>
<td>&gt;23.8 mmol/L</td>
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<tr>
<td>Magnesium, Serum, Low</td>
<td>&lt;ULN - 1.2 mg/dL</td>
<td>&lt;1.2 - 1.8 mg/dL</td>
<td>&lt;1.8 - 2.4 mg/dL</td>
<td>&lt;2.4 mg/dL</td>
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<tr>
<td></td>
<td>&lt;ULN - 0.5 mmol/L</td>
<td>&lt;0.5 - 1.2 mmol/L</td>
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<td>Magnesium, Serum, High</td>
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<td>&gt;2.3 - 3.0 mg/dL</td>
<td>&gt;3.0 - 4.0 mg/dL</td>
<td>&gt;4.0 mg/dL</td>
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<tr>
<td></td>
<td>&gt;ULN - 1.2 mmol/L</td>
<td>&gt;1.2 - 1.5 mmol/L</td>
<td>&gt;1.5 - 2.0 mmol/L</td>
<td>&gt;2.0 mmol/L</td>
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<td>Phosphate, Serum, Low</td>
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<td>&lt;3.0 - 3.5 mg/dL</td>
<td>&lt;3.5 mg/dL</td>
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<tr>
<td></td>
<td>&lt;ULN - 0.8 mmol/L</td>
<td>&lt;0.8 - 1.2 mmol/L</td>
<td>&lt;1.2 - 1.5 mmol/L</td>
<td>&lt;1.5 mmol/L</td>
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<td>Potassium, Serum, Low</td>
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<td>&lt;3.0 - 3.5 mmol/L</td>
<td>&lt;3.5 - 4.0 mmol/L</td>
<td>&lt;4.0 mmol/L</td>
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<td>&gt;5.5 - 6.5 mmol/L</td>
<td>&gt;6.5 - 7.5 mmol/L</td>
<td>&gt;7.5 mmol/L</td>
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<tr>
<td>Protein, Serum, Low</td>
<td>5.5 - 6.0 g/dL</td>
<td>&lt;5.5 - 6.0 g/dL</td>
<td>&lt;5.5 - 6.0 g/dL</td>
<td>&lt;5.5 g/dL</td>
</tr>
<tr>
<td>Sodium, Serum, Low</td>
<td>&lt;ULN - 140 mmol/L</td>
<td>&lt;140 - 150 mmol/L</td>
<td>&lt;150 - 160 mmol/L</td>
<td>&lt;160 mmol/L</td>
</tr>
<tr>
<td>Sodium, Serum, High</td>
<td>&gt;ULN - 150 mmol/L</td>
<td>&gt;150 - 160 mmol/L</td>
<td>&gt;160 - 170 mmol/L</td>
<td>&gt;170 mmol/L</td>
</tr>
<tr>
<td>Triglycerides High</td>
<td>&gt;100 - 200 mg/dL</td>
<td>&gt;200 - 400 mg/dL</td>
<td>&gt;400 - 600 mg/dL</td>
<td>&gt;600 mg/dL</td>
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<tr>
<td></td>
<td>&gt;1.71 - 3.42 mmol/L</td>
<td>&gt;3.42 - 6.7 mmol/L</td>
<td>&gt;6.7 - 10.0 mmol/L</td>
<td>&gt;10.0 mmol/L</td>
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<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>
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Clinical Toxicity Grades for HCV Studies

v1.1, 08 June 2009
### Clinical Toxicity Grades for HCV Studies (Continued)

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<th>ENZYMES</th>
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<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
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<tr>
<td>ALT/SGPT</td>
<td>&gt;ULN × 3.0 × ULN</td>
<td>&gt;5.0 - 6.0 × ULN</td>
<td>&gt;20.0 - 30.0 × ULN</td>
<td>&gt;20.0 × ULN</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>&gt;ULN × 3.0 × ULN</td>
<td>&gt;5.0 - 6.0 × ULN</td>
<td>&gt;20.0 - 30.0 × ULN</td>
<td>&gt;20.0 × ULN</td>
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<tr>
<td>ALKALINE PHOSPHATASE</td>
<td>&gt;ULN × 2.5 × ULN</td>
<td>&gt;2.5 - 5.0 × ULN</td>
<td>&gt;5.0 - 30.0 × ULN</td>
<td>&gt;20.0 × ULN</td>
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<tr>
<td>AMYLASE</td>
<td>&gt;ULN × 1.5 × ULN</td>
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<td>&gt;2.0 - 6.0 × 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 - 6.0 × 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 D. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Number of Subjects to be Enrolled:
Previously read:

Approximately 300 subjects.

Has been changed to read:

Approximately 380 subjects.

Section 1.2 Synopsis
Subsection Methodology:
Third paragraph, first sentence previously read:

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 300 subjects are enrolled at approximately 75 sites.

Has been changed to read:

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 380 subjects are enrolled at approximately 75 sites.

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

After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms.
Has been changed to read:

After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms.

Section 1.2 Synopsis
Subsection Methodology:
Delete: first sentence and second sentence from fifth paragraph

No more than 150 treatment-experienced subjects will be allowed to enroll. The combined number of prior relapsers and prior partial responders will be limited to no more than 70.

Section 1.2 Synopsis
Subsection Methodology:
Delete: sixth paragraph

No more than 150 treatment-experienced subjects will be allowed to enroll. The combined number of prior relapsers and prior partial responders will be limited to no more than 70.

Section 1.2 Synopsis
Subsection Sample Size:
First sentence previously read:

With a sample size of 150 subjects in each treatment arm and assuming that 68% of the subjects in each arm will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90% power to demonstrate superiority with a two-sided 97.5% lower confidence bound greater than 54%.

Has been changed to read:

With a total sample size of about 380 subjects and assuming that 68% of the subjects in each arm will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90%
power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54%.

**Section 5.1 Overall Study Design and Plan: Description**

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

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 300 subjects are enrolled at approximately 75 sites.

**Has been changed to read:**

Subjects meeting the eligibility criteria will be randomized to the 12- and 24-week treatment arms until approximately 380 subjects are enrolled at approximately 75 sites.

**Section 5.1 Overall Study Design and Plan: Description**

**Third paragraph, third sentence previously read:**

After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms.

**Has been changed to read:**

After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms.

**Section 5.1 Overall Study Design and Plan: Description**

**Delete: eighth sentence from third paragraph**

No more than 150 treatment-experienced subjects will be allowed to enroll. The combined number of prior relapsers and prior partial responders will be limited to no more than 70.
Figure 1. Study Schematic
Previously read:

Has been changed to read:

Section 5.1.1 Screening
Fourth paragraph, first sentence previously read:

The study is designed to enroll 300 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study is designed to enroll approximately 380 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1.2 Treatment Period (TP)
First paragraph, second sentence previously read:

Approximately 300 subjects will be randomized.
Has been changed to read:

Approximately 380 subjects will be randomized.

