1.0 Title Page

Clinical Study Protocol M14-004

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 Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (TURQUOISE-I)

Incorporating Administrative Change 1 and Amendments 1 and 2

AbbVie Investigational Product: ABT-450/r/ABT-267, ABT-333
Date: 17 July 2014
Development Phase: 2/3
Study Design: This is a randomized, open-label combination drug study
EudraCT Number: 2012-005143-24
Investigators: Multicenter; Investigator information on file at AbbVie
Sponsor: AbbVie*
Sponsor/Emergency Contact:

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:

- Clarify the minimum and maximum number of subjects with no HIV-1 protease inhibitor (PI) exposure other than darunavir allowed to enroll in Part 1b in Section 1.2 Synopsis and Section 5.1 Overall Study Design and Plan: Description.

  Rationale: To ensure that a balanced number of previously PI-naïve and PI-experienced subjects are enrolled.

- Update Section 5.2.1 Inclusion Criteria, Section 5.2.3.3 Other Concomitant Therapy and Section 6.7.5 Management of Transaminase Elevations with language related to hormonal contraceptives for female subjects of childbearing potential.

  Rationale: To more clearly define the acceptable approaches to contraception during the study, including the use of progestin-only hormonal contraceptive methods.

- Update Section 5.2.1 Inclusion Criterion 13 to have confirmation of plasma HIV-1 RNA below LLOQ at least twice during the 24 weeks prior to screening.

  Rationale: To ensure potential subjects demonstrate plasma HIV-1 RNA virologic suppression for the period prior to study entry.

- Clarify the once-daily (QD) and twice daily (BID) dose of darunavir that is to be taken for subjects assigned to Arms C and D in Section 1.2 Synopsis, Section 5.1.3 Pre-Treatment Period (Part 1b only), Section 5.2.3.2 Prior and Concomitant HIV-1 Therapy, and Section 5.7.5 Selection of Doses in the Study.

  Rationale: Administrative change for clarity.

- Remove an "X" on Table 9 Part 1b: Study Activities – Post-Treatment (PT) Period table at PT Wk 24 and PT Wk 48 for the activities of "Hepatocellular Carcinoma Screening" for subjects in Part 1b and update footnote "d."

  Rationale: Administrative change for clarity as it was inadvertently included in the protocol amendment 1. In addition, clarification is added to footnote
"d" regarding when to complete the HCC screening during the Post-Treatment Period if a 12-week treatment arm is extended to 24 weeks treatment.

- Minor clerical updates made throughout the protocol.

Rationale: For clarification and consistency throughout the protocol.

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

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<tr>
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<th>Protocol Number: M14-004</th>
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<tbody>
<tr>
<td><strong>Name of Study Drug:</strong></td>
<td><strong>Phase of Development:</strong> 2/3</td>
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<tr>
<td>ABT-450/r/ABT-267, ABT-333</td>
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<tr>
<td><strong>Name of Active Ingredient:</strong></td>
<td><strong>Date of Protocol Synopsis:</strong> 17 July 2014</td>
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<tr>
<td>ABT-450</td>
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<td>ABT-333</td>
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<td><strong>Protocol Title:</strong></td>
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<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 Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (TURQUOISE-I)</td>
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<td><strong>Objectives:</strong></td>
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<td>The primary objectives of this study are to assess the safety of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in HCV genotype 1-infected subjects with HIV-1 coinfection and to evaluate the percentage of subjects achieving SVR12 (HCV RNA &lt; lower limit of quantification [LLOQ] 12 weeks following treatment) within the 12- and 24-week treatment groups compared to the historical SVR rate of pegIFN and RBV therapy in the corresponding population. The secondary objectives of this study are to compare the SVR12 rates between the 12- and 24-week treatment groups and to assess the percentage of subjects with on-treatment HCV virologic failure, the percentage of subjects with HCV virologic relapse, and the percentage of subjects with plasma HIV-1 viral suppression at the end of treatment and at Post-Treatment Week 12 in each treatment group.</td>
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<td><strong>Investigator:</strong></td>
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<td>Multicenter; Investigator information on file at AbbVie</td>
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<td><strong>Study Sites:</strong></td>
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<td>Approximately 60 sites</td>
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<td><strong>Study Population:</strong></td>
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<td>Adult subjects with genotype (GT) 1 HCV infection and HIV-1 coinfection on a stable HIV-1 antiretroviral therapy (ART), who are HCV treatment-naïve or pegylated interferon (alfa-2a or alfa-2b)/ribavirin (pegIFN/RBV)-experienced with and without compensated cirrhosis.</td>
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<td><strong>Number of Subjects to be Enrolled:</strong></td>
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<tr>
<td>Approximately 300 subjects</td>
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<td><strong>Methodology:</strong></td>
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<td>This is a Phase 2/3, 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 adults with HCV GT 1/HIV-1 coinfection who are HCV treatment-naïve or pegIFN/RBV–experienced with and without compensated cirrhosis.</td>
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Methodology (Continued):

This study will consist of a Phase 2 pilot cohort (Part 1a and Part 1b) and a Phase 3 cohort (Part 2). Both Part 1 and Part 2 of this study will consist of a Treatment Period and a Post-Treatment Period. In addition, Part 1b will consist of a lead-in period (Pre-Treatment Period) for approximately 2 weeks prior to the initiation of the Treatment Period. Patients with an unquantifiable plasma HIV-1 RNA and a CD4+ count ≥ 200 cells/mm³ or a CD4+% ≥ 14% while on a stable atazanavir (ATV), raltegravir (RAL), or darunavir (DRV) containing HIV-1 ART regimen will be eligible.

Part 1 is designed as a pilot cohort to evaluate the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in approximately 90 HCV GT 1/HIV-1 coinfected, treatment-naïve and pegIFN/RBV-experienced adults. The pilot cohort consists of two parts, Part 1a (approximately 60 subjects) and Part 1b (approximately 30 subjects).

Part 1a consists of 2 ART-regimen subgroups (atazanavir [ATV] and raltegravir [RAL]), each containing at least 20 subjects. Subjects meeting eligibility criteria will be randomized to receive ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks (Arm A) or 24 weeks (Arm B).

Part 1b consists of approximately 30 subjects who are currently stable on an HIV-1 ART regimen containing the protease inhibitor (PI) darunavir (DRV) once daily (QD). Subjects meeting eligibility criteria will be randomized to receive DRV 800 mg QD (Arm C) or switch to DRV 600 mg twice daily (BID) administration (Arm D) for a minimum of 14 days prior to starting study treatment. Beginning on Study Day 1, subjects in Part 1b will also receive ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks.

If the SVR4 rates are at least 80% and there is an acceptable safety profile for subjects in Part 1a, then enrollment of Part 2 may be initiated for subjects on an HIV-1 ART regimen containing ATV and RAL. The inclusion of subjects on a DRV-based HIV-1 ART regimen (DRV QD and/or DRV BID) into Part 2 will be determined based on an evaluation of an acceptable safety and efficacy profile during Part 1b, including the rate of failure to maintain HIV-1 RNA suppression for each DRV treatment strategy during the period of co-administration with study treatment.

Part 2, the Phase 3 cohort, further evaluates the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks. Approximately 210 additional HCV GT 1/HIV-1 coinfected, treatment-naïve and pegIFN/RBV-experienced adults will be randomly assigned to receive ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 weeks (Arm A) or 24 weeks (Arm B).

Randomized subjects in Parts 1a and 2 will be stratified by prior HCV treatment history (treatment-naïve versus treatment-experienced) and presence of cirrhosis (cirrhotic or non-cirrhotic). Treatment-naïve subjects will also be stratified by interleukin 28B (IL28B) genotype (CC versus non-CC). PegIFN/RBV-experienced subjects will also be stratified by type of previous response to pegIFN/RBV (null responder; partial responder, or relapser). Randomized subjects in Part 1b will be stratified by prior HIV treatment history (previously PI-naïve subjects [i.e., no PI exposure other than DRV] and previously PI-experienced subjects [i.e., received non-DRV PI prior to current DRV treatment]). A minimum of 10 but no more than 20 subjects that are previously HIV-1 PI-naïve will be allowed to enroll in Part 1b of the study.

HCV GT 1/HIV-1 coinfected adults with compensated cirrhosis will be eligible for enrollment in both Parts 1 and 2.
Methodology (Continued):
The primary analysis will occur after all randomized subjects enrolled in Part 1 and Part 2 (N = 300) have completed Post-Treatment Week 12 or prematurely discontinued from the study. All efficacy and safety analyses will be performed on the appropriate population combining both Part 1 and Part 2.
The following criteria will be considered evidence of HCV virologic failure for the purpose of subject management. 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 log10 IU/mL above nadir) at any time point during treatment;
- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after HCV RNA < LLOQ during treatment.

Plasma HIV-1 RNA will be monitored throughout the study for the purpose of subject management. Subjects who experience one of the following criteria during the Treatment Period should be discontinued from study drug; however, if the investigator believes that the loss of plasma HIV-1 RNA suppression can be managed medically without study treatment discontinuation, then the AbbVie Study Designated Physician should be contacted to discuss continued study drug administration with medical management:

- HIV-1 RNA ≥ 40 copies/mL followed by a repeat HIV-1 RNA ≥ 200 copies/mL, or
- 3 consecutive HIV-1 RNA values ≥ 40 copies/mL.

All subjects in Parts 1 and 2 who receive at least one dose of DAAs will be monitored for up to 48 weeks following the last dose of DAAs to monitor for the durability of HCV viral response, and for the emergence and persistence of HCV resistant viral variants in the Post-Treatment Period. Resistance monitoring following the end of therapy will take place regardless of whether subjects receive additional anti-HCV therapy post-treatment.

Diagnosis and Main Criteria for Inclusion/Exclusion:
Main Inclusion:
1. Male or female and age is between 18 and 70 years, inclusive, at time of screening.
2. Subjects must be HCV treatment-naïve or pegIFN/RBV-experienced. If pegIFN/RBV-experienced, subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:

   - Null responder:
     1. Received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12 (Subjects will be considered to meet this definition if the lack of treatment response was documented between Weeks 10 – 16 of treatment); or
     2. Received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < 1 log10 IU/mL reduction in HCV RNA at Week 4 (Subjects will be considered to meet this definition if the lack of treatment response was documented after ≥ 25 days of treatment); or
   - Partial responder: Received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 log10 IU/mL reduction in HCV RNA at Week 12 (Subjects will be considered to meet this definition if the treatment response was documented between Weeks 10 – 16 of treatment), but failed to achieve HCV RNA undetectable at or after Week 20 of treatment; or
**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

### Main Inclusion (Continued):
- **Relapser:** Received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after Week 36 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 response should have been obtained in relation to the previous pegIFN/RBV treatment. Interferon-based therapy (e.g., pegIFN/RBV) must have been completed no less than 2 months prior to the Screening Visit.

Note: Genotype 1a, null responders with cirrhosis will not be eligible for enrollment in Part 1b.

3. Screening laboratory result indicating HCV genotype-1 infection.
4. Plasma HIV-1 RNA < 40 copies/mL during screening using Abbott RealTime HIV-1 assay.
5. CD4+ count $\geq$ 200 cells/mm$^3$ or CD4+% $\geq$ 14% during screening.

6. On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to screening. The HIV-1 ART regimen must include two nucleoside/nucleotide reverse transcriptase inhibitors plus one of the following ritonavir boosted protease inhibitors, or the integrase inhibitor, raltegravir.

The nucleoside/nucleotide reverse transcriptase inhibitor combinations in the stable qualifying HIV-1 ART regimen must be either:

- a. Tenofovir disoproxil fumarate (TDF) PO QD plus emtricitabine (FTC) PO QD (Individual components or as the fixed dose combination TDF/FTC, Truvada®), or
- b. Tenofovir disoproxil fumarate (TDF) PO QD plus lamivudine (3TC) PO QD or 3TC PO BID (Individual components or as the fixed dose combination TDF/3TC).

The ritonavir boosted protease inhibitor in the stable qualifying HIV-1 ART regimen must be either:

- a. Atazanavir (ATV) PO QD coadministered with ritonavir (RTV) PO QD, or
- b. Darunavir (DRV) PO QD coadministered with ritonavir (RTV) PO QD.

The integrase inhibitor in the stable qualifying HIV-1 ART regimen must be:

- a. Raltegravir (RAL) PO BID.

### Main Exclusion:
1. Positive test result at screening for Hepatitis B surface antigen (HBsAg).
2. Prior therapy with DAAs for the treatment of HCV, including telaprevir and boceprevir.
3. Any current or past clinical evidence of liver decompensation including ascites, variceal bleeding, or hepatic encephalopathy.
4. 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.
5. Chronic human immunodeficiency virus, type 2 (HIV-2) infection.

### Investigational Products:
- **ABT-450/ritonavir/ABT-267:** 75 mg/50 mg/12.5 mg tablet
- **ABT-333:** 250 mg tablet
- **Ribavirin:** 200 mg tablet
Doses:
- ABT-450/ritonavir/ABT-267: 150 mg/100 mg/25 mg QD
- ABT-333: 250 mg BID
- Ribavirin: Weight-based dosing 1000 or 1200 mg divided twice daily

Mode of Administration: Oral

Duration of Treatment:
Subjects will receive ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 or 24 weeks.

Criteria for Evaluation

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

Patient Reported Outcomes (PROs):
The change in patient reported outcomes (PROs) will be measured using several instruments. Non-disease-specific Health Related Quality of Life (HRQoL) will be assessed using the Short Form 36, version 2 (SF-36v2) questionnaire. Health State Utility will be measured using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L). HCV specific function and wellbeing will be assessed using the HCV Patient Reported Outcomes (HCVPRO) instrument.

Resistance:
For subjects who do not achieve SVR_{12}: the variants at each amino acid position by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence, the variants at signature resistance-associated amino acid positions at available post-baseline time points by population and/or clonal nucleotide sequencing compared to the appropriate prototypic reference sequence, and the variants at each amino acid position by population and/or clonal nucleotide sequencing at available post-baseline time points compared to the baseline sequence will be tabulated and summarized.

HIV-1 drug resistance genotyping for protease (PR), reverse transcriptase (RT) and integrase (IN), as appropriate, will be performed for protocol-defined eligible specimens.

Pharmacokinetic:
Individual plasma concentrations of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be tabulated and summarized for treated subjects. Plasma concentrations of HIV-1 ARVs in Part 1a and Part 2 for individual subjects, or a group of subjects or for the whole study will be analyzed based on HCV RNA and/or plasma HIV-1 RNA results and summarized. Plasma concentrations for darunavir will be analyzed for all subjects in Part 1b.

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, RBV and DRV including the C_{max}, T_{max}, C_{trough}, and AUC will be determined by noncompartmental methods using data from subjects who participate in Part 1b. For the DAAs and RBV these parameters will be calculated at Treatment Period Week 4. For DRV and ritonavir, these parameters will be calculated on Study Day –1 (DRV without DAAs) and Treatment Period Week 4 (DRV when administered with DAAs). Additional parameters or summaries may be determined if useful in the interpretation of the data.
**Criteria for Evaluation (Continued):**

**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 achieving SVR$_{12}$ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) within the 12-week treatment group (i.e., Arms A, C, and D) and within the 24-week treatment group (i.e., Arm B). The percentage of subjects achieving SVR$_{12}$ within each treatment group will be calculated and a 2-sided 97.5% confidence interval (CI) of the percentage will be computed using the Wilson score method for the binomial proportion. A gatekeeping testing procedure will be used to control the Type I error rate at 0.05 and the primary endpoints will be tested separately within each treatment group:

- **SVR$_{12}$:** Superiority of the 12-week treatment group to the historical SVR rate for pegIFN and RBV therapy; the Lower Confidence Bound (LCB) of the 97.5% CI for the percentage of subjects achieving SVR$_{12}$ in the 12-week treatment group must exceed 36% to achieve superiority.
- **SVR$_{12}$:** Superiority of the 24-week treatment group to the historical SVR rate for pegIFN and RBV therapy; the LCB of the 97.5% CI for the percentage of subjects achieving SVR$_{12}$ in the 24-week treatment group must exceed 36% to achieve superiority.

The secondary efficacy endpoints are:
1. The percentage of subjects achieving SVR$_{12}$ in the 24-week treatment group compared to the 12-week treatment group;
2. The percentage of subjects with on-treatment HCV virologic failure during the Treatment Period in the 12-week and 24-week treatment groups;
3. The percentage of subjects with HCV post-treatment relapse in the 12-week and 24-week treatment groups.
4. The percentage of subjects with plasma HIV-1 RNA suppression at the end of treatment and Post-Treatment Week 12 for the 12-week and 24-week treatment groups.

If success was demonstrated for both primary efficacy endpoints, then the gatekeeping testing procedure will continue to the first secondary efficacy endpoint to compare the percentage of subjects achieving SVR$_{12}$ following 12 or 24 weeks of treatment.

The percentages (with 2-sided 95% confidence intervals using the Wilson score method for the binomial proportion) of the subjects with HCV virologic failure during treatment, post-treatment relapse, and plasma HIV-1 RNA suppression at the end of treatment and Post-Treatment Week 12 using the FDA Snapshot Algorithm will be calculated and summarized for the 12-week and 24-week treatment groups. These endpoints will not be part of the gatekeeping testing procedure as no hypothesis is being tested.
**Statistical Methods (Continued)**

**PROs:**

The change in non-disease-specific HRQoL, health state utility, and HCV-specific function and wellbeing will be measured using the SF-36v2, EQ-5D-5L and HCVPRO, instruments, respectively. SF-36v2 and HCVPRO will be analyzed by their total/component scores, as appropriate. The EQ-5D-5L will be analyzed by utility score and by Visual Analogue Scale (VAS) response. Change from baseline in the Patient Reported Outcome (PRO) summary measures will be summarized and compared between the 12-week and 24-week treatment groups using ANCOVA models with a treatment group factor and the baseline score as a covariate.

**Resistance:**

The following resistance information will be analyzed for subjects receiving study drugs who do not achieve SVR12 regardless of the reason (and who have samples with HCV RNA ≥ 1000 IU/mL):

1. the amino acid variants at signature resistance-associated positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence,
2. the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population and/or clonal nucleotide sequencing and comparison to the appropriate reference sequence,
3. the amino variants in available post-baseline samples identified by population and/or clonal nucleotide sequencing and comparison to the baseline sequences,
4. variants found at signature resistance-associated amino acid positions by population sequencing and variants at any amino acid position that emerge or become enriched in isolates from at least 2 subjects of the same subgenotype will be summarized.

HIV-1 drug resistance genotyping for protease (PR), reverse transcriptase (RT), and integrase (IN), as appropriate, will be performed for protocol-defined eligible specimens.

**Pharmacokinetic:**

Plasma concentrations for ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, RBV, and ritonavir will be determined and summarized at each study visit up to the end of treatment 12 or 24 weeks. HIV-1 ARVs, if measured, will be summarized at each study visit through the end of the Treatment Period (Week 12 or Week 24) and Post-Treatment Week 2 and Week 4.

Pharmacokinetic exposure parameters of darunavir (such as C_{max}, AUC and C_{trough}) in Part 1b will be compared when the HIV-1 ART regimen was administered alone (Study Day –1) and with co-administration of the HIV-1 ART regimen with the DAA regimen (Treatment Period Week 4 visit). Additional comparisons can be done, if appropriate. To assess the effect of the DAA regimen on darunavir, a repeated measures analysis will be performed for the natural logarithms of C_{max}, AUC and C_{trough} using the SAS® Version 9.2 PROC MIXED utilizing data from the Study Day –1 visit and the Treatment Period Week 4 visit. Additional comparisons may be done, if appropriate.
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 group, and comparisons will be performed using Fisher's exact test. Additional tabulations will be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by severity 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 group with potentially clinically significant values will be calculated and compared between the treatment groups using Fisher's exact test.

Sample Size:
It is planned to enroll approximately 300 subjects into the study, where approximately 60 subjects will be randomized in a 1:1 ratio to the 12-week treatment group or the 24-week treatment group in Part 1a, approximately 30 additional subjects will be allocated to the 12-week treatment group in Part 1b (randomized in a 1:1 ratio to receive QD or BID DRV), and approximately 210 additional subjects will be randomized in a 1:1 ratio to the 12-week treatment group or the 24-week treatment group in Part 2.

The study design will allow for a total of approximately 165 subjects in the 12-week treatment group and a total of approximately 135 subjects in the 24-week treatment group. With a sample size of at least 135 subjects in each treatment group and assuming that 51% of the subjects in each treatment group will achieve SVR12, this study has at least 90% power to demonstrate superiority compared to the historical control rate with a 2-sided 97.5% LCB greater than 36% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority). No adjustment for dropouts is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR12.
1.3 List of Abbreviations and Definition of Terms

Abbreviations

3TC Lamivudine
AARDEX Advanced Analytical Research on Drug Exposure
Ab Antibody
ABT-450/r/ABT-267 ABT-450 co-formulated with ritonavir and ABT-267
AIDS Acquired Immune Deficiency Syndrome
AE Adverse event
ALT Alanine aminotransferase
ANC Absolute neutrophil count
ANCOVA Analysis of covariance
ANOVA Analysis of variance
APRI Aspartate aminotransferase-to-Platelet Ratio Index
aPTT Activated partial thromboplastin time
ART Antiretroviral Treatment
ARV Antiretroviral
AST Aspartate aminotransferase
ATV Atazanavir
AUC Area Under the Curve
BID Twice Daily
BMI Body mass index
BUN Blood urea nitrogen
C\textsubscript{12} \text{C\textsubscript{trough} concentration 12 hours after dose for twice daily dosing}
C\textsubscript{24} \text{C\textsubscript{trough} concentration 24 hours after dose for once daily dosing}
CFR Code of Federal Regulations
CI Confidence Interval
CL/F Apparent Oral Clearance
C\textsubscript{max} Maximum observed plasma concentration
CPK Creatinine phosphokinase
CrCL Creatinine clearance
CRF Case report form
CT Computed tomography
C\textsubscript{trough} Trough plasma concentration
<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>CYP2C8</td>
<td>Cytochrome P450 2C8</td>
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<td>CYP3A</td>
<td>Cytochrome P450 3A</td>
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<tr>
<td>DAA</td>
<td>Direct-acting antiviral agent</td>
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<tr>
<td>D/C</td>
<td>Discontinuation</td>
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<td>DDI</td>
<td>Drug-drug interaction</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>DRV</td>
<td>Darunavir</td>
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<tr>
<td>EACS</td>
<td>European AIDS Clinical Society</td>
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<tr>
<td>EC₅₀</td>
<td>Half maximal effective concentration</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>eCRF</td>
<td>Electronic case report form</td>
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<td>EDC</td>
<td>Electronic data capture</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>EMEA</td>
<td>European Agency for the Evaluation of Medicinal Products</td>
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<tr>
<td>ESLD</td>
<td>End-Stage Liver Disease</td>
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<td>End of treatment</td>
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</tr>
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<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<td>FTC</td>
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<tr>
<td>GAM</td>
<td>Generalized additive method</td>
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<td>granulocyte colony stimulating factor</td>
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<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
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<td>Hepatitis B surface antigen</td>
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HCV GT 1  
HCVPRO  
Hemoglobin A1c  
HIV  
HIV-1  
HIV-2  
HIV Ab  
HME  
HRQoL  
IB  
ICF  
ICH  
IDUs  
IEC  
IFN  
IL28B  
IMP  
IN  
INR  
IP-10  
IRB  
IRT  
ITT  
IU  
LCB  
LLN  
LLOD  
LLOQ  
LTFU  
MCS  
MedDRA  
MEMS  
mL  

Hepatitis C virus antibody  
Hepatitis C virus genotype 1  
Hepatitis C Virus Patient Reported Outcomes Instrument  
Glycated hemoglobin  
Human immunodeficiency virus  
Human immunodeficiency virus type 1  
Human immunodeficiency virus type 2  
Human immunodeficiency virus antibody  
Hot melt extrusion  
Health Related Quality of Life  
Investigator’s Brochure  
Informed Consent Form  
International Conference on Harmonization  
Injection Drug Users  
Independent ethics committee  
Interferon  
Interleukin 28B  
Investigational Medical Product  
Integrase  
International normalized ratio  
Interferon gamma-induced protein 10  
Institutional Review Board  
Interactive Response Technology  
Intent-to-Treat  
International units  
Lower Confidence Bound  
Lower limit of normal  
Lower limit of detection  
Lower limit of quantification  
Lost to follow-up  
Mental Component Summary  
Medical Dictionary for Regulatory Activities  
Medication Event Monitoring System  
Milliliter
mRNA	Messenger Ribonucleic acid
MRI	Magnetic Resonance Imaging
NONMEM	Non-linear mixed-effect modeling
NRTI	Nucleoside/Nucleotide reverse transcriptase inhibitor
NS3	Nonstructural viral protein 3
NS3A	Nonstructural viral protein 3A
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OI	Opportunistic Infections
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PD	Pharmacodynamic
PegIFN	Pegylated-interferon alfa-2a or alfa-2b
PG	Pharmacogenetic
PO	By mouth, orally
PK	Pharmacokinetics
POR	Proof of Receipt
PI	Protease Inhibitor
PR	Protease
PRO	Patient Reported Outcomes
PSI	Polymerase Inhibitor
PT	Post-Treatment
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's correction formula
RAL	Raltegravir
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
RT	Reverse Transcriptase
RTV	Ritonavir
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<td>sAFP</td>
<td>Serum Alpha-Fetoprotein</td>
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<td>SAS</td>
<td>Statistical Analysis System</td>
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<td>Standard Deviation</td>
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<td>ULN</td>
<td>Upper limit of normal</td>
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<td>USPI</td>
<td>US Prescribing Information</td>
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<td>VAS</td>
<td>Visual analogue scale</td>
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<td>VF</td>
<td>Virologic failure</td>
</tr>
<tr>
<td>V/F</td>
<td>Volume of distribution</td>
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<td>WBC</td>
<td>White Blood Count</td>
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**Definition of Terms**

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<tr>
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<td>First day a subject took study drug</td>
</tr>
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<td>Day of randomization until first day a subject took study drug for subjects in Part 1b</td>
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<td>Treatment Period</td>
<td>Baseline/Day 1 through last dose of study drug</td>
</tr>
<tr>
<td>Post-Treatment Period</td>
<td>Day after the last dose of study drug through Post-Treatment Week 48 or Post-Treatment Discontinuation</td>
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3.0 Introduction

Of the 33.4 million persons infected with human immunodeficiency virus (HIV) worldwide in 2009, it is estimated that approximately 5 million had hepatitis C virus (HCV) infection.1,2 In addition to the high prevalence of chronic HCV, particularly among HIV-infected injection drug users (IDUs), the rate of incident infections with HCV is increasing among HIV-infected men who have sex with men (MSM).3 Outcomes of HCV infection include: chronic viral hepatitis, cirrhosis, end-stage liver disease (ESLD), hepatocellular carcinoma (HCC) and liver-related mortality.4,5 In the era of effective antiretroviral (ARV) HIV therapy, chronic HCV infection is a leading cause of liver disease and mortality in HIV-infected patients. Although treatment of HIV with antiretroviral treatment (ART) appears to slow the progression of liver disease, coinfected patients remain at greater risk for HCV disease progression than patients with HCV monoinfection.6 Accordingly, effective HCV treatment is a priority in this population.