Section 8.2 Determination of Sample Size
First, second and third sentence previously read:

It is planned to enroll 300 subjects in a 1:1 ratio to a 12- or 24-week treatment duration arm with 150 subjects in each arm. The primary efficacy endpoint of SVR$_{12}$ will be assessed within each arm. With a sample size of 150 subjects in each arm and assuming that 68% of the subjects in each arm will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90% power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).$^{25-27}$

Has been changed to read:

It is planned to enroll about 380 subjects to a 12- or 24-week treatment duration arm. The primary efficacy endpoint of SVR$_{12}$ will be assessed within each arm. With a total sample size of about 380 subjects and assuming that 68% of the subjects in each arm will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90% power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority using EAST 5.4).$^{25-27}$

Section 8.2 Determination of Sample Size
Add: new second paragraph

For the comparison of SVR$_{12}$ between Arms A and B, a total sample size of approximately 380 subjects provides 80% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 13% assuming underlying SVR$_{12}$ rates of 68% and 81% in Arms A and B, respectively. If the SVR$_{12}$
rates are higher, then there is 80% power to detect a difference of approximately 10.5% with SVR_{12} rates of 80.5% and 91% in Arms A and B, respectively.

**Section 8.3 Randomization Methods**

First paragraph previously read:

Randomization to the 12- and 24-week treatment arms will occur until approximately 300 subjects are enrolled. In the study overall, subjects will be randomized in a 1:1 ratio to each arm. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, 100 subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. This allows more subjects to be enrolled to the 24-week arm at the start of the study which will expose more subjects to a 24-week duration until the adequacy of a 12-week duration has been established in a population of HCV genotype 1 subjects with compensated cirrhosis.

Has been changed to read:

Randomization to the 12- and 24-week treatment arms will occur until approximately 380 subjects are enrolled. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. This allows more subjects to be enrolled to the 24-week arm at the start of the study which will expose more subjects to a 24-week duration until the adequacy of a 12-week duration has been established in a population of HCV genotype 1 subjects with compensated cirrhosis.

**Section 8.3 Randomization Methods**

Delete: fifth sentence from second paragraph

No more than 150 treatment-experienced subjects will be allowed to enroll. Enrollment of the combined number of prior relapers and prior partial responders will be limited to no more than 70.
Appendix B. List of Protocol Signatories

Previously read:

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Functional Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theresa Brouillard</td>
<td>Clinical Research Management Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Sabine Kaleta</td>
<td>Sr. Clinical Supply Project Manager</td>
<td>Global Drug Supply Management</td>
</tr>
<tr>
<td>Sandra Lovell</td>
<td>Manager</td>
<td>Statistics</td>
</tr>
<tr>
<td>Thomas Podsadecki</td>
<td>Project Director</td>
<td>Clinical</td>
</tr>
<tr>
<td>Roger Trinh</td>
<td>Associate Medical Director</td>
<td>Clinical</td>
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</table>

Has been changed to read:

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tr>
<td>Theresa Brouillard</td>
<td>Clinical Research Management Associate</td>
<td>Clinical</td>
</tr>
<tr>
<td>Sandeep Dutta</td>
<td>Director</td>
<td>Pharmacokinetics</td>
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<td>Sandra Lovell</td>
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<td>Thomas Podsadecki</td>
<td>Project Director</td>
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<td>Roger Trinh</td>
<td>Associate Medical Director</td>
<td>Clinical</td>
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<tr>
<td>Heidi Wells</td>
<td>Clinical Supply Project Manager</td>
<td>Global Drug Supply Management</td>
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Study M13099 - A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis - Amendment 4 - EudraCT 2012-003088-23 - 07May2013

**Document Approval**

Version: 1.0  Date: 08-May-2013 03:22:04 PM  Abbott ID: 05082013-00F9F68040F7A7-00001-en

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<td>07-May-2013 01:57:34 P</td>
<td>Approver</td>
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<tr>
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<td>07-May-2013 02:09:52 P</td>
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<td>Brouillard_Theresa</td>
<td>08-May-2013 03:22:01 P</td>
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1.0 Title Page

Statistical Analysis Plan

Study M13-099

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (TURQUOISE-II)

25 November 2013
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3.0 Introduction

This is the first version of the statistical analysis plan (SAP) for Study M13-099. Study M13-099 examines the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 co-administered with ribavirin (RBV) for 12 or 24 weeks in adults with genotype 1, chronic hepatitis C virus (HCV) infection and compensated 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 and end of study analysis will be conducted for Study M13-099 (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 assess the safety and to compare the SVR\textsubscript{12} rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR\textsubscript{12} [HCV ribonucleic acid (RNA) < lower limit of quantification (LLOQ) 12 weeks following treatment]) of coformulated ABT-450, ritonavir and ABT-267 (ABT-450/r/ABT-267) and ABT-333 coadministered with ribavirin (RBV) for 12 or 24 weeks to the historical SVR rate of telaprevir plus pegIFN and RBV in HCV genotype 1-infected adults with compensated cirrhosis.

The secondary objectives of this study are to compare the SVR\textsubscript{12} rates between the 12- and 24-week treatment arms and assess the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.
4.2 Design Diagram

This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks in HCV genotype 1, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis.

The treatment arms are:

Arm A: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks

Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 24 weeks

* RBV will be administered weight-based 1000 – 1200 mg divided twice daily.

Subjects will be stratified by previous pegIFN/RBV treatment experience (treatment-experienced) versus being treatment-naïve. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B (Interleukin 28B) genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responder, partial responder, or relapser) and by HCV subgenotype (1a versus non-1a).

All subjects administered 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 12-week Treatment Period for subjects randomized to Arm A and a 24-week Treatment Period for subjects randomized to Arm B, and a 48-week Post-Treatment (PT) Period for all subjects who receive at least one dose of study drug.

**Treatment Period (TP)**

Subjects meeting the eligibility criteria will be randomized to either the 12- or 24-week treatment arms. At the start of the trial, the first 200 subjects will be randomized in a 3:5 ratio to the 12- and 24-week arms. After the first 200 subjects are enrolled, the remaining subjects will be randomized in a 3:1 ratio to the 12- and 24-week arms. Subjects will receive ABT-450/r/ABT-267 orally once daily and ABT-333 and RBV orally twice daily for 12 weeks or 24 weeks.

Based on efficacy breakthrough criteria observed during treatment, subjects ongoing in either 12-week or 24-week arm may be offered add-on pegIFN/RBV treatment. In this case, the AbbVie regimen will be continued for 12 or 24 weeks as specified while pegIFN at standard doses is added on to continue beyond the end of the AbbVie regimen for a total of 48 weeks. Based upon criteria of virologic relapses post-treatment, subjects randomized to 12-week treatment arm who are in the Treatment Period at the time of the criteria met, may have the duration of their treatment extended to 24 weeks.
**Post-Treatment Period**

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant viral variants and assessment of PROs for an additional 48 weeks following the last dose of study drug.