Among the HIV/HCV coinfected population, the only approved treatment options are pegylated interferon (pegIFN) plus ribavirin (RBV) for 48 weeks treatment duration, or pegIFN/RBV plus the nucleotide analog NS5B polymerase inhibitor, sofosbuvir for 12 weeks treatment duration.

With pegIFN/RBV treatment alone, the overall effectiveness of HCV treatment in this patient population is significantly lower than among those with HCV monoinfection. The reasons for limited effectiveness include low rates of treatment initiation, high prevalence of relative and absolute contraindications to the drugs, and, among those treated, low rates of sustained virologic response (SVR) – especially for individuals infected with HCV genotype 1 (HCV GT 1). At least 15% to 23% of HCV-infected patients may have contraindications to interferon treatment based on eligibility criteria from clinical trials. In addition, based on prescribing information and observational naturalistic studies, 4% to 16% of HCV-infected patients who initiate interferon/RBV are unable to tolerate therapy. Each of these groups represents a large global population for which inadequate treatment is currently available. Even in those patients who are able to take pegIFN-based treatment
regimens, adverse effects of the combination of pegIFN with RBV limit the number of patients who initiate and complete treatment.\textsuperscript{7-14}

The regimen of pegIFN/RBV plus sofosbuvir for the treatment of HCV genotype 1-infected adults with HIV-1 coinfection, has not been studied in this special population.\textsuperscript{15} A regimen of sofosbuvir plus weight-based RBV for 24 weeks treatment duration was evaluated in 114 HCV treatment-naïve, genotype 1-infected adults with HIV-1 coinfection in an open-label clinical trial (Study PHOTON-1). The SVR\textsubscript{12} rate was 82\% (74/90) in subjects with genotype 1a infection and 54\% (13/24) in subjects with genotype 1b infection, with relapse accounting for the majority of treatment failures. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Elevated total bilirubin (Grade 3 or 4) was observed in 30/32 (94\%) subjects receiving atazanavir as part of the antiretroviral regimen. None of the subjects had concomitant transaminase increases. Among subjects not taking atazanavir, Grade 3 or 4 elevated total bilirubin was observed in 2 (1.5\%) subjects, similar to the rate observed with HCV monoinfected subjects receiving sofosbuvir plus ribavirin in Phase 3 trials.

The HCV nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitors, telaprevir and boceprevir were first approved in 2011 for use in combination with pegIFN/RBV in HCV monoinfected patients; however, their use is not approved for the treatment of HCV infection in persons with HIV-1 coinfection.\textsuperscript{16,17} Preliminary data, reported from small Phase 2 studies of telaprevir and boceprevir in combination with pegIFN/RBV in HCV GT 1/HIV-1 coinfected subjects, suggest the possibility of improved efficacy relative to pegIFN/RBV alone\textsuperscript{18,19} but less than optimal efficacy, poor tolerability and the potential for drug interactions may limit their widespread use in coinfected subjects.\textsuperscript{6} The percentage of subjects who achieved undetectable HCV RNA at treatment Week 4 with telaprevir/pegIFN/RBV was 70\% compared to 5\% of subjects treated with pegIFN/RBV alone.\textsuperscript{18} Similarly, SVR rates 12 weeks following treatment (SVR\textsubscript{12}), were 60.7\% and 26.5\% in subjects treated with boceprevir/pegIFN/RBV and pegIFN/RBV, respectively.\textsuperscript{19} Both agents have been associated with significant adverse events (rash, anemia, and anorectal symptoms with telaprevir; anemia and neutropenia
with boceprevir) that have added to the toxicity of coadministered pegIFN/RBV (fatigue, fever, depression, neutropenia and anemia). As such IFN-free HCV therapies with improved tolerability and efficacy are needed in individuals coinfected with HIV-1.\textsuperscript{6}

Combinations of direct-acting antiviral agents (DAAs) targeting different steps of viral replication have the potential to significantly improve HCV treatment compared to the current interferon-containing regimens for HCV GT1 infection by increasing SVR rates, eliminating IFN as a component of therapy, increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. In addition, wider application of DAA therapy and better responses with combination DAA regimens could significantly reduce the public health burden of this disease.

AbbVie's IFN-free regimen for the treatment of chronic HCV GT1 infection includes 3 DAAs targeting different steps in HCV replication. ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor co-administered with the pharmacokinetic enhancer, ritonavir (ABT-450/r); ABT-267 is a NS5A inhibitor, and ABT-333 is a NS5B non-nucleoside polymerase inhibitor.\textsuperscript{20-22} The 3 DAA regimen has been studied with and without RBV in over 2,300 patients in Phase 3 trials across a variety of patient populations including compensated cirrhotics. Based on Phase 3 data, the regimen with or without RBV is safe, well tolerated and efficacious in treatment-naïve and treatment-experienced HCV GT1-infected subjects including those with compensated cirrhosis. The overall efficacy results (intent to-treat) from the Phase 3 studies are listed in Table 1.\textsuperscript{23-27}
Table 1. Pooled SVR<sub>12</sub> Rates (Intent-to-treat, missing = failure) from Phase 3 Studies by Subpopulation of Subtype, Prior Treatment History, and Presence or Absence of Cirrhosis

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<th>3-DAA + RBV 12 Weeks SVR&lt;sub&gt;12&lt;/sub&gt;</th>
<th>3-DAA + RBV 24 Weeks SVR&lt;sub&gt;12&lt;/sub&gt;</th>
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<td>98.9</td>
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</tr>
<tr>
<td>Null</td>
<td>100</td>
<td>94.4</td>
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<tr>
<td>Partial</td>
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</tr>
<tr>
<td>Relapser</td>
<td>100</td>
<td>98.5</td>
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<tr>
<td>Genotype 1a non-cirrhotic</td>
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<tr>
<td>Naïve</td>
<td>90.2</td>
<td>95.7</td>
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<td>Null</td>
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<td>95.4</td>
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<td>Partial</td>
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* Based on N = 7; 6/7 achieved SVR.

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

Study M11-646 and Study M13-098 are randomized, placebo-controlled studies to assess the safety and efficacy of 12 weeks therapy with 3-DAA + RBV in HCV G1-infected treatment-naïve (Study M11-646) and prior pegIFN/RBV non-responders (Study M13-098) without cirrhosis. ABT-450/r/ABT-267 with ABT-333 was given for 12 weeks of treatment in combination with RBV. Subjects randomized to the placebo arm
received placebo for 12 weeks, after which they received open-label ABT-450/r/ABT-267 with ABT-333 in combination with RBV for 12 week.

In Study M11-646, a total of 631 subjects were randomized and received at least one dose of study drug, of which 67.7% had HCV GT1a and 32.3% had HCV GT1b. The SVR12 rate for treatment-naïve subjects receiving 3-DAA + RBV for 12 weeks was 96.2%. Virologic failure was noted in 7/322 (2.2%) GT1a subjects (on treatment virologic failure: n = 1; relapse: n = 6) and 1/151 (0.7%) GT1b subjects (relapse).

In Study M13-098, a total of 394 subjects were randomized and received at least one dose of study drug, of which 58.4% had HCV GT1a, 41.4% had HCV GT1b, 49.0% were prior pegIFN/RBV null responders, 21.9% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers. The SVR12 rate for treatment-experienced subjects receiving 3-DAA + RBV for 12 weeks was 96.3%. Virologic failure (all relapse) was noted in 5/173 (2.9%) GT1a subjects and 2/123 (1.6%) GT1b subjects.

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

Studies M13-389, M13-961, and M14-002 are randomized, regimen-controlled trials that assessed the safety and efficacy of 12 weeks of treatment with 3 DAAs with or without RBV. Study M13-961 and Study M14-002 are placebo-controlled studies, while Study M13-389 is an open-label study. The patient population was different in each of the 3 studies. Study M13-389 enrolled GT1b-infected subjects with prior non-response to pegIFN/RBV, Study M13-961 enrolled GT1b-infected subjects who were treatment-naïve, and Study M14-002 enrolled GT1a-infected subjects who were treatment-naïve. All three studies excluded subjects with cirrhosis.

In Study M13-389, a total of 186 subjects were randomized and received at least one dose of study drug, of which 34.9% were prior pegIFN/RBV null responders, 28.5% were prior pegIFN/RBV partial responders, and 36.6% were prior pegIFN/RBV relapsers. The SVR12 rates were 96.6% in the 3-DAA + RBV arm and 100% in the 3-DAA without RBV arm. The difference in SVR12 rates between the 2 regimens met the protocol-specified
criteria for noninferiority; hence, the 3-DAA regimen without RBV demonstrated noninferiority compared to 3-DAA + RBV. No subject in either arm experienced on-treatment virologic failure or post-treatment relapse.

In Study M13-961, a total of 419 subjects were randomized and received at least one dose of study drug. The SVR12 rates for treatment-naïve subjects with HCV GT1b infection who received either 3 DAAs with or without RBV for 12 weeks were 99.5% and 99.0%, respectively. The difference in SVR12 rates between the 2 regimens in this study also met the protocol-specified criteria for noninferiority. One of the 419 treated subjects (3-DAA + RBV arm) experienced on-treatment virologic failure.

In Study M14-002, 305 subjects were randomized and received at least one dose of study drug. The SVR12 rates for treatment-naïve subjects with HCV GT1a infection who received either 3 DAAs with or without RBV for 12 weeks in Study M14-002 were 97.0% and 90.2%, respectively. The SVR12 rate in the 3-DAA arm did not achieve noninferiority to the 3-DAA + RBV arm. Virologic failure was noted in 2/100 (2.0%) subjects (on treatment virologic failure: n = 1; relapse: n = 1) in the RBV-containing regimen and 16/205 (7.8%) subjects (on treatment virologic failure: n = 6; relapse: n = 10) in the RBV-free regimen. The difference between arms demonstrates that RBV contributes to the efficacy in GT1a-infected patients and suggests that 3-DAA + RBV is the optimal regimen for these patients.

**Phase 3 Study in Compensated (Child-Pugh class A) Cirrhotics: Study M13-099**

Study M13-099 is a randomized, multicenter, open-label trial in treatment-naïve subjects or subjects previously treated with pegIFN/RBV with chronic HCV GT1 infection with compensated (Child-Pugh A, score ≤ 6) cirrhosis. The 3 DAAs + RBV were administered for either 12 or 24 weeks of treatment.

A total of 380 subjects were randomized and received at least one dose of study drug, of which 68.7% had HCV GT1a, 31.3% had HCV GT1b, 42.1% were treatment-naïve,
36.1% were prior pegIFN/RBV null responders, 8.2% were prior pegIFN/RBV partial responders, and 13.7% were prior pegIFN/RBV relapsers.

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

Analyses of subgroups suggest that the overall difference in SVR\textsubscript{12} rates was driven largely by a lower SVR\textsubscript{12} rate among GT1a prior null responders who received 12 weeks of treatment, while other subgroups had comparable response rates when treated for 12 or 24 weeks. Thus, a 12-week treatment regimen is recommended for all patients with cirrhosis with the exception of GT1a prior null responders, for whom 24 weeks of treatment provides a higher SVR.

**Integrated Safety Results**

A summary of treatment-emergent adverse events from the pooled analyses of data from the Phase 3 studies is presented in Table 2. A majority of subjects experienced at least one event, but most subjects experienced events that were mild in severity. Rates of severe adverse events and adverse events leading to discontinuation were low across studies but numerically higher in the study of subjects with cirrhosis.
Table 2. Overview of Treatment-Emergent Adverse Events (AE)

<table>
<thead>
<tr>
<th></th>
<th>Placebo-Controlled</th>
<th>Regimen-Controlled</th>
<th>Cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-wk</td>
<td>12-wk</td>
<td>12-wk</td>
</tr>
<tr>
<td></td>
<td>3-DAA + RBV</td>
<td>PBO</td>
<td>3-DAA + RBV</td>
</tr>
<tr>
<td>Events, %</td>
<td>N = 770</td>
<td>N = 255</td>
<td>N = 401</td>
</tr>
<tr>
<td>Subjects ≥ 1 AE</td>
<td>89.0</td>
<td>76.9</td>
<td>82.8</td>
</tr>
<tr>
<td>Severe AE</td>
<td>3.5</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>3.9</td>
<td>0.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>2.1</td>
<td>0.4</td>
<td>2.2</td>
</tr>
<tr>
<td>AE leading to</td>
<td>0.8</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>0.1\textsuperscript{a}</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PBO = Placebo
\textsuperscript{a}. Lung cancer.
\textsuperscript{b}. Metformin toxicity, lactic acidosis, multi-organ system failure.

The most common adverse events regardless of causality are listed in Table 3. Adverse events that occurred at a ≥ 5% incidence in the 3-DAA + RBV regimen versus the placebo were considered to be adverse drug reactions related to the study treatment. These include fatigue, nausea, pruritus, insomnia, asthenia, and anemia. The frequency of these events was generally lower in the arm treated without RBV. In general, rates of adverse events were similar in patients with cirrhosis versus patients without cirrhosis.
<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Events, %</th>
<th>Placebo-Controlled</th>
<th>Regimen-Controlled</th>
<th>Cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 770</td>
<td>N = 255</td>
<td>N = 401</td>
</tr>
<tr>
<td>Headache</td>
<td>34.3</td>
<td>29.8</td>
<td>24.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34.2</td>
<td>26.3</td>
<td>29.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.3</td>
<td>14.9</td>
<td>15.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15.7</td>
<td>4.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.0</td>
<td>7.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.5</td>
<td>9.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>13.5</td>
<td>6.7</td>
<td>9.0</td>
</tr>
<tr>
<td>Rash</td>
<td>10.0</td>
<td>5.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cough</td>
<td>8.7</td>
<td>5.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Irritability</td>
<td>5.3</td>
<td>4.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>5.3</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9.7</td>
<td>5.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Laboratory Events, %</td>
<td>N = 765</td>
<td>N = 254</td>
<td>N = 401</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>N = 254</td>
<td>N = 401</td>
<td>N = 509</td>
</tr>
<tr>
<td>&lt; 10 g/dL (Gr 2)</td>
<td>5.5</td>
<td>0</td>
<td>6.2</td>
</tr>
<tr>
<td>&lt; 8.0 g/dL (Gr 3)</td>
<td>0.1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td>1.2</td>
<td>3.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2.6</td>
<td>0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

PBO = Placebo

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

Transient elevations in total (predominantly indirect) bilirubin may occur due ABT-450 inhibition of OATP1B1 and OATP1B3, and RBV-induced hemolysis. The elevations generally peaked by Week 1 and declined through the end of treatment and returned to within the normal range by 4 weeks post-treatment.
Rates of hyperbilirubinemia were lower in subjects treated with 3-DAA without RBV compared to 3-DAA with RBV. The rates and degree of hyperbilirubinemia were higher in patients with cirrhosis, but the temporal pattern of elevation followed by resolution was similar and few were symptomatic (jaundice). Rates of ≥ Grade 2 hemoglobin reductions were 6% among subjects without cirrhosis who received the 3-DAA + RBV regimen for 12 weeks, and 7% and 11% among subjects with cirrhosis who received the 3-DAA + RBV regimen for 12 and 24 weeks, respectively. Grade 3 hemoglobin values were rare. The decline in hemoglobin was largely managed with RBV dose reductions. Anemia observed during the clinical trials was largely attributable to the presence of RBV as it was not observed when the 3-DAA regimen was administered without RBV.

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

In summary, the 3-DAA regimen, with or without RBV, was well tolerated with a low discontinuation rate. Adverse events were typically mild, and many of the adverse events and laboratory abnormalities observed were attributable to the presence of RBV. Transient, asymptomatic serum ALT elevations were observed at a low rate, were not associated with hepatic dysfunction and generally resolved with ongoing treatment.
A detailed discussion of the preclinical toxicology, metabolism, pharmacokinetics and drug-drug interactions can be found in the Investigator's Brochure for ABT-267, ABT-450, ABT-333 and product label for RBV.\textsuperscript{20-22,30}

**Combination Dosing of DAAs with HIV-1 Antiretroviral Agents**

Several Phase 1 drug-drug interaction (DDI) studies of AbbVie DAA combinations with HIV-1 antiretroviral (ARV) drugs have been conducted or are currently ongoing in healthy volunteers. Pharmacokinetic and safety data, to date, from these studies is summarized below.

**Tenofovir Disoproxil Fumarate and Emtricitabine**

In Study M13-783, ABT-450/r 150/100 mg QD with ABT-267 25 mg QD ± ABT-333 400 mg BID are being coadministered with tenofovir disoproxil fumarate (TDF) 300 mg QD and emtricitabine 200 mg QD to steady state for a duration of 7 to 14 days. Pharmacokinetic analysis shows that TDF and emtricitabine exposures at steady state were not affected (≤ 25% higher) by coadministration of ABT-450/r + ABT-333 + ABT-267. The steady state exposures of ABT-450, ABT-333 and ABT-267 were also not affected (up to ± 30% change) when ABT-450/r + ABT-333 + ABT-267 were coadministered with TDF and emtricitabine. The coadministration of multiple doses of TDF and emtricitabine with ABT-450/r + ABT-333 +ABT-267 was safe and well tolerated. Adverse events and laboratory abnormalities were mostly mild (Grade 1) and not considered clinically significant. There were no clinically significant changes from baseline in vital signs, clinical laboratory tests or ECGs. Based on the pharmacokinetic and safety data, no dose adjustment is expected to be required for TDF and emtricitabine, ABT-450/r, ABT-333 and ABT-267 during coadministration in Phase 3 trials.

**Lamivudine**

A Phase 1, drug-drug interaction study of the DAA combination with lamivudine has not been conducted. The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion with renal clearance representing about 70% of the total
clearance and metabolism being a minor route of elimination.\textsuperscript{28} The DAAs show minimal renal elimination and are not expected to inhibit organic cationic transporters. Consequently, a pharmacokinetic drug interaction is not expected during coadministration of DAAs and lamivudine because of differences in elimination pathways with DAAs being primarily hepatically eliminated and lamivudine renally eliminated.

\textbf{Atazanavir}

In Study M13-394, ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID was coadministered with atazanavir 300 mg QD to steady state for a duration of 14 days in healthy volunteers. Pharmacokinetic analysis shows that atazanavir exposures at steady state were not affected (≤10\% lower) by coadministration of ABT-450/r + ABT-333 + ABT-267. The steady state exposures of ABT-333, ABT-267 and ritonavir were not affected (up to ±20\% change), while ABT-450 exposures were about 100\% higher, when ABT-450/r + ABT-333 + ABT-267 were coadministered with atazanavir. The coadministration of atazanavir with ABT-450/r + ABT-333 + ABT-267 was safe and well tolerated. Adverse events and laboratory abnormalities were mostly mild (Grade 1) and not considered clinically significant. There were no clinically significant changes from baseline in vital signs, clinical laboratory tests or ECGs. The majority of subjects experienced a Grades 2 – 3 total bilirubin during the study with 13/24 (54.2\%) of subjects experienced a Grade 3 total bilirubin elevation (consistent with known effect of atazanavir). Worsening of bilirubin elevations were generally not seen when DAAs were added to atazanavir with no subjects being prematurely discontinued. Bilirubin elevations returned to baseline while on treatment. Four subjects experiencing hyperbilirubinemia developed scleral icterus, etc. Doses of ABT-450 resulting in exposures similar to those observed during coadministration of ABT-450/r + ABT-333 + ABT-267 with atazanavir in Study M13-394 have been administered in previous HCV monoinfection studies and were well tolerated. Based on the pharmacokinetic and safety data in Study M13-394, as well as in the previous Phase 2 studies in patients with HCV monoinfection, no dose adjustment is expected to be required for atazanavir, ABT-450/r, ABT-333 and ABT-267 during coadministration in Phase 3 trials.
**Raltegravir**

In Study M13-392, ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID was coadministered with raltegravir 400 mg BID to steady state for a duration of 14 days in healthy volunteers. Based on the pharmacokinetic analysis, no clinically relevant changes in ABT-450, ABT-267, ABT-333 or ABT-333 M1 exposures (based on comparison with historical data) were observed during coadministration of the 3-DAA regimen with raltegravir. The exposures of raltegravir during coadministration with the 3-DAA regimen were 2- to 2.3-fold of raltegravir administered alone. Based on the US Food and Drug Administration (FDA) summary basis of approval for raltegravir, up to 2 fold increase in raltegravir exposures are expected to be safe. In addition in the Phase 3 studies of raltegravir, coadministration of raltegravir with acid suppressing agents, which showed 3- to 4-fold increases in raltegravir exposures in Phase 1 studies were demonstrated to be safe. During coadministration of raltegravir with the 3-DAA regimen, no clinically significant vital signs or laboratory measurements were observed. The coadministration of DAAs with raltegravir was safe and generally well tolerated by the subjects and based on the available safety information for raltegravir no dose adjustment is expected to be required for ABT-450/r, ABT-267, ABT-333 or raltegravir during coadministration.

**Darunavir**

In Study M13-506, ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID (3-DAA combination) was co-administered with darunavir (DRV) 600 mg + ritonavir 100 mg BID and DRV 800 mg + ritonavir 100 mg QD to steady state for a duration of 14 days in healthy volunteers. Pharmacokinetic analysis shows that during coadministration of the 3-DAA combination with DRV 600 mg + ritonavir 100 mg BID, the steady state exposures ($C_{\text{max}}$ and AUC) of ABT-267 and ABT-333 were unaffected (up to about 25% lower), while ABT-450 was modestly lower (up to 40% lower). During coadministration of the 3-DAA combination with DRV 800 mg + ritonavir 100 mg QD, the steady state exposures of ABT-267 and ABT-333 were unaffected, while ABT-450 exposures were modestly higher (about 30% to 50%). Darunavir exposures ($C_{\text{max}}$ and
AUCₜ) at steady state were not affected (up to 25% lower) following coadministration of the 3-DAA combination with DRV + ritonavir QD and BID regimens; but, darunavir C₁₂ levels were about 43% lower and C₂₄ levels were only about 10% lower during coadministration of DRV 600 mg + ritonavir 100 mg BID with 3-DAA combination. Similarly, darunavir C₂₄ levels were about 50% lower during coadministration of DRV 800 mg + ritonavir 100 mg QD with the 3-DAA combination. The comparable Cₘₐₓ, AUC and lower C₁₂ or C₂₄ levels of darunavir observed with coadministration of DAA are not expected to significantly affect the safety or efficacy of darunavir based on the previous clinical trials. The pharmacokinetic-pharmacodynamic (PK-PD) analyses of darunavir from two large Phase 3 trials, the ODIN and ARTEMIS studies, showed no apparent relationships between darunavir AUC₂₄ and Cₙₐₜₙg (C₂₄) and the change in log₁₀ HIV viral load from baseline at Week 48 and the proportion of patients achieving plasma viral load < 50 copies/mL at Week 48. In these studies, the median darunavir Cₙₐₜₙg was about 37-fold higher than the EC₅₀ of the wild-type virus. Hence, during coadministration with the 3-DAA regimen, darunavir C₂₄ from the DRV 800 mg + ritonavir 100 mg QD regimen is expected to be ~18-fold higher. Also, darunavir exposure (AUC and Cₙₐₜₙg [C₁₂ or C₂₄]) during co-administration of darunavir 600 mg + ritonavir 100 mg BID with the 3-DAA regimen were comparable to those achieved with administration of darunavir 800 mg + ritonavir 100 mg QD regimen alone. Hence, during co-administration with the 3-DAA regimen, the darunavir 600 mg + ritonavir 100 mg BID regimen could be an alternative to darunavir 800 mg + ritonavir 100 mg QD regimen to provide comparable darunavir exposure.

The coadministration of darunavir + ritonavir as QD and BID regimens with the 3-DAA combination was safe and well tolerated with adverse events and laboratory abnormalities being mostly mild and not clinically significant. There were no clinically significant changes from baseline in vital signs, clinical laboratory tests or ECGs. Hence, based on the pharmacokinetic data from drug-drug interaction study of darunavir with DAAs and the PK-PD relationships from the ODIN and ARTEMIS studies, no dose adjustment is expected to be required for ABT-450/r, ABT-333 and ABT-267 and darunavir during coadministration in this study.
In a recently presented randomized trial, a switch to lower-dose darunavir (600 mg of darunavir with 100 mg of ritonavir once daily) among adult patients virologic suppressed for at least 3 months on a HIV-1 ART regimen including 800 mg of darunavir with 100 mg of ritonavir once daily plus two nucleoside/nucleotide reverse transcriptase inhibitors yielded a noninferior 48-week virologic response rate (compared with maintaining a regimen of 800 mg of darunavir with 100 mg of ritonavir once daily). Darunavir trough concentrations were comparable with the two dosing strategies.44

**Pharmakokinetics of DAAs in Subjects with Cirrhosis (Child-Pugh A)**

The pharmacokinetics and safety of the single dose administration of the 3-DAA combination of ABT-450/r + ABT-267 + ABT-333 under non-fasting conditions in subjects with mild hepatic impairment (Child-Pugh A), and matched healthy control subjects were evaluated in Study M12-215. In subjects with mild hepatic impairment, the 3-DAA combination was safe and well-tolerated and the DAA and ritonavir exposures (both total and unbound) were minimally affected (AUCs were approximately ± 35% different), except ABT-450 and ritonavir unbound AUC being approximately 50% lower, compared to the matched healthy control subjects. The Phase 3 formulation of ABT-450/r/ABT-267 provides about 60% higher ABT-450 exposure than the ABT-450 SDD tablets used in the Phase 2 studies; hence, partly compensating for the lower ABT-450 exposure. Consequently, these changes in DAA exposures were not considered to be clinically significant; hence, no dose adjustment for DAAs was done in the study of the 3-DAA combination with ribavirin in HCV GT 1-infected adults with compensated cirrhosis (Child-Pugh A [Study M13-099]).