The Post-Treatment Period will begin the day following the last dose of study drug treatment.

**4.3 Sample Size**

This study is planned to enroll about 380 subjects to a 12- or 24-week treatment duration arm. The primary efficacy endpoint of SVR$_{12}$ will be assessed within each arm. With a total sample size of about 380 subjects and assuming that 68% of the subjects in each arm will achieve SVR$_{12}$, this study has greater than 90% power to demonstrate non-inferiority with a 2-sided 97.5% lower confidence bound greater than 43% and 90% power to demonstrate superiority with a 2-sided 97.5% lower confidence bound greater than 54% (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$_{12}$.

For the comparison of SVR$_{12}$ between Arms A and B, a total sample size of approximately 380 subjects provides 80% power using Fisher's exact test with a 2-sided significance level of 0.05 to detect a difference of approximately 13% assuming underlying SVR$_{12}$ rates of 68% and 81% in Arms A and B, respectively. If the SVR$_{12}$ rates are higher, then there is 80% power to detect a difference of approximately 10.5% with SVR$_{12}$ rates of 80.5% and 91% in Arms A and B, respectively.
4.4 Planned Analyses

4.4.1 Futility Analysis

Study M13-099 is the first study to evaluate ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in HCV genotype 1-infected subjects with compensated cirrhosis. For that reason, virologic futility rules were used in the protocol to minimize the number of virologic failures. The M13-099 protocol described the futility rules as follows (Protocol Section 5.4.1.2, Efficacy Treatment Adjustment Criteria). Virologic breakthrough is defined as confirmed HCV RNA ≥ LLOQ (two consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during the Treatment Period. Virologic relapse is defined as confirmed HCV RNA ≥ LLOQ after completing treatment for a subject with HCV RNA < LLOQ at the end of treatment.

1. Virologic breakthrough: Across both treatment arms, if ≥ 10 of the first 20 subjects enrolled experience virologic breakthrough during treatment, the Sponsor and DMC will review the data to determine whether further enrollment should be terminated. Enrollment may be terminated for the entire study population or for certain subgroups (e.g., GT-1a infected subjects). If enrollment is terminated for an arm in its entirety or for a subgroup, add-on pegIFN treatment will be offered to the corresponding subjects who are in the Treatment Period. If enrollment is terminated for only a subgroup of subjects (e.g., GT-1a infected subjects), enrollment in the study may be resumed for subjects not in that subgroup (e.g., GT-1b infected subjects).
2. Virologic relapse: In the 12-week treatment arm, if ≥ 5 of the first 10 subjects who complete 12 weeks of therapy experience virologic relapse after treatment, then the Sponsor and DMC will review the data to determine whether the treatment should be extended from 12 to 24 weeks for all subjects on treatment or only for a subgroup of subjects. Enrollment into the study may continue during the data review process. For any subgroup of subjects for whom treatment duration is extended to 24 weeks, the remaining subjects in that subgroup will be enrolled in the 24-week arm. For groups of subjects whose treatment is not extended to 24 weeks, enrollment in both treatment arms may continue.

An additional assessment of relapse will be performed once data through Post-Treatment Week 4 is obtained for 50 subjects completing treatment in the 12-week treatment arm. If the relapse rate in these 50 subjects is greater than 20%, then the Sponsor and DMC will review the results to determine whether treatment duration should be extended to 24 weeks for a subgroup of ongoing subjects (e.g., if the relapses are concentrated in a difficult-to-treat population such as null responders) or for all ongoing subjects in the 12-week treatment arm (if the relapses occur broadly across all subgroups). Similar assessments to extend the 12-week treatment arm may be performed at other timepoints based on ongoing monitoring of relapse rates.

During enrollment, virologic breakthrough was assessed weekly to determine the potency of the regimen. As subjects began completing treatment, virologic relapse was assessed weekly to determine the adequacy of treatment duration. These assessments continued on a weekly basis until all Arm A subjects completed treatment.

Neither efficacy treatment adjustment criteria were met.

4.4.2 Primary Analysis

The primary analysis will occur after all randomized subjects have completed the Treatment Period through Post-Treatment Week 12 or prematurely discontinued from the study. For the primary analysis, data will be locked after performing appropriate data
cleaning. Results from the primary (e.g., SVR$_{12}$ data) analysis will be described in the primary clinical study report (CSR) and submitted to regulatory agencies as part of the NDA/MAA submission.

Data collected after the primary analysis 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. 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 study drug will be included in the ITT population. Efficacy analyses will be performed on the ITT population. The data from the ITT population will be presented by the treatment group assigned at the time of randomization (12-week treatment duration [Arm A] or 24-week treatment duration [Arm B]).

However, if ongoing subjects in the 12-week arm have his/her treatment extended to 24 weeks, then these subjects will be grouped with the 24-week arm in all efficacy analyses. If the efficacy breakthrough criteria are met and pegIFN/RBV add-on therapy is offered, subjects who chose to add-on pegIFN/RBV treatment will be removed from the analysis of the efficacy endpoints for the 12- and 24-week arms and summarized separately.

Note that no subjects were offered add-on pegIFN/RBV treatment, and treatment duration was not extended for any Arm A subjects.
Safety Population

All randomized subjects who receive at least one dose of study drug will be included in the safety population and will be the same as the ITT population for this study.

5.2 Variables Used for Stratification of Randomization

The first 200 subjects will be randomized in a 3:5 ratio to Arm A or Arm B at the start of the study. Then the remaining subjects will be randomized in a 3:1 ratio to Arm A or Arm B. Subjects will be stratified by having received previous pegIFN/RBV treatment (treatment-experienced) versus being treatment-naïve. The treatment-naïve subjects will be stratified by HCV subgenotype (1a versus non-1a) and by IL28B genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of non-response to previous pegIFN/RBV treatment (null responders, partial responders, or relapsers) and by 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, except for HCV RNA, on Study 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. For HCV RNA, samples will be collected on Day 1 prior to dosing and 2 hours after dosing. Therefore, the baseline HCV RNA value will be determined by the last non-missing measurement collected prior to dosing.

If multiple measurements are recorded on the same day, the last measurement recorded prior to dosing will be used as the baseline value. 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 Treatment and PT Periods.

**Definition of Study Days (Days Relative to the First Dose of Study Drug)**

Study Days are calculated for each time point in the Treatment Period relative to the first dose of study drug. Study Days are negative values when the time point of interest is prior to the first study drug dose day. Study Days are positive values when the time point of interest is after the first study drug dose day. There is no Study Day 0. Study Day 1 is the day of the first dose of study drug.

**Definition of Study Drug End Days (Days Relative to the Last Dose of Study Drug)**

For all subjects who receive at least one dose of study drug, study drug end days are calculated relative to the last dose of study drug. The last day of 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 and on or before Study Drug End Day 2.