### 3.1 Differences Statement

This is the first study in which ABT-450/r/ABT-267 and ABT-333 coadministered with RBV will be evaluated in HCV GT 1/HIV-1 coinfected adults. ABT-450/r/ABT-267 and ABT-333 coadministered with RBV have been administered for as long as 24 weeks in treatment-naïve and treatment-experienced HCV GT 1 monoinfected adults without cirrhosis in Study M11-652. Study M13-099, is evaluating the safety and efficacy of
ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in treatment-naïve and experienced HCV GT 1 monoinfected adults with compensated cirrhosis.

3.2 Benefits and Risks

Study M14-004 will evaluate ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for durations of either 12 or 24 weeks in HCV GT 1/HIV-1 coinfected adults. The safety and efficacy of a pegIFN-free DAA regimen in HCV/HIV-1 coinfected adults has been evaluated in a limited number of studies.

The likelihood of achieving an HCV SVR12 in HCV GT 1/HIV-1 coinfected adults following 12 or 24 weeks of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV is unknown. However, results from Phase 3 studies in which ABT-450/r/ABT-267 and ABT-333 was coadministered with RBV for 12 weeks in HCV genotype 1-infected, treatment-naïve and pegIFN/RBV-experienced adults without cirrhosis showed SVR12 rates of 96.2% (Study M11-646) and 96.3% (Study M13-098), respectively. When ABT-450/r, ABT-267 and ABT-333 was coadministered with RBV for 12 or 24 weeks in HCV genotype 1-infected, treatment-naïve and pegIFN/RBV-experienced adults with cirrhosis, the SVR12 rates were 91.8% and 95.9% (Study M13-099), respectively.35

ABT-450/r, ABT-267 and ABT-333 coadministered with RBV have been well tolerated. Adverse events that are known, and those not previously described, may occur with the DAAs or RBV as detailed in the Informed Consent Form (ICF) 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 are detailed in the Investigator's Brochure (IB).

The safety of ABT-450/r/ABT-267 and ABT-333 administered in combination with HIV ARVs is not fully known. However, the drug-drug interaction studies that have been performed in healthy volunteers (summarized above) do not suggest an impact on the DAA or HIV-1 ARVs that could adversely affect safety or efficacy.
The coadministration of ABT-450/r, ABT-267 and ABT-333 with atazanavir resulted in the frequent development of hyperbilirubinemia in healthy adult subjects; however, few subjects developed scleral icterus or jaundice, and the elevations in bilirubin largely resolved with continued coadministration of the DAAs. The coadministration of ABT-450/r, ABT-267 and ABT-333 with atazanavir resulted in up to 2-fold higher ABT-450 exposures. Increased ABT-450 exposures may increase risk for the development of ALT elevations. The coadministration of ABT-450/r, ABT-267 and ABT-333 with raltegravir resulted in about 2-fold higher raltegravir exposures. This increased exposure could result in greater raltegravir-associated adverse events such as headache or laboratory abnormalities such as creatinine phosphokinase (CPK) elevation. Thus, Part 1 of this two-part study will evaluate a smaller group of subjects on the various ART regimens to evaluate this risk prior to dosing a larger group of subjects in Part 2 of the study.

Co-administration of ABT-450/r/ABT-267 + ABT-333) with darunavir 800 mg + ritonavir 100 mg QD (evening or morning administration) or darunavir 600 + ritonavir 100 mg BID regimens resulted in no clinically relevant effect on DAA exposures or darunavir C\text{max} and AUC; however, darunavir C\text{trough} were about 40% to 50% lower. During co-administration with the 3-DAA regimen, switching patients from a stable darunavir 800 mg + ritonavir 100 mg QD regimen to a darunavir 600 mg + ritonavir 100 mg BID regimen could provide an alternative which will maintain comparable darunavir exposures after the addition of the DAAs. This change in the darunavir + ritonavir regimen is not expected to adversely affect the safety or efficacy of darunavir.

The safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV in HCV GT 1 infected adults with compensated cirrhosis is currently being evaluated in Study M13-099 and has informed the design of the current study.

Given the potential high rate of cure in this population of HCV GT 1/HIV-1 coinfected subjects, and the design of the study to minimize risk, the risk-benefit comparison is considered favorable.
4.0 Study Objective

4.1 Primary Objectives

The primary objectives of this study are to assess the safety of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks in HCV GT 1 infected subjects with HIV-1 coinfection and to evaluate the percentage of subjects achieving SVR\textsubscript{12} (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) within the 12- and 24-week treatment groups compared to the historical SVR rate of pegIFN and RBV therapy in the corresponding population.

4.2 Secondary Objectives

The secondary objectives of this study are to compare the SVR\textsubscript{12} rates between the 12- and 24-week treatment groups and to assess the percentage of subjects with on-treatment HCV virologic failure, the percentage of subjects with HCV virologic relapse, and the percentage of subjects with plasma HIV-1 viral suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm in each treatment group.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2/3, 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 adults with HCV GT 1/HIV-1 coinfection who are HCV treatment-naïve or pegIFN/RBV-experienced with and without compensated cirrhosis.

This study will consist of a Phase 2 pilot cohort (Part 1a and Part 1b) and a Phase 3 cohort (Part 2). The study design for the overall study is shown in Figure 1. Patients with an unquantifiable plasma HIV-1 RNA and a CD4\textsuperscript{+} count \( \geq 200 \) cells/mm\textsuperscript{3} or CD4\% \( \geq 14\% \) while on a stable atazanavir (ATV), raltegravir (RAL), or darunavir (DRV) containing HIV-1 ART regimen will be eligible.
In Part 1a, approximately 60 eligible subjects on a stable ATV- or RAL-containing HIV-1 ART regimen will be randomized in a 1:1 ratio to either:

**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

In Part 1b, approximately 30 eligible subjects on a stable once-daily (QD) DRV-containing HIV-1 ART regimen will be randomized in a 1:1 ratio on the Enrollment Day to either receive DRV QD (Arm C) or to switch to DRV BID (Arm D) administration. Beginning on Study Day 1, subjects in Part 1b will also receive ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks as detailed in Section 5.6.1.

Part 2, the Phase 3 cohort, further evaluates the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with RBV for 12 and 24 weeks and will be initiated based upon criteria described in Section 5.4. Approximately 210 additional HCV GT 1/HIV-1 coinfected, treatment-naïve and pegIFN/RBV-experienced adults will be randomly assigned to receive ABT-450/r/ABT-267 and ABT-333 coadministered with RBV* for 12 (Arm A) or 24 weeks (Arm B).

* RBV will be administered weight-based 1000 or 1200 mg divided twice daily.
Randomized subjects in Parts 1a and 2 will be stratified by prior HCV treatment history (treatment-naïve versus treatment-experienced) and by presence of cirrhosis (cirrhotic or...
non-cirrhotic). Treatment-naïve subjects will also be stratified by IL28B (interleukin 28B) genotype (CC versus non-CC). PegIFN/RBV-experienced subjects will also be stratified by type of previous response to pegIFN/RBV (null responder, partial responder, or relapser). Randomized subjects in Part 1b will be stratified by prior HIV treatment history (previously PI-naïve subjects [i.e., no PI exposure other than DRV] and previously PI-experienced subjects [i.e., received non-DRV PI prior to current DRV treatment]). A minimum of 10 but no more than 20 subjects that are previously HIV-1 PI-naïve will be allowed to enroll in Part 1b of the study.

HCV GT 1/HIV-1 coinfected adults with compensated cirrhosis will be eligible for enrollment in Part 1 and Part 2.

The primary analysis will occur after all randomized subjects enrolled in Part 1 and Part 2 (N = 300) have completed through Post-Treatment Week 12 or prematurely discontinued from the study.

An interim analysis of the data from Part 1a of the study will occur after all randomized subjects enrolled in Part 1a have completed through Post-Treatment Week 12 or prematurely discontinued from the study. An additional interim analysis of the data from Part 1b of the study will occur after all randomized subjects enrolled in Part 1b have completed through Post-Treatment Week 12 or prematurely discontinued from the study.

Parts 1 and 2 of this study will consist of a Treatment Period and a Post-Treatment Period. In addition, Part 1b will consist of a lead-in period (Pre-Treatment Period) for approximately 2 weeks prior to the initiation of the Treatment Period.

As this is an open-label study, safety and efficacy evaluations will occur throughout the Treatment and Post-Treatment Periods of Part 1 and Part 2. Treatment arms may be terminated or extended based upon evaluations of HCV failures by AbbVie as outlined in Section 5.5.1.3.
5.1.1 Screening

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via 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 the Enrollment Day (for subjects in Part 1b) or Study Day 1 (for subjects in Part 1a or in Part 2) 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. In addition, subjects will be provided with an HIV-1 ARV dosing card as described in Section 5.3.1.1.

Screening may be paused by AbbVie after enrollment has begun in Part 1 or Part 2. Criteria for the initiation of Part 2 are described in Section 5.4. AbbVie will notify investigators prior to pausing screening and again when screening is reopened.

Subjects that were screened in Part 1, but were unable to enroll in Part 1 before enrollment is completed, may be allowed to screen for Part 2. This will be considered an entirely new screening. These subjects will not require approval from AbbVie to screen for Part 2. Subjects will be required to sign a new informed consent form prior to completing screening procedures for Part 2 and will receive a new unique subject number via the IRT system.

For subjects who do not meet the study eligibility criteria or for eligible subjects that are not able to enroll due to enrollment being completed, the site personnel must register the subject as a screen failure in both IRT and EDC systems.

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.

5.1.2 Rescreening

Subjects may be rescreened as follows:

- Subjects who meet all eligibility criteria with the exception of one exclusionary laboratory parameter may rescreen once without prior AbbVie approval with the exception of an exclusionary HCV genotype, a positive hepatitis B virus (HBV), plasma HIV-1 RNA ≥ 200 copies/mL, or a positive serum pregnancy test. Subjects with any of these exclusionary laboratory parameters are not eligible to rescreen.

- Subjects who otherwise meet all eligibility criteria, but have an exclusionary positive urine alcohol screen, may have only the urine alcohol screen repeated within the Screening Period. If the repeat urine alcohol screen is negative and all other entrance criteria are met, the subject may be considered eligible.

- For subjects who have multiple exclusionary laboratory results or for subjects who failed screening on two occasions, approval is required from the AbbVie Study Designated Physician prior to rescreening the subject.

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, HIV Ab, HIV Western blot, IL28B genotype, FibroTest/FibroScan/liver biopsy and, if applicable, diagnostic imaging of the liver for hepatocellular carcinoma (HCC), which do not need to be repeated).

Eligible subjects who fail to enroll within 35 days of screening, regardless of the reason for falling outside the 35-day screening window, may be allowed to rescreen only once unless approved by the AbbVie Study Designated Physician. The subject must be rescreened for all laboratory and eligibility criteria, (with the exception of HCV genotype, HIV Ab, HIV Western blot, IL28B genotype, FibroTest/FibroScan/liver biopsy and, if
applicable, diagnostic imaging of the liver for hepatocellular carcinoma (HCC) which do not need to be repeated).

Subjects meeting any of the above criteria for rescreening may wait to have a liver biopsy performed until their rescreening visit.

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

5.1.3 Pre-Treatment Period (Part 1b only)

After meeting the eligibility criteria, subjects in Part 1b will be randomized via IRT at the Enrollment Day to either receive DRV dosing 800 mg QD or begin dosing DRV 600 mg BID for at least 14 days prior to initiating study drugs. Randomized subjects will have up to 21 days from the Enrollment Day to begin dosing of study drugs on Study Day 1. Details regarding dosing instructions for DRV are described in Section 5.2.3.2. On Study Day –1 (day prior to dosing with the DAAs), subjects will be required to return to the study site for 12-hour intensive pharmacokinetic sampling as described in Section 5.3.2.1. The investigator will review the HIV-1 ARV dosing card completed during the Pre-Treatment Period to assess if the subject has been adherent with their HIV-1 ARV regimen and remains a suitable candidate to continue study participation prior to the initiation of the 12-hour intensive pharmacokinetic sampling. In the event that the dosing card is not available at the Study Day –1 visit, the investigator may obtain dosing information via patient interview in order to assess if the subject has been adherent with their HIV-1 ARV regimen and remains a suitable candidate to continue study participation. If the investigator believes that the subject is no longer a suitable candidate to continue to the Treatment Period, the subject should prematurely discontinue study participation.

Subjects who prematurely discontinue from the Pre-Treatment Period (prior to receiving study drugs) should return to the study site for a Premature Discontinuation Visit and undergo the study procedures as outlined in Table 8. Subjects who prematurely
discontinue during the Pre-Treatment Period will not be followed during the Post-Treatment Period.

### 5.1.4 Treatment Period (TP)

After meeting the eligibility criteria, subjects in Part 1a and Part 2 will be randomized via IRT to either 12 or 24 weeks of treatment. Subjects in Part 1b that completed the Pre-Treatment Period will be assigned via IRT to receive 12 weeks of treatment.

An approximate total of 300 subjects (90 in Part 1 and 210 in Part 2) will be randomized. On Study Day 1, subjects will be administered study drugs at the site and given instructions about the study drugs and the dosing schedule.

ABT-450/r/ABT-267 will be administered orally (PO) once daily (QD) and ABT-333 and RBV will be dosed orally twice daily (BID) as described in Section 5.6.1. 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 or 1200 mg daily divided BID per local label (e.g., < 75 kg = 1000 mg daily divided BID or ≥ 75 kg = 1200 mg daily divided BID)

Non-weight based RBV dosing may be permitted only with prior approval of the AbbVie Study Designated Physician.

All subjects will continue to return to the site on an outpatient basis up through Week 12 or Week 24 depending on treatment group assignment, for the study procedures identified in Table 6 and Table 8. Sites should ensure that subjects adhere to the study visits listed in Table 6 and Table 8. Subjects that cannot complete their study visits per the visit schedule should ensure they do not run out of study drug prior to their next study visit. Some of the Treatment Period study visits and visit activities (including but not limited to vital signs, clinical laboratory tests, and concomitant medication assessment) may be
conducted in the home or non-hospital/clinic environment by qualified individuals at the request of the Investigator, with approval from AbbVie, and with the agreement of the subject.

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

Safety and tolerability of the treatments will be assessed throughout the study. Laboratory testing will include chemistry, hematology, and urinalysis (refer to Table 6, Table 8 and Table 10). Patient Reported Outcomes (PROs) will also be assessed at the visits listed in Table 6 and Table 8.

Ongoing review of the data is planned in order to determine if subjects meet the HCV virologic failure criteria (Section 5.5.1.1). HCV virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.5.1.1. AbbVie will evaluate HCV efficacy treatment adjustment criteria throughout the Treatment and Post-Treatment Periods in this open-label study as detailed in Section 5.5.1.3.

Failure to maintain HIV virologic suppression and the criteria for study treatment discontinuation will be evaluated and applied by the Investigator as detailed in Section 5.5.1.2.

Subjects who prematurely discontinue from the Treatment Period should return to the study site for a Treatment Period Discontinuation Visit and undergo the study procedures as outlined in Table 6 and Table 8 and as described in Section 5.1.5. 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 with the exception of add-on pegIFN/RBV, if applicable. Subjects who complete or discontinue treatment will be monitored for HCV RNA, HCV virologic resistance, plasma HIV-1 RNA and HIV resistance in the 48-week Post-Treatment Period as detailed in Section 5.1.5, Section 5.5.1.1 and Section 5.5.1.2.
5.1.5 Post-Treatment (PT) Period

All subjects who received at least one dose of DAAs 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 HCV viral variants, plasma HIV-1 RNA, HIV resistance and assessment of PROs for an additional 48 weeks following the last dose of study drug as detailed in Table 7 and Table 9.

The Post-Treatment Period will begin the day after the last dose of study drug. Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a Post-Treatment Discontinuation Visit as outlined in Table 7 and Table 9.

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

5.2 Selection of Study Population

The study population consists of HCV GT 1/HIV-1 coinfected adults, with and without compensated cirrhosis, who are either HCV treatment-naïve or pegIFN/RBV-experienced. Refer to Section 5.2.3.1 for details regarding required documentation for pegIFN/RBV treatment failures.

In addition, the study population consists of HCV GT 1/HIV-1 coinfected subjects who are currently HIV-1 virologically suppressed and currently on a stable antiretroviral treatment (ART) regimen containing ATV, RAL, or DRV. Refer to Section 5.2.3.2 for details.

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

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

2. Female who is:
   - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle),
   - sexually active with female partners only,
   - of childbearing potential and sexually active with male partner(s):
     - currently using at least one effective method of birth control at the time of screening and agree to practice two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents), starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment.)
   - not of childbearing potential, defined as:
     - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or
     - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or has a vasectomized partner(s),

3. Females must have negative results for pregnancy tests performed:
   - at Screening by serum specimen within 35 days prior to randomization, and
   - at the Enrollment Day by urine specimen (for subjects in Part 1b only, prior to randomization), and
   - at Study Day 1 (Baseline, prior to dosing for subjects in Parts 1a and 2) by urine specimen.

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 Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label.

5. Subjects must be HCV treatment-naïve or pegIFN/RBV-experienced. If pegIFN/RBV-experienced, subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:

- Null responder:
  1. received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a $2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Subjects will be considered to meet this definition if the lack of treatment response was documented between Weeks 10 – 16 of treatment); or
  2. received at least 4 weeks of pegIFN/RBV for the treatment of HCV and achieved a < $1 \log_{10}$ IU/mL reduction in HCV RNA at Week 4 (Subjects will be considered to meet this definition if the lack of treatment response was documented after ≥ 25 days of treatment); or

Note: Genotype 1a, prior pegIFN/RBV null responders with cirrhosis will not be eligible for enrollment in Part 1b.

- Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Subjects will be considered to meet this definition if the treatment response was documented between Weeks 10 – 16 of treatment), but failed to achieve HCV RNA undetectable at or after Week 20 of treatment; or

- Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after Week 36 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 response should have been obtained in relation to the previous pegIFN/RBV treatment. Interferon-based therapy (e.g., pegIFN/RBV) must have been completed no less than 2 months prior to the Screening Visit.
6. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

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

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

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

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

11. Subject has HCV RNA level $> 10,000$ IU/mL at Screening.

12. Positive test result for anti-Human Immunodeficiency Virus antibody (HIV Ab) at Screening.

13. Plasma HIV-1 RNA $< 40$ copies/mL during screening using Abbott RealTime HIV-1 assay, and plasma HIV-1 RNA below LLOQ by an approved plasma HIV-1 RNA quantitative assay (including but not limited to: COBAS® Ampliprep/COBAS® Taqman® HIV-1 Test, v 2.0 or Abbott RealTime HIV-1 assay) at least twice during the 24 weeks prior to screening including one qualifying result at least 8 weeks prior to screening.

Subjects with a solitary (unconfirmed) plasma HIV-1 RNA above LLOQ and $< 200$ copies/mL within 24 weeks of screening may be eligible for enrollment with approval of the AbbVie Study Designated Physician.

14. CD4+ count $\geq 200$ cells/mm$^3$ or CD4+% $\geq 14$% during screening.
15. On a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to screening. The HIV-1 ART regimen must include two nucleoside/nucleotide reverse transcriptase inhibitors plus one of the following ritonavir-boosted protease inhibitors, or the integrase inhibitor, raltegravir.

The nucleoside/nucleotide reverse transcriptase inhibitor combinations in the stable qualifying HIV-1 ART regimen must be either:
- Tenofovir disoproxil fumarate (TDF) PO QD plus emtricitabine (FTC) PO QD (Individual components or as the fixed dose combination TDF/FTC, Truvada®), or
- Tenofovir disoproxil fumarate (TDF) PO QD plus lamivudine (3TC) PO QD or 3TC PO BID (Individual components or as the fixed dose combination TDF/3TC).

The ritonavir boosted protease inhibitors in the stable qualifying HIV-1 ART regimen must be either:
- Atazanavir (ATV) PO QD coadministered with ritonavir (RTV) PO QD, or
- Darunavir (DRV) PO QD coadministered with ritonavir (RTV) PO QD.

The integrase inhibitor in the stable qualifying HIV-1 ART regimen must be:
- Raltegravir (RAL) PO BID.

Subjects receiving any other HIV-1 ART in addition to those noted above would not be eligible for enrollment in the study.

Subjects will be considered to be non-cirrhotic and included in the study if the following criteria are met:

16. Per local standard practice, documented results of one of the following:
- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR Score of 3 or less, Ishak score of 4 or less; or
- A screening FibroScan result of < 12.5 kPa (FibroScan must be approved by the local regulatory agency to qualify for entrance criteria); or
A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 (Subjects with a screening FibroTest result that is ≤ 0.72 and an APRI > 2, or a FibroTest result that is ≥ 0.73 and an APRI ≤ 2 must have a FibroScan or liver biopsy to determine the presence or absence of cirrhosis).

Subjects will be considered to have compensated cirrhosis and included in the study if the following criteria are met:

17. Per local standard practice, documentation of cirrhosis by one of the following methods:
   - Previous histologic diagnosis of cirrhosis on liver biopsy, e.g., Metavir Score of > 3 (including 3 – 4 or 3/4), Ishak score of > 4 or on a liver biopsy conducted during screening; or
   - A screening FibroScan score ≥ 12.5 kPa (FibroScan must be approved by the local regulatory agency to qualify for entrance criteria); or
   - A screening FibroTest result that is ≥ 0.73 and an APRI > 2 (Subjects with a screening FibroTest result that is ≤ 0.72 and an APRI > 2, or a FibroTest result that is ≥ 0.73 and an APRI ≤ 2 must have a FibroScan or liver biopsy to determine the presence or absence of cirrhosis).

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

19. Absence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or a negative ultrasound at Screening. Subjects who have an ultrasound with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

**Rationale for Inclusion Criteria**

(1, 5, 9 – 19) 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) in concentrated extract formulations (e.g., tablets or capsules), 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. Female subjects with a borderline hCG at Screening 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. 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).

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

7. Use of any medications listed in Table 4, within 2 weeks prior to study drug administration or 10 half lives (if known), whichever is longer, including but not limited to:
### Table 4. Medications Contraindicated for Use with the Study Drug Regimen

<table>
<thead>
<tr>
<th>Alfuzosin</th>
<th>Lovastatin</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>Methylergonovine</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Methylergometrine</td>
<td>Sildenafil***</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Midazolam (oral)</td>
<td>Simvastatin</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>Phenobarbital</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Phenytoin</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>Pimozide</td>
<td>Triazolam</td>
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<tr>
<td>Fusidic Acid</td>
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<td></td>
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<tr>
<td>Estrogen-containing Medications for Systemic Use**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
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</tr>
</tbody>
</table>

Not all medications contraindicated with HIV-1 antiretroviral agents (ARVs) and ribavirin are listed above. Refer to the most current package inserts or product labeling for a complete list of contraindicated medications.

* Subjects receiving Atripla® (TDF/FTC/efavirenz) or an HIV-1 ART regimen containing efavirenz are not eligible for enrollment.

** Progestin-only hormonal contraceptive agents are allowed for use with the study drug regimen

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

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

9. Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, or propoxyphene that in the opinion of the investigator could preclude adherence to the protocol or a positive result of a urine alcohol screen at the Screening Visit. A positive drug screen result associated with medical short-term or chronic stable use of a medication in that class is not exclusionary.

10. Clinically significant abnormalities, other than HCV/HIV-1 coinfection, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG) that make the subject an unsuitable candidate for this study in the opinion of the investigator.
11. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) level > 8.5% at the Screening Visit, or an active or suspected malignancy or history of malignancy (other than basal cell skin cancer, cutaneous Kaposi's Sarcoma, or cervical or anal carcinoma in situ) in the past 5 years.

12. HCV genotype performed during screening indicating unable to genotype or coinfection with any HCV genotype other than GT 1.

13. Any current or past clinical evidence of liver decompensation including ascites, variceal bleeding, or hepatic encephalopathy.

14. Evidence of past virologic failure to more than one HIV-1 ART regimen.

15. Evidence of darunavir resistance-associated substitutions per local darunavir label.

16. Treatment for an AIDS-associated opportunistic infection (OI) within 12 months of screening or prophylaxis for an AIDS-associated opportunistic infection within 6 months of screening.

17. Diagnosis of any clinical AIDS-defining event within 12 months prior to screening, including:
### Table 5. List of Clinical AIDS-Defining Events

<table>
<thead>
<tr>
<th>List of Clinical AIDS-Defining Events³⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis of bronchi, trachea, or lungs</td>
</tr>
<tr>
<td>Candidiasis of esophagus †</td>
</tr>
<tr>
<td>Cervical cancer, invasive ‡</td>
</tr>
<tr>
<td>Coccidioidomycosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>Cryptosporidiosis, chronic intestinal (&gt; 1 month's duration)</td>
</tr>
<tr>
<td>Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age &gt; 1 month</td>
</tr>
<tr>
<td>Cytomegalovirus retinitis (with loss of vision) †</td>
</tr>
<tr>
<td>Encephalopathy, HIV related</td>
</tr>
<tr>
<td>Herpes simplex: chronic ulcers (&gt; 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age &gt; 1 month)</td>
</tr>
<tr>
<td>Histoplasmosis, disseminated or extrapulmonary</td>
</tr>
<tr>
<td>Isosporiasis, chronic intestinal (&gt; 1 month's duration)</td>
</tr>
</tbody>
</table>

† Condition that might be diagnosed presumptively.
‡ Only among adults and adolescents aged > 13 years.
* Diagnosis of cutaneous Kaposi's Sarcoma is not exclusionary.

18. Any primary 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.

19. Screening laboratory analyses showing any of the following abnormal laboratory results:
   - Alanine aminotransferase (ALT) $> 7 \times$ Upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) $> 7 \times$ ULN
   - Calculated creatinine clearance (using Cockcroft-Gault method) $< 60$ mL/min
   - Albumin $< 2.8$ g/dL
   - International normalized ratio (INR) $> 1.5$. Subjects with a known inherited blood disorder or receiving chronic anticoagulation with warfarin (Coumadin) and an INR $> 1.5$ may be enrolled with prior approval of the AbbVie Study Designated Physician
   - Hemoglobin $< 12$ g/dL in males and $< 11$ g/dL in females
   - Platelets $< 60,000$ cells per mm$^3$
   - Absolute neutrophil count (ANC) $< 1200$ cells/μL ($< 1000$ cells/μL for subjects of black race or subjects of African descent who are black)
   - Indirect bilirubin $> 1.5 \times$ ULN and direct bilirubin $> ULN$. Subjects receiving atazanavir as part of their HIV-1 ART regimen not meeting this criterion may be eligible for enrollment with prior approval of the AbbVie Study Designated Physician.

20. Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) $> 450$ msec at Screening for subjects without cirrhosis or $> 470$ msec at Screening for subjects with compensated cirrhosis.

21. 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.

22. 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.
23. 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 prior 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 prior approval by the AbbVie Study Designated Physician.

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

25. 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.

26. Chronic human immunodeficiency virus, type 2 (HIV-2) infection.

Subjects with compensated cirrhosis will be excluded if any one of the following criteria are met:

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

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

29. Any current or past clinical evidence of Child-Pugh B or C classification. Subjects receiving atazanavir as part of their HIV-1 ART regimen with a screening total bilirubin > 3 mg/dL (> 51.3 μmol/L) may be eligible for enrollment with prior approval of the AbbVie Study Designated Physician.

30. Genotype 1a, previous null responders to pegIFN/RBV treatment (excluded from Part 1b only).
Rationale for Exclusion Criteria

(1, 10, 11, 19, 20, 22, 25, 27, 28, 30) To ensure safety of the subjects throughout the study.

(2, 4, 7 – 9, 21; 23, 24) To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications.

(3) RBV has known teratogenic effects.

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

(6, 12 – 17, 26, 29) To select the appropriate subject population with sufficient disease severity for evaluation.

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements, and any prohibited medications) that the subject is receiving from the time of signing the informed 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. Please refer to Section 5.2.3.4 for details regarding prohibited medications.

Information regarding each subjects qualifying, stable HIV-1 ART medications including start date, dose and frequency will be recorded into the eCRF at screening. In addition, subjects will be requested to record information for the last two doses of their HIV-1 ART medications taken (dosing dates, times, and number of pills) prior to the study visits detailed in Table 6, Table 7, Table 8 and Table 9 and site personnel will record this information in the eCRF. Subjects in Part 1b will also be requested to record information for doses of their HIV-1 ART medications taken during the Pre-Treatment Period.
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 and HIV 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 but not limited to: IFN, pegIFN, telaprevir, boceprevir, simeprevir, sofosbuvir or RBV. Subjects who previously participated in trials of anti-HCV agents for treatment of HCV may be enrolled with the prior approval of the AbbVie Study Designated Physician if they can provide documentation that they received only placebo.

PegIFN/RBV-experienced subjects must have previously received pegIFN and RBV and failed treatment as defined in Section 5.2.1. 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. PegIFN/RBV-experienced subjects must have discontinued interferon-based 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, simeprevir, and sofosbuvir, excludes a subject from this study. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled with the prior approval of the AbbVie Study Designated Physician if they can produce documentation that they received only placebo.

5.2.3.2 Prior and Concomitant HIV-1 Therapy

Subjects must currently be on a stable, qualifying HIV-1 ART regimen for at least 8 weeks prior to screening. The HIV-1 ART regimen must include
two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus one of the ritonavir-boosted protease inhibitors noted below, or the integrase inhibitor, raltegravir (RAL).

The nucleoside/nucleotide reverse transcriptase inhibitor combinations in the stable, qualifying ART regimen must be either:

- Tenofovir disoproxil fumarate (TDF) PO QD plus emtricitabine (FTC) PO QD (individual ARV components or as the fixed-dose combination TDF/FTC, Truvada®), or
- Tenofovir disoproxil fumarate (TDF) PO QD plus lamivudine (3TC) PO QD or PO BID (individual ARV components or as the fixed-dose combination TDF/3TC).

The ritonavir boosted protease inhibitor in the stable qualifying ART regimen must be either:

- Atazanavir (ATV) PO QD coadministered with ritonavir (RTV) PO QD, or
- Darunavir (DRV) PO QD coadministered with ritonavir (RTV) PO QD.

The integrase inhibitor in the stable qualifying ART regimen must be:

- Raltegravir (RAL) PO BID.

Subjects receiving any other HIV-1 ART in addition to those noted above would not be eligible for enrollment in the study.

In this study, the DAA regimen is ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + weight-based RBV. The DAA morning dose includes 100 mg of ritonavir. Hence, subjects receiving an HIV-1 ART regimen that includes:

- Atazanavir PO QD coadministered with ritonavir PO QD will stop the ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen. Subjects that were taking the atazanavir component of their
HIV-1 ART regimen in the evening prior to enrollment must change to morning administration of atazanavir at Study Day 1. The atazanavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333).

- Darunavir PO QD coadministered with ritonavir PO QD will be randomized approximately 14 days prior to starting the study DAA regimen to either receive DRV 800 mg PO QD coadministered with ritonavir 100 mg PO QD or switch to DRV 600 mg PO BID coadministered with ritonavir 100 mg PO BID during the Pre-Treatment Period. Subjects on a darunavir QD regimen that were taking the darunavir component of their HIV-1 ART regimen in the evening prior to enrollment must change to morning administration of darunavir at randomization.
  - Subjects that are randomized to receive DRV 800 mg PO QD administration will stop the ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen on Study Day 1. The darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333).
  - Subjects that are randomized to switch to DRV 600 mg PO BID administration will stop the AM ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen on Study Day 1. The AM dose of darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333). Subjects will administer their PM dose of ritonavir with the PM dose of darunavir and the PM dose of ABT-333.

- Raltegravir PO BID will maintain the same dose and dosing interval upon initiating the study DAA regimen on Study Day 1 so that the morning dose of raltegravir is taken with the morning dose of DAAs (ABT-450/r/ABT-267 and ABT-333) and the evening dose of raltegravir is taken with the evening dose of DAAs (ABT-333).

Subjects will maintain the same dose and dosing interval of their N(t)RTI backbone upon initiating the study DAA regimen.
In the case of study treatment interruption, subjects should resume the ritonavir component of their HIV-1 ART regimen (ritonavir 100 mg co-administered with atazanavir PO QD, ritonavir 100 mg co-administered with darunavir PO QD, or ritonavir 100 mg co-administered with the morning dose of darunavir PO BID), during the interruption.

Study participants will resume all HIV-1 ART regimen doses and dosing intervals used at Screening at Post-Treatment Day 1 of the study.

Subjects must remain on the same HIV-1 ART regimen for the entire Treatment Period. Any change in the HIV-1 ART regimen during the study must be discussed with the AbbVie Study Designated Physician prior to the change, unless the change is being made to address an immediate safety concern.

5.2.3.3 Other Concomitant Therapy

Subjects must be able to safely discontinue any prohibited medications or herbal supplements at least 2 weeks prior to initial study drug administration through 2 weeks after completion of the Treatment Period. Subjects must be consented prior to discontinuing any prohibited medications or herbals supplements for the purpose of meeting study inclusion criteria.

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

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.
Flu shots and all essential vaccinations in this subject population are allowed during Screening through the Post-Treatment Period.

**Contraceptives**

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

**5.2.3.4 Prohibited Therapy**

In addition to the medications listed in Table 4, use of known strong inducers of CYP3A or CYP2C8, and inhibitors of CYP2C8 or any herbal supplements (including milk thistle) available in concentrated extract formulations, e.g., tablets or capsules, are prohibited within 2 weeks or 10 half-lives of the respective medication/supplement (if known), whichever is longer, prior to the initial dose of study drugs through the first 2 weeks after the subject has completed study drugs in the Treatment Period.

Refer to the RBV labeling for a list of prohibited medications.

Atripla® (TDF/FTC/efavirenz) or regimens containing efavirenz are prohibited in this study. During coadministration of ABT-450/r and ABT-333 with Atripla®, a fixed dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate in healthy subjects, 3 subjects experienced Grade 3 ALT elevations leading to early termination of the study. These findings were believed to be due to the efavirenz component of Atripla® as co-dosing of these DAAs with emtricitabine, and tenofovir disoproxil fumarate was safe and well tolerated; however, similar side effects were reported in healthy subjects during coadministration of efavirenz with saquinavir/ritonavir.
and also during coadministration of rifampin (which induces CYP3A similar to efavirenz), with ritonavir-boosted protease inhibitors.29

The use of additional ritonavir as part of an HIV-1 ART regimen is prohibited while the subject is receiving ABT-450/r/ABT-267, with the exception of the PM dose of ritonavir for subjects receiving darunavir PO BID.

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.

The investigator should contact the AbbVie Study Designated Physician before prescribing prophylaxis against opportunistic infections during the Treatment Period.

5.2.3.5 Add-on PegIFN/RBV Therapy

If a treatment arm is terminated from further enrollment, due to reaching the efficacy treatment adjustment criterion as defined in Section 5.5.1.3 or based on data from ongoing studies, the subjects of the discontinued arm and in the Treatment Period will be offered either the option to continue their assigned DAA regimen or the option to add on a 48-week course of pegIFN/RBV therapy to their assigned DAA regimen. This is an optional offer and the sponsor will provide funding to reimburse the investigator for obtaining commercial pegIFN and RBV for the subject, if allowed by local rules or regulations.

The subject should use the remaining study labeled RBV dispensed during the Treatment Period (if applicable), with pegIFN added to the regimen. Once the Treatment Period has ended, the subject would continue taking pegIFN/RBV through the Post-Treatment Period until completing a total of 48 weeks of pegIFN/RBV therapy.
Prior to initiating pegIFN/RBV, the principal investigator will determine if a subject is an appropriate candidate for pegIFN/RBV. No subject should be started on pegIFN/RBV if such treatment is contraindicated. The start date and end date of the add-on pegIFN/RBV will be recorded in the eCRF.

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart
Table 6. Part 1a and Part 2: Study Activities – Treatment Period (TP)

<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;c,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Wk 1</td>
<td>Wk 2</td>
</tr>
<tr>
<td>Informed Consent&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provide RBV Medication Guide&lt;sup&gt;f&lt;/sup&gt; and Partner Risk Fact Sheet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense/Review HIV-1 ART Dosing Card</td>
<td>X (dispense only)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital Signs, Weight, Height&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis/ Coagulation Panel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test [serum (s) urine (u)&lt;sup&gt;j&lt;/sup&gt;]</td>
<td>X (s)</td>
<td>X (u, s)</td>
<td>X (u)</td>
<td>X (u)</td>
</tr>
<tr>
<td>FSH (all females)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg, Anti-HCV Ab, Anti HIV Ab</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug/Alcohol Screen</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Insulin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Biopsy or FibroTest, or FibroScan&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Part 1a and Part 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;c,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 4</td>
</tr>
<tr>
<td>Child-Pugh Score&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
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<tr>
<td>Clinical Assessment of Hepatic Decompensation</td>
<td>X&lt;sup&gt;4&lt;/sup&gt;</td>
<td>X</td>
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<tr>
<td>HCC Screening: Liver Ultrasound &amp; Alpha Fetoprotein&lt;sup&gt;l&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomization</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Reported Outcomes (PROs)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Adverse Event Assessment</td>
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<td>X</td>
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<tr>
<td>Study Drugs Dispensed</td>
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<tr>
<td>Study Drug Returned for IRT Reconciliation</td>
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<td>X</td>
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<tr>
<td>MEMS cap dispensed</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MEMS Downloaded/Review Compliance/Collect MEMS Caps&lt;sup&gt;m&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>HCV RNA Samples</td>
<td>X</td>
<td>X</td>
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<tr>
<td>HIV-1 RNA&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>X</td>
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</table>
Table 6. Part 1a and Part 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(^{c,d})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening(^a)</td>
<td>Day 1(^b)</td>
<td>Wk 1</td>
<td>Wk 2</td>
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<tr>
<td>HCV Resistance Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pharmacokinetic Sparse Samples(^e)</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Pharmacokinetic Intensive Samples(^g)</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Flow Cytometry Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Serum Sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV Genotype and Subgenotype</td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>IL28B Sample</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>HgbA1c</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Interferon gamma-induced protein 10 (IP-10) Sample</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Pharmacogenetic DNA Sample (optional)(^p)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Urine Albumin(^q)</td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>Messenger RNA (mRNA) Sample (optional)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Day 1 of the 24-week treatment period.
\(^b\) Day 1 of the 12-week treatment period.
\(^c\) Patients who withdraw from the study and are discontinued from the study are generally followed up to complete scheduled visits.
\(^d\) Treatment period for some patients may extend beyond the scheduled end of treatment.
\(^e\) Sparse samples are obtained at Wks 1, 2, 4, 6, and 8.
\(^g\) Intensive samples are obtained at Wks 10, 12, and 24.
\(^p\) Pharmacogenetic DNA samples are optional and are collected at Wks 2, 4, 6, 8, 10, 12, and 24.
\(^q\) Urine albumin is collected at Wks 1, 2, 4, 6, and 8.
Table 6. Part 1a and Part 2: Study Activities – Treatment Period (TP) (Continued)