**Definition of Final Post-Treatment Value**

The final post-treatment value for each subject 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 and Table 2 describe how efficacy data are assigned to protocol-specified time points during Treatment and PT Periods, respectively. All time points and corresponding time windows are defined based on the blood sample collection date.
Table 3 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., SVR4, SVR12, SVR24, SVR12planned, and SVR24planned); 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 4 and Table 5 describe how data are assigned to protocol specified time points during the Treatment and PT Periods, respectively.
## Table 1. Analysis Time Windows for HCV RNA and Resistance Endpoints (Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day/ Time (Study Day)</th>
<th>Time Window (Study Days Range)</th>
<th>Time Window (Hours Post Dose Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>--</td>
<td>≤ 1</td>
<td>--</td>
</tr>
<tr>
<td>Baseline/Study Day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Prior to the morning dose (0 hour) on Study Day 1</td>
<td>1</td>
<td>≤ 0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Study Day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 hours after the morning dose (2 hour) on Study Day 1</td>
<td>1</td>
<td>&gt; 0 hrs</td>
</tr>
<tr>
<td>Week 1</td>
<td>7</td>
<td>2 to 10</td>
<td>--</td>
</tr>
<tr>
<td>Week 2</td>
<td>14</td>
<td>11 to 21</td>
<td>--</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>22 to 35</td>
<td>--</td>
</tr>
<tr>
<td>Week 6</td>
<td>42</td>
<td>36 to 49</td>
<td>--</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>50 to 63</td>
<td>--</td>
</tr>
<tr>
<td>Week 10</td>
<td>70</td>
<td>64 to 77</td>
<td>--</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>78 to 98</td>
<td>--</td>
</tr>
<tr>
<td>Week 16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>112</td>
<td>99 to 126</td>
<td>--</td>
</tr>
<tr>
<td>Week 20&lt;sup&gt;c&lt;/sup&gt;</td>
<td>140</td>
<td>127 to 154</td>
<td>--</td>
</tr>
<tr>
<td>Week 24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>168</td>
<td>155 to 182</td>
<td>--</td>
</tr>
<tr>
<td>Final Treatment Visit&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR&lt;sub&gt;12planned&lt;/sub&gt; (Arm A)</td>
<td>168</td>
<td>141 to 210</td>
<td>--</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;24planned&lt;/sub&gt; (Arm A)</td>
<td>252</td>
<td>211 to 294</td>
<td>--</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;12planned&lt;/sub&gt; (Arm B)</td>
<td>252</td>
<td>225 to 294</td>
<td>--</td>
</tr>
<tr>
<td>SVR&lt;sub&gt;24planned&lt;/sub&gt; (Arm B)</td>
<td>336</td>
<td>295 to 378</td>
<td>--</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Baseline/Study Day 1 at 0 hours (prior to the morning dose) is applicable for HCV RNA and will be used as Baseline for all HCV RNA analyses. Study Day 1 at 2 hours after the first morning dose is applicable for HCV RNA.

<sup>b</sup> If dosing time or draw time is missing, the blood draw will be assumed to be pre-dose for HCV RNA measurements. For resistance measurements, the blood draw will be assumed to be pre-dose.

<sup>c</sup> Visits at Weeks 16 – 24 are only applicable to subjects assigned to 24 weeks of treatment (e.g., Arm B subjects).

<sup>d</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>e</sup> For SVR windows, the last value in the window will be used.

Note: Data must also have Study Drug End Day ≤ 2 for all windows, except SVR<sub>12planned</sub> and SVR<sub>24planned</sub>. The result closest to the scheduled time point will be used, except for SVR<sub>12planned</sub> and SVR<sub>24planned</sub>.
### Table 2. 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>SVR₄</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>SVR₁₂</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>SVR₃₄</td>
<td>168</td>
<td>127 to 210</td>
</tr>
</tbody>
</table>

*Note: Data must have Study Drug End Day > 2 for all windows. The result closest to the scheduled time point will be used, except for SVR₄, SVR₁₂, and SVR₃₄. For SVR endpoints, the last value in the window will be used.*
### Table 3. Analysis Time Windows for PRO Instruments

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Study Day)</th>
<th>Time Window (Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1/Baseline</td>
<td>1</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>2 to 42</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>71 to 98</td>
</tr>
<tr>
<td>Week 16(^a,b)</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td>Week 20(^a,b)</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td>Week 24(^a)</td>
<td>168</td>
<td>155 to 182</td>
</tr>
<tr>
<td>Final Treatment Visit(^c)</td>
<td>2 to ≤ 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

<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 4</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24</td>
<td>168</td>
<td>127 to 252</td>
</tr>
<tr>
<td>Post-Treatment Week 48</td>
<td>336</td>
<td>253 to 378</td>
</tr>
<tr>
<td>Final Post-Treatment Visi(^d)</td>
<td>&gt; 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

a. Applicable to subjects with 24 weeks of treatment.
b. PRO data was not collected at Weeks 16 and 20. Values in the analysis windows for Weeks 16 and 20 will not be displayed in mean change from baseline summary tables.
c. The last value within the window will be used to define the final on-treatment value. The upper bound of this Final window is Study Drug End Day ≤ 2.
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 with no upper bound.

Note: The result closest to the scheduled time point will be used. For visits through Week 24 of the Treatment Period, data must also be within 2 days of the last dose of study drug. For post-treatment visits, data must also have Study Drug End Day > 2.
### Table 4. Laboratory Data and Vital Sign Visit Windows (Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day/Time (Study Day)</th>
<th>Time Window (Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1/Baseline</td>
<td>1</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Week 16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td>Week 20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td>Week 24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>168</td>
<td>155 to 182</td>
</tr>
<tr>
<td>Final Treatment Visit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Applicable to subjects with 24 weeks of treatment.

<sup>b</sup> The last value within the window will be used to define the final on-treatment value. The upper bound of this Final window is Study Drug End Day ≤ 2.

Notes: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day ≤ 2.

IP-10 is measured at Baseline, Week 4, Week 8, Week 12, Week 24, or EOT. Total Insulin is measured at Baseline, Week 12, Week 24, or EOT. Clinical assessments of ascites and hepatic encephalopathy for Child-Pugh classification are collected at Screening, Baseline, Week 12, Week 24, or EOT.
### Table 5. Laboratory Data and Vital Sign Visit Windows (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>Final Post-Treatment Visit</td>
<td>&gt; 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

Note: 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 with no upper bound.

### 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 four 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 and overall on the safety population. The summary of demographics also will be provided by country.
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 or Europe), country, BMI category (< 30 or ≥ 30 kg/m²), and women of childbearing potential (females between the ages of 18 and 55 years, inclusive).

Baseline characteristics will include prior HCV treatment history (treatment-naïve or pegIFN/RBV treatment-experienced [null responder (definition 1 or 2), partial responder, or relapser]), 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; < 7 or ≥ 7 log_{10} IU/mL), baseline IP-10 (continuous), baseline IP-10 (< 600 or ≥ 600 ng/L), baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L²), Child-Pugh score at Screening (5 or 6), baseline Child-Pugh score (5, 6, or > 6), baseline longitudinal FibroTest score (continuous), baseline platelet counts (continuous), baseline platelet counts (< 60, 60 to < 90, 90 to < 120, or ≥ 120 × 10⁹/L), baseline albumin (continuous), baseline albumin (< 28, 28 to < 33, 33 to < 40, 40 to 49, and > 49 g/L), baseline alpha fetoprotein (continuous), 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), 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 anytime 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, Puerto Rico, and USA will be grouped under North America and
sites in Belgium, France, Germany, Italy, Spain, and United Kingdom will be grouped under Europe.

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 is defined as 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 Child-Pugh score is determined by the Day 1 assessment of ascites and hepatic encephalopathy along with the baseline values of total bilirubin, serum albumin, and INR. The Child-Pugh score is the sum of the point assigned for each of the five observed findings as defined in Table 6. Child-Pugh score at all other visits will be based on the total score automatically calculated on the eCRF.
Table 6. Child-Pugh Classification of Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Assigned for Observed Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L (mg/dL)</td>
<td>&lt; 34.2</td>
</tr>
<tr>
<td></td>
<td>(&lt; 2)</td>
</tr>
<tr>
<td>Serum albumin, g/L (g/dL)</td>
<td>&gt; 35</td>
</tr>
<tr>
<td></td>
<td>(&gt; 3.5)</td>
</tr>
<tr>
<td>INR</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Ascites*</td>
<td>None</td>
</tr>
<tr>
<td>Hepatic encephalopathy**</td>
<td>None</td>
</tr>
</tbody>
</table>

* None.

Slight ascites = Ascites detectable only by ultrasound examination.
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.
Severe ascites = Large or gross ascites with marked abdominal distension.

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

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 (12 weeks versus 24 weeks). 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.

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 and overall. 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 and overall. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. The number and percentage of subjects taking prior or concomitant medications will be summarized by generic drug name based on the WHO Drug Dictionary. The prior HCV medications (pegIFN and RBV) taken by the treatment experienced subjects 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 study drug;
- Subjects who completed study drug;
- Subjects who discontinued from 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.

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 arm 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.

A table that lists reasons for discontinuation of study drug will be provided for women of childbearing potential who discontinued study drug.

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 arm, as applicable, will be summarized for:

• Subjects with interruptions of all study drugs for toxicity management;
• Subjects with any RBV dose modifications;
  ○ Subjects with RBV dose modification due to decrease in hemoglobin;
  ○ Subjects with RBV dose modification due to decrease in creatinine clearance;
  ○ Subjects with RBV dose modification due to other reasons;
• Subjects with any RBV dose modification to 0 mg (i.e., RBV interruptions).

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

The duration of exposure to study drug will be summarized for each treatment group and overall in the safety 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.

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.
- 1 to 15 days, 16 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 150 days, and >150 days.

9.2 Compliance

At each protocol-specified visit, 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, ABT-333, and RBV) within the 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 day). 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, 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.

In addition, adherence to each drug (ABT-450/r/ABT-267, ABT-333, and RBV) 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. In addition, dosing together adherence, which measures the proportion of times the assigned tables are taken within 30 or 60 minutes of each other, will also be provided.

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 population. The data from the ITT population will be presented by the treatment group assigned at the time of randomization (12-week arm or 24-week arm).

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.

**Breakthrough** = confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment.

**Rebound** = confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 log_{10} IU/mL above nadir) at any time point during treatment or Breakthrough. A single rebound value (≥ LLOQ or > 1 log_{10} above nadir) followed by lost to follow-up would be considered a rebound (i.e., will not require confirmation).

**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 (Arm A) or in the Week 24 window (Arm B).

**SVR_{4}** = HCV RNA < LLOQ in the SVR_{4} window (4 weeks after the last actual dose of 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 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 study drug [i.e., Week 24 (Arm A) or Week 36 (Arm B)]) 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 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 study drug [i.e., Week 36 (Arm A) or Week 48 (Arm B)]) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

Relapse\textsubscript{4} = confirmed HCV RNA ≥ LLOQ between end of treatment and 4 weeks after last actual dose of 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.

Relapse\textsubscript{12} = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of 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.

Relapse\textsubscript{overall} = 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.

Relapse\textsubscript{24} = confirmed HCV RNA ≥ LLOQ within the SVR\textsubscript{24} window for a subject who achieved SVR\textsubscript{12} and has HCV RNA data available in the SVR\textsubscript{24} window.
Relapse\textsubscript{late} = confirmed HCV RNA $\geq$ LLOQ at any time after the SVR\textsubscript{24} assessment time point for a subject who achieved SVR\textsubscript{24} and has post-SVR\textsubscript{24} HCV RNA data available.

For relapse analyses, the completion of treatment is defined as a study drug duration $\geq$ 77 days for subjects assigned to 12 weeks of treatment (Arm A) or study drug duration $\geq$ 154 days for subjects assigned to 24 weeks of treatment (Arm B). If the last available post-treatment value is $\geq$ 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\textsubscript{12} Non-Response**

Subjects who do not achieve SVR\textsubscript{12} (SVR\textsubscript{12} 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\textsubscript{12}** definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR\textsubscript{12} non-responder who prematurely discontinued study drug (duration $< 77$ days for Arm A or duration $< 154$ days for Arm B) and did not meet the **On-treatment virologic failure definition**);
4. Missing follow-up data in the SVR\textsubscript{12} window [defined as any subject who completed study drug without data in the SVR\textsubscript{12} window after applying the imputation rules and not meeting the definitions of (1), (2), or (3)];
5. Other [defined as any SVR\textsubscript{12} non-responder not meeting the definitions of (1) – (4), such as a subject with a single quantifiable value within the SVR\textsubscript{12} window followed by an undetectable value beyond the SVR\textsubscript{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 for Arm A or duration < 154 days for Arm B] 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_{24} rates, as reported in the telaprevir US Prescribing Information (USPI),\textsuperscript{7} for telaprevir plus pegIFN and RBV therapies in HCV genotype 1, treatment-naïve or treatment-experienced subjects with cirrhosis from the ADVANCE, ILLUMINATE, and REALIZE trials are presented in Table 7 and Table 8, respectively. A fixed-effect meta-analysis was used to calculate the estimated SVR rate and 95% confidence interval in the treatment-naïve population (Table 7). A weighted average of the corresponding SVR rates among treatment-naïve
and treatment-experienced (prior null responders, partial responders, and relapsers) subjects was calculated to reflect the population expected to enroll in Study M13-099 (Table 8).

For a regimen to be considered superior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower confidence bound of the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for telaprevir plus pegIFN and RBV presented in Table 8 (i.e., 54%). To be considered non-inferior to the historical SVR rate for telaprevir plus pegIFN and RBV, the lower confidence bound of the SVR rate must exceed 43%. The value of 43% used for the non-inferiority comparison represents the 54% historical SVR rate adjusted for a non-inferiority margin of 10.5%. The non-inferiority margin of 10.5% used for comparisons to the historical SVR rate for telaprevir plus pegIFN and RBV is based on the telaprevir ILLUMINATE study which used the same non-inferiority margin.

Table 7. SVR Rates for Telaprevir Plus PegIFN and RBV in Treatment-Naïve Subjects

<table>
<thead>
<tr>
<th>Telaprevir Studies</th>
<th>ADVANCE</th>
<th>ILLUMINATE</th>
<th>Meta Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir Studies</td>
<td>T12/PR</td>
<td>T12/PR</td>
<td>T12/PR</td>
</tr>
<tr>
<td>Treatment-naïve subjects with cirrhosis(^7)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>[95% CI]</td>
</tr>
<tr>
<td>15/21 (71)</td>
<td>31/61 (51)</td>
<td>56 [45, 67]</td>
<td></td>
</tr>
</tbody>
</table>

GT1a = genotype 1a; GT1b = genotype 1b
### Table 8. Estimated SVR Rates for Telaprevir plus PegIFN and RBV in Cirrhotic Subjects

<table>
<thead>
<tr>
<th>REALIZE&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Telaprevir-Treated Subjects with Cirrhosis n/N (%)</th>
<th>Projected Enrollment in Study M13-099 (%)</th>
<th>Population-Based Weighted Average % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta Analysis of ADVANCE and ILLUMINATE Studies (Table 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naïve Subjects</td>
<td>(56)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>REALIZE Study&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior relapers</td>
<td>48/57 (84)</td>
<td>12</td>
<td>47 [41, 54]</td>
</tr>
<tr>
<td>Prior partial responders</td>
<td>11/32 (34)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Prior null responders</td>
<td>7/50 (14)</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

### 10.3 Handling of Multiplicity

In order to control the Type I error rate at 0.05, a gatekeeping testing procedure<sup>12</sup> will be used to proceed through the primary and secondary efficacy endpoints. The primary efficacy endpoints are the percentage of subjects with SVR<sub>12</sub> within each treatment arm. The overall 2-sided significance level of 0.05 will be split between the two arms using a Bonferroni correction of 0.025 for each arm. The primary endpoints within Arm A will be tested separately from Arm B in the following order:

A1. SVR<sub>12</sub>: Non-inferiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the lower confidence bound (LCB) of the 97.5% CI for the percentage of subjects with SVR<sub>12</sub> in Arm A must exceed 43% to achieve non-inferiority.

A2. SVR<sub>12</sub>: Superiority of Arm A to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR<sub>12</sub> in Arm A must exceed 54% to achieve superiority.
B1. **SVR}_{12}: Non-inferiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR}_{12} in Arm B must exceed 43% to achieve non-inferiority.

B2. **SVR}_{12}: Superiority of Arm B to the historical SVR rate for telaprevir plus pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects with SVR}_{12} in Arm B must exceed 54% to achieve superiority.

Within Arm A, only if success has been demonstrated for non-inferiority of the SVR}_{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A1) will the testing continue to superiority of the SVR}_{12} rate in Arm A to the historical rate for telaprevir plus pegIFN and RBV therapy (A2). Within Arm B, only if success has been demonstrated for non-inferiority of the SVR}_{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B1) will the testing continue to superiority of the SVR}_{12} rate in Arm B to the historical rate for telaprevir plus pegIFN and RBV therapy (B2). Otherwise, statistical testing will stop. If success is achieved for all of the primary endpoints (A1, A2, B1, and B2), then the first secondary endpoint to compare the percentage of subjects with SVR}_{12} following 12 or 24 weeks of treatment will be tested; otherwise, statistical testing will stop.

**10.4 Primary Efficacy Analysis**

The primary efficacy endpoints are A1, A2, B1 and B2 defined in Section 10.3. The percentage and a 2-sided 97.5% confidence interval (CI) of subjects achieving SVR}_{12} within each treatment arm 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.

To test the hypothesis that the percentage of treatment-naïve and pegIFN/RBV treatment-experienced HCV genotype 1 infected subjects with compensated cirrhosis treated with ABT-450/r/ABT-267 + ABT-333 + RBV for 12 or 24 weeks who achieve SVR}_{12} is non-inferior or superior to the historical SVR rate for the corresponding
population treated with telaprevir plus pegIFN and RBV, the LCB of the 97.5% CI must be greater than 43% in order for the regimen to be considered non-inferior, and the LCB of the 97.5% CI of the SVR\textsubscript{12} rate must be greater than 54% in order for the regimen to be considered superior.

The value of 54% used in the endpoints as the historical SVR rate for telaprevir plus pegIFN and RBV represents the upper confidence bound of the 2-sided 95% confidence interval of the combined SVR rate as described in Section 10.2. The value of 43% used for the non-inferiority comparison represents the historical SVR rate (54%) adjusted for a non-inferiority margin of 10.5%.

HCV RNA and SVR\textsubscript{12} will be imputed as described in Section 6.3.

### 10.5 Secondary Efficacy Analyses

The secondary efficacy endpoint included in the gatekeeping testing procedure is:

- The percentage of subjects with SVR\textsubscript{12} in the 24-week arm compared to the 12-week arm.

Other secondary endpoints not included in the gatekeeping testing procedure are:

- The percentage of subjects in each arm with on-treatment virologic failure during the Treatment Period (defined per On-treatment virologic failure definition) out of all subjects in the ITT population;
- The percentage of subjects in each arm with post-treatment relapse (defined per Relapse\textsubscript{12} definition).

To test the hypothesis that the percentages of subjects who achieve SVR\textsubscript{12} is different between Arm A and Arm B, the percentages will be compared using a logistic regression model with treatment arm, baseline log\textsubscript{10} HCV RNA level, HCV subgenotype (1a, non-1a), IL28B genotype (CC, non CC), and pegIFN/RBV treatment history (treatment-naïve or treatment-experienced) as predictors.
The percentages (with 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 for each arm. These endpoints will not be part of the multiple 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_{12} imputed as described in Section 6.3, SVR_{12} will be presented using the following other methods to impute missing post-treatment virologic results:

- no imputation such that all missing HCV RNA values will be treated as failures;
- imputing any missing HCV RNA values in the SVR_{12} window by carrying forward the last non-missing (post-baseline) HCV RNA value prior to the SVR_{12} window;
- impute as described in Section 6.3 but exclude local laboratory HCV RNA data;
- impute as described in Section 6.3 but exclude SVR_{12} non-responders who were categorized as "prematurely discontinued study drug with no on-treatment virologic failure" or "missing follow-up data in the SVR_{12} window."

For each of these, the simple percentage of subjects with SVR_{12} will be presented along with a 2-sided 95% CI.

10.6.2 Responses Across Stratification Variables

The number and percentage of subjects achieving SVR_{12} within each of the stratum will be summarized. The ten stratum are:
1. Treatment-naïve/HCV genotype 1a/IL28B CC
2. Treatment-naïve/HCV genotype 1a/IL28B non-CC
3. Treatment-naive/HCV genotype non-1a/IL28B CC
4. Treatment-naive/HCV genotype non-1a/IL28B non-CC
5. Treatment-experienced/prior null responder/HCV genotype 1a
6. Treatment-experienced/prior null responder/HCV genotype non-1a
7. Treatment-experienced/prior partial responder/HCV genotype 1a
8. Treatment-experienced/prior partial responder/HCV genotype non-1a
9. Treatment-experienced/prior relapser/HCV genotype 1a
10. Treatment-experienced/prior relapser/HCV genotype non-1a

10.7 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized on the ITT population by treatment group and overall.

- the percentage of subjects with RVR (HCV RNA < LLOQ at Week 4 of the Treatment Period);
- the percentage of subjects with EOTR (HCV RNA < LLOQ at Week 12 (Arm A) or Week 24 (Arm B) of the Treatment Period);
- the percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
- the number of subjects with virologic rebound at each protocol-specified visit in the Treatment Period;
- the percentage of subjects who failed to suppress HCV RNA (never achieving HCV RNA < LLOQ) during the Treatment Period and received at least 6 weeks treatment (defined as 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 Treatment Period;

- the percentage of subjects achieving SVR4;
- the percentage of subjects achieving SVR_{12planned};
- the percentage of subjects achieving SVR_{24};
- the percentage of subjects achieving SVR_{24planned};
- time to relapse at any time post-treatment (defined in text below with additional relapse analyses);
- the percentage of subjects who achieved SVR_{24} who subsequently relapsed (Relapse_{late});
- mean change from baseline in longitudinal FibroTest scores to each applicable post-baseline timepoint.

In addition to analyzing the difference with a logistic regression model, the difference in SVR_{12} rates between treatment arms will be analyzed using the stratum-adjusted Mantel-Haenszel (MH) proportion with a continuity correction for variance, adjusting for each of the 10 randomization stratum (defined in Section 10.6.2). In addition, the unadjusted difference in SVR_{12} rates between treatment arms will be summarized.

The mean change from baseline will be summarized for the FibroTest score, and analyses of mean change from baseline to post-treatment Week 12 in FibroTest score will be compared between treatment arms using an analysis of covariance (ANCOVA) model with treatment arm as a factor and baseline score as a covariate.

The percentage of subjects with RVR, EOTR, SVR_{4}, SVR_{12}, SVR_{12planned}, SVR_{24}, and SVR_{24planned} 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\textsubscript{12} will be presented along with the number of subjects who do not achieve SVR\textsubscript{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\textsubscript{24} will be presented along with the number of subjects who do not achieve SVR\textsubscript{24} by reason for non-response (defined in Section 10.1). The non-responders will be presented in a listing.

The number and percentage of subjects who fail to suppress HCV RNA and received at least 6 weeks of treatment (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 any time during treatment and within each protocol-specified visit (defined in Table 1) 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 for subjects assigned to Arm A and $\geq$ 154 days for subjects assigned to Arm B) with final on-treatment HCV RNA < LLOQ who relapse within the SVR\textsubscript{4} window, within the SVR\textsubscript{12} window, within the SVR\textsubscript{24} window (defined in Table 2), after the SVR\textsubscript{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 for subjects assigned to Arm A and $<$ 154 days for subjects assigned to Arm B) 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 study drug and displayed graphically using a Kaplan-Meier (KM) curve by treatment arm. For time to relapse analyses, time to event will be measured as the number of days from the last dose of study drug to event or censoring time. The time of relapse post-treatment is defined as the first of two consecutive HCV RNA values $\geq$ LLOQ between the end of the 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.

The time to suppression on treatment will be calculated for each subject treated with study drug and displayed graphically using a KM curve by treatment arm. For time to suppression analyses, time to event will be measured as the number of days from the first dose of study drug to event or censoring time. The time of suppression is defined as the first occurrence of HCV RNA values < LLOQ during the Treatment Period. Subjects who do not suppress will be censored at the date of the last HCV RNA value within the 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 SVR\(_4\) and SVR\(_{12}\) will be assessed by the agreement between SVR\(_4\) and SVR\(_{12}\) and by the positive predictive value (PPV) and negative predictive value (NPV) of SVR\(_4\) on SVR\(_{12}\). The agreement between SVR\(_4\) and SVR\(_{12}\) is a percentage defined as the number of subjects achieving both SVR\(_4\) and SVR\(_{12}\) and the number of subjects not achieving both SVR\(_4\) and SVR\(_{12}\) out of all subjects in the ITT population. The PPV of SVR\(_4\) on SVR\(_{12}\) is the proportion of subjects who achieve SVR\(_4\) and SVR\(_{12}\) 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 study drug 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 ≥ 77 days for subjects assigned to 12 weeks of treatment (Arm A) or study drug duration ≥ 154 days for subjects assigned to 24 weeks of treatment (Arm B); or (3) 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 SVR₁₂ 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 SVR₁₂ 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 ≤ 1000 IU/mL).

Subjects treated with study drug who do not achieve SVR₁₂ 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 ≥ 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 ≥ 1000 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 ≥ 1000 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 IU/mL, the sample closest in time after the failure with an HCV RNA level ≥ 1000 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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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 $\geq 1000$ 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 treated subjects who experience VF after Post-Treatment Week 12, 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 for all randomized subjects. 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. The HCVPRO, EQ-5D-5L, and SF-36v2 will also be collected at Week 24 for subjects assigned to 24 weeks of treatment. 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 change from Baseline to Final Treatment Visit and PT Week 12 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 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 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 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

\[ ScaledScore = \frac{Sum \times 100}{64} \]

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). The VAS score will be measured separately. The SF-36v2 1,2 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 for the change from baseline to Final Treatment Visit and the change from baseline to PT Week 12. An ANCOVA analysis will be performed on the change from baseline 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 Treatment Visit in the SF-36v2 PCS and MCS. The percentage of subjects in each treatment group with a change from Baseline to Final 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 Treatment Visit in the HCVPRO total score and in the EQ-5D-5L health index score:

- Change from Baseline to Final Treatment Visit in SF-36 PCS > –5 [yes/no];
- Change from Baseline to Final Treatment Visit in SF-36 MCS > –5 [yes/no].

Change from Baseline to Final is defined as the Final Score – Baseline Score within the 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 $(1 – \text{sensitivity})^2 + (1 – \text{specificity})^2$. 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 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 Treatment Visit in EQ-5D-5L health index score. The percentage of subjects in each treatment group with a change from Baseline to Final 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 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:

- Prior HCV treatment history (treatment-naïve or treatment-experienced);
- For treatment-experienced subjects, type of non-response to previous pegIFN/RBV treatment (null responder [definition 1 or 2], partial responder, or relapser);
- HCV genotype 1 subtype (1a 1b, or other);
- IL28B genotype (CC or non-CC) and (CC, CT, or TT);
- Sex (male or female);
- Age (< 55 or $\geq$ 55 years) and (< 65 or $\geq$ 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 or Europe) and Country (as appropriate);
- BMI (< 30 or $\geq$ 30 kg/m$^2$);
- Baseline HCV RNA levels (< 800,000 or $\geq$ 800,000 IU/mL);
- Baseline IP-10 (< 600 or $\geq$ 600 ng/L);
- Baseline HOMA-IR (< 3 or $\geq$ 3 mU × mmol/L$^2$);
● Baseline Child-Pugh Score (5, 6, or > 6);
● Baseline platelets (< 90 or ≥ 90 × 10⁹/L);
● Baseline albumin (< 35 or ≥ 35 g/L);
● Baseline alpha fetoprotein [AFP] (< 20 or ≥ 20 ng/mL);
● 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 SVR₁₂ 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 43%.

A logistic regression model will be used to explore the associations between each of the subgroup variables and SVR₁₂ by fitting a logistic regression model on all subjects in the ITT population. A stepwise logistic regression approach will be used to assess the strength of each subgroup variable in predicting SVR₁₂, 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 non-response to previous pegIFN/RBV treatment.

11.0 Safety Analysis

11.1 General Considerations

All subjects who receive at least one dose of study drug will be included in the safety analyses. For safety analyses, data from both treatment groups will be summarized, and
comparisons between treatment groups will be performed where specified. All tabulations of safety data also will include a total column combining all subjects.

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 through 30 days after the last dose of study drug. 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 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 by treatment group and overall.

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 treatment groups will be performed using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

**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 treatment groups 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 total of both treatment groups combined. 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 treatment groups 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 Rash
  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 to 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. Non-serious 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 non-serious 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 study drug (DAA 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),
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, alpha2-macroglobulin, haptoglobin, apolipoprotein A1, and alpha fetoprotein.

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:

\[
GFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times \text{Serum Creatinine} \times (1.154) \times \text{Age} \times (0.203) \times 1.212 \\
\text{(if Black)} \times 0.742 \text{ (if Female)}.
\]

The Criteria for Potentially Clinically Significant (PCS) Laboratory Findings are described in Table 9 and Table 10.
Table 9. 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>Hemoglobin</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>Platelets Count</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>White Blood Cell Count</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>Absolute Neutrophil Count</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>Lymphocyte Count</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>Eosinophil Count</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>aPTT</td>
<td>&gt; 2 × ULN</td>
<td></td>
</tr>
<tr>
<td>International Normalized Ratio</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 10. Criteria for Potentially Clinically Significant Chemistry Values

<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>$&gt; 5 \times \text{ULN}$ and $\geq 2 \times \text{baseline}$</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td></td>
<td>$&gt; 5 \times \text{ULN}$ and $\geq 2 \times \text{baseline}$</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td></td>
<td>$&gt; 1.5 \times \text{ULN}$</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>$\ \geq 2.0 \times \text{ULN}$</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mcmol/L)</td>
<td>$\geq 132.605$</td>
<td></td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>$\geq 1.5$</td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>$&lt; 50$</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>$&gt; 5 \times \text{ULN}$</td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mcmol/L)</td>
<td>$&gt; 713.817$</td>
<td></td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>$&gt; 12.0$</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>
Table 10. 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 Treatment Period. The baseline value will be the last measurement on or before the day of the first dose of study drug. This same baseline value will be used for all change from baseline tables in the Treatment Period and Post-Treatment Period.

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, minimum, maximum, and median.

During the Treatment period, 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 Treatment period 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 Period meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 9 and Table 10) will be summarized by treatment group. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. Comparisons between treatment groups will be performed on 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 11) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. 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. Treatment group 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)) 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.

The hemoglobin by maximum CTCAE grade table, described above, also will be summarized for subjects with and without treatment-emergent adverse events of dyspnea (defined by preferred terms of "dyspnoea" or "dyspnoea exertional").

For subjects with a Grade 3 or higher total bilirubin elevation, a listing of treatment-emergent adverse events (defined as preferred terms within the "Cholestasis and
jaundice of hepatic origin" (broad search) SMQ, excluding preferred terms within the "Investigations" SOC) will be provided.

Table 11. 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>
</tr>
<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.

For subjects meeting the criterion of ALT < 3 × ULN and total bilirubin ≥ 2 × ULN, the number and percentage of subjects with a total bilirubin value in the categories of ≤ ULN, > ULN – < 2 × ULN, and ≥ 2 × ULN at the Final Treatment Visit will be summarized. A similar summary will be provided for Post-Treatment Week 4.
In addition, for subjects meeting the criterion of ALT < 3 × ULN and total bilirubin ≥ 2 × ULN (based on the maximum ratio relative to the ULN), the ratio of indirect bilirubin to total bilirubin will be calculated. The following summary statistics will be presented for each treatment group for the ratio at baseline and for the ratio associated with the peak total bilirubin value during the Treatment Period: sample size, mean, standard deviation, minimum, maximum, and median. In addition, the number and percentage of subjects with a ratio < 0.75 and < 0.50 will be presented for baseline and peak.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

Vital sign variables are body temperature, 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 12.

<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>Pulse 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>A decrease of ≥ 15% from baseline</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 at each visit during the Treatment Period. The baseline value will be the last measurement on or before the day of the
first dose of study drug. This same baseline value will be used for all change from baseline tables in the Treatment 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, minimum, maximum, and median.

The number and percentage of subjects with post baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant Vital Signs values (Table 12) 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. Comparisons between treatment groups of the percentage of subjects experiencing a value meeting the criteria in the 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 8.0 of M13-099 Protocol Amendment 4) and this SAP.

- Definition of on-treatment virologic failure
  - The definition in the protocol was "confirmed HCV RNA $\geq$ LLOQ after HCV RNA $<\text{LLOQ}$ 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 $<\text{LLOQ}$ 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.
- Additional efficacy subgroup analyses were added as appropriate for the population of HCV patients with compensated cirrhosis.
- Continuous plots for the HCVPRO total score, and other quality of life data, will be presented for the change from baseline rather than the percent change from baseline. Continuous plots by treatment arm will be provided with the change from baseline on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis. Change from baseline is used in these plots for consistency across summaries of quality of life data.

13.0 References


4. VICTRELIS® (boceprevir) [package insert]. Merck and Company, Inc.; Whitehouse Station, NJ.
5. COPEGUS® (ribavirin) [package insert]. Genentech; South San Francisco, CA.
6. PEGASYS® (peginterferon alfa-2a) [package insert]. Genentech; South San Francisco, CA.
7. INCIVEK™ (telaprevir) [package insert]. Vertex Pharmaceuticals Inc.; Cambridge, MA.
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