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>All screening procedures need to be completed within 35 days of Study Day 1.</td>
</tr>
<tr>
<td>b.</td>
<td>All procedures, including pharmacokinetic sample collection, to be performed prior to first dose.</td>
</tr>
<tr>
<td>c.</td>
<td>Treatment visits:</td>
</tr>
<tr>
<td></td>
<td>• Subjects randomized to a 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 and study drug will only be dispensed to subjects assigned to the 24-week treatment arm unless a 12-week treatment arm is extended to 24-weeks treatment. Refer to Appendix E for study activities to be completed if a 12-week treatment arm is extended to 24-weeks of treatment.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• Subjects who prematurely discontinue the Treatment Period (Week 12 or Week 24) should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).</td>
</tr>
<tr>
<td>d.</td>
<td>Subjects should begin the Post-Treatment Period after the subject completes study drug treatment or prematurely discontinues Treatment Period.</td>
</tr>
<tr>
<td>e.</td>
<td>Subjects will need to sign an informed consent for the study prior to performing any screening or study-specific procedures.</td>
</tr>
<tr>
<td>f.</td>
<td>Where applicable/locally available.</td>
</tr>
<tr>
<td>g.</td>
<td>Medical history will be updated at the Study Day 1 Visit. This updated medical history will serve as the Baseline for clinical assessment.</td>
</tr>
<tr>
<td>h.</td>
<td>Height will be measured at Screening only. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes.</td>
</tr>
<tr>
<td>i.</td>
<td>Evaluate the Study Day 1 ECG prior to dosing.</td>
</tr>
<tr>
<td>j.</td>
<td>Urine pregnancy testing is not required after the Study 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.</td>
</tr>
<tr>
<td>k.</td>
<td>Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, Liver Ultrasound and Alpha Fetoprotein are only performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures.</td>
</tr>
<tr>
<td>l.</td>
<td>Short Form 36, version 2 (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 following order: SF-36v2, EQ-5D-5L, HCVPRO.</td>
</tr>
<tr>
<td>m.</td>
<td>MEMS caps will be collected upon completion of study drug (TP Week 12 or Week 24 or Premature D/C from Treatment).</td>
</tr>
</tbody>
</table>
Table 6. Part 1a and Part 2: Study Activities – Treatment Period (TP) (Continued)

n. If a subject's plasma HIV-1 RNA level was < 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing at an unscheduled visit for confirmation of plasma HIV-1 RNA as detailed in Section 5.5.1.2.

o. Blood samples for DAA and HIV-1 ARV pharmacokinetic assay will be collected as described in Section 5.3.2.

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

q. Done at Study Day 1/Baseline and collected for decrease in Creatinine Clearance as defined in Section 6.7.6.
Table 7. Part 1a and Part 2: Study Activities – Post-Treatment (PT) Period$a$

<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$a$</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/Coagulation/Urinalysis</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)$^3$</td>
<td>X</td>
<td></td>
<td></td>
<td>(Weeks 12, 16, 20, 24, 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense/Review HIV-1 ART Dosing Card</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Score$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound and Alpha Fetoprotein$^c,d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO Instruments$^e$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medication Assessment$^f$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event Assessment$^g$</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA$^h$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>HCV Resistance Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archive Plasma Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Serum Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pharmacokinetic Samples$^i$</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IP-10 Sample</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
### Table 7. Part 1a and Part 2: Study Activities – Post-Treatment (PT) Period* (Continued)

<table>
<thead>
<tr>
<th>Wk</th>
<th>Week; PT D/C = Post-Treatment Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 of the Post-Treatment Period will be defined as the day after the last dose of study drug.</td>
</tr>
<tr>
<td>a.</td>
<td>Subjects who prematurely discontinue from the Post-Treatment Period should return to the site to complete the PT D/C Visit procedures.</td>
</tr>
<tr>
<td>b.</td>
<td>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. Subjects may elect to have an unscheduled visit for pregnancy testing at PT Weeks 16, 20 and 28 (if required by local RBV label) or to perform the tests at home with test kits provided by the site. Any additional pregnancy testing should be completed using the unscheduled test kit.</td>
</tr>
<tr>
<td>c.</td>
<td>For the subjects with cirrhosis at baseline.</td>
</tr>
<tr>
<td>d.</td>
<td>Liver Ultrasound and Alpha Fetoprotein are performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures.</td>
</tr>
<tr>
<td>e.</td>
<td>PRO instruments should be administered before any study procedures and in the following order: SF-36v2, EQ-5D-5L, and HCVPRO.</td>
</tr>
<tr>
<td>f.</td>
<td>Only medications related to the treatment of HCV and HIV and medications prescribed in association with an SAE will be collected after 30 days post-dosing.</td>
</tr>
<tr>
<td>g.</td>
<td>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 pegIFN/RBV only therapy and for 30 days following the end of pegIFN/RBV only therapy.</td>
</tr>
<tr>
<td>h.</td>
<td>If a subject's plasma HIV-1 RNA level was &lt; 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing at an unscheduled visit for confirmation for plasma HIV-1 RNA as detailed in Section 5.5.1.2.</td>
</tr>
<tr>
<td>i.</td>
<td>Pharmacokinetic Samples for HIV ART only will be drawn at Post Treatment Weeks 2 and 4.</td>
</tr>
</tbody>
</table>
### Table 8. Part 1b: Study Activities – Pre-Treatment Period and Treatment Period (TP)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pre-Treatment Visits</th>
<th>Treatment Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrollment Day</td>
<td>Day -1</td>
</tr>
<tr>
<td>Informed Consent&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Provide RBV Medication Guide and Partner Risk Fact Sheet</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dispense/Review HIV-1 ART Dosing Card&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
<td>(dispense only)</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs, Weight, Height&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test [serum (s) urine (u)]&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
<td>(s)</td>
</tr>
<tr>
<td>FSH (all females)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HBsAg, Anti-HCV Ab, Anti HIV Ab</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Drug/Alcohol Screen</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Total Insulin</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Liver Biopsy or FibroTest, or FibroScan&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Part 1b: Study Activities – Pre-Treatment Period and Treatment Period (TP) (Continued)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screening&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pre-Treatment Visits</th>
<th>Treatment Visits</th>
<th>Pre-Treatment D/C&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Treatment D/C&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrollment Day</td>
<td>Day -1</td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 4</td>
</tr>
<tr>
<td>Child-Pugh Score&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Assessment of Hepatic Decompensation</td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound and Alpha Fetoprotein&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Reported Outcomes Instruments (PROs)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Study Drugs Dispensed</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug Returned for IRT Reconciliation</td>
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<tr>
<td>MEMS cap dispensed</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEMS Downloaded/Review Compliance/Collect MEMS Caps&lt;sup&gt;k&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV RNA Samples</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV-1 RNA&lt;sup&gt;k&lt;/sup&gt;</td>
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<td></td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>HCV Resistance Sample</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic Sparse Samples&lt;sup&gt;j&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic Intensive Samples&lt;sup&gt;j&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Flow Cytometry Sample</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activity</td>
<td>Screening&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pre-Treatment Visits</td>
<td>Treatment Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enrollment Day</td>
<td>Day -1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Premature D/C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Day 1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Wk 1</td>
</tr>
<tr>
<td>Archive Serum Sample</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HCV Genotype and Subgenotype</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL28B Sample</td>
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<tr>
<td>HgbA1c</td>
<td></td>
<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Interferon gamma-induced protein 10 (IP-10)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic DNA Sample (optional)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Albumin&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>X</td>
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<td></td>
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</tr>
<tr>
<td>Messenger RNA (mRNA) Sample (optional)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**a.** All screening procedures need to be completed within 35 days of the Enrollment Day.

**b.** Subjects will complete the screening though Week 12 study visit procedures. Week 12 will be the final visit in the Treatment Period and study drug will only be dispensed to subjects assigned to a 12-week treatment arm that is extended to 24-weeks treatment. Refer to Appendix E for study activities to be completed if a 12-week treatment arm is extended to 24-weeks.

- Subjects who prematurely discontinue the Treatment Period (Week 12) should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy).
- Subjects who prematurely discontinue during the Pre-Treatment Period (prior to Study Day 1) should return to the site to complete the Pre-Treatment Period Premature D/C Visit procedures.

**c.** All procedures, including pharmacokinetic sample collection, to be performed prior to first dose.

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

**e.** Subjects will need to sign an informed consent for the study prior to performing any screening or study-specific procedures.
Table 8. Part 1b: Study Activities – Pre-Treatment Period and Treatment Period (TP) (Continued)

f. Where applicable/locally available.

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

h. Height will be measured at Screening only. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes.

i. Evaluate the Study Day 1 ECG prior to dosing.

j. Urine pregnancy testing is not required after the Study 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.

k. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, Liver Ultrasound and Alpha Fetoprotein are only performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures.

l. Short Form 36, version 2 (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 following order: SF-36v2, EQ-5D-5L, HCVPRO.

m. MEMS caps will be collected upon completion of study drug (TP Week 12 or Premature D/C from Treatment).

n. If a subject's plasma HIV-1 RNA level was < 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing at an unscheduled visit for confirmation of plasma HIV-1 RNA as detailed in Section 5.5.1.2.

o. Blood samples for DAA and HIV-1 ARV pharmacokinetic assay will be collected as described in Section 5.3.2.

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

q. Done at Study Day 1/Baseline and collected for decrease in Creatinine Clearance as defined in Section 6.7.6.

r. The HIV-1 ART Dosing Card provided to subjects at the Enrollment Day will be used to record information for all doses of their HIV-1 ART medications taken during the Pre-Treatment Period.
### Table 9. Part 1b: 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/Coagulation/Urinalysis</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)</td>
<td>X</td>
<td>X</td>
<td>(Weeks 12, 16, 20, 24, 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense/Review HIV-1 ART Dosing Card</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Child-Pugh Score</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound and Alpha Fetoprotein</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>PRO Instruments</td>
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<td>X</td>
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<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HCV Resistance Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Archive Plasma Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Archive Serum Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic Samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>mRNA Sample (optional)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP-10 Sample</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 9. Part 1b: Study Activities – Post-Treatment (PT) Period* (Continued)**

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.

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. Subjects may elect to have an unscheduled visit for pregnancy testing at PT Weeks 16, 20 and 28 (if required by local RBV label) or to perform the tests at home with test kits provided by the site. Any additional pregnancy testing should be completed using the unscheduled test kit.

c. For the subjects with cirrhosis at baseline.

d. Liver Ultrasound and Alpha Fetoprotein are performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures. If a 12-week treatment arm is extended to 24-weeks treatment, HCC screening will be performed during the Post-Treatment Period at PT Wk 24 and PT Wk 48 for subjects who did not have a qualifying historical liver ultrasound.

e. PRO instruments should be administered before any study procedures and in the following order: SF-36v2, EQ-5D-5L, and HCVPRO.

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

g. 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 pegIFN/RBV only therapy and for 30 days following the end of pegIFN/RBV only therapy.

h. If a subject's plasma HIV-1 RNA level was < 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing at an unscheduled visit for confirmation for plasma HIV-1 RNA as detailed in Section 5.5.1.2.

i. Pharmacokinetic Samples for HIV ART only will be drawn at Post Treatment Weeks 2 and 4.
5.3.1.1 Study Procedures

The study procedures outlined in Table 6, Table 7, Table 8 and Table 9 are discussed in detail in this section with the exception of the collection of blood samples for pharmacogenetic analysis (Section 5.3.1.4), the collection of blood samples for pharmacokinetic analysis (Section 5.3.2), and the collection of adverse event information (Section 6.4). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to AbbVie electronically from the individual laboratory(ies).

Informed Consent and RBV Information

Signed study-specific informed consent will be obtained from each 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 (if applicable) will be taken from each subject during the Screening Visit. The subject's medical history will be updated at the Study Day 1 Visit (Treatment Period). This updated medical history collected at Study Day 1 will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Table 6 and Table 8, or upon subject discontinuation. A symptom-directed physical examination may be performed at any other visit, when necessary.
The physical examination performed on Study Day 1 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, blood pressure, pulse and body weight will be measured at the visits specified in Table 6, Table 7, Table 8 and Table 9 or upon subject discontinuation. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Study Day 1 will serve as the baseline for clinical assessment. The subject should wear lightweight clothing and no shoes during weighing. Height will only be measured at Screening; the subject will not wear shoes.

**12-lead Electrocardiogram**

A 12-lead resting ECG will be obtained at the visits indicated Table 6 and Table 8 or upon subject discontinuation from the Treatment Period (or as clinically needed). The Study 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 10 at the visits specified in Table 6, Table 7, Table 8 and Table 9.

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 drugs should be instructed to fast after midnight. Subjects whose visits occur following the morning dose of study drugs should be instructed to fast after breakfast until the study visit occurs. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study 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 [redacted]. Depending on the location of the study site, samples will be sent to one of the following addresses:

(For sites in Canada, Mexico, Puerto Rico and USA)
(For sites in France, Germany, Italy, Spain, Russia and UK)

(For sites in Australia and New Zealand)
# Table 10. Clinical Laboratory Tests

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Clinical Chemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Creatinine</td>
<td>Ketones</td>
</tr>
<tr>
<td>Red Blood Cell (RBC) count</td>
<td>Total bilirubin a, b</td>
<td>pH</td>
</tr>
<tr>
<td>White Blood Cell (WBC) count</td>
<td>Direct and indirect bilirubin</td>
<td>Protein</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Serum glutamic-pyruvic transaminase (SGPT/ALT)</td>
<td>Blood</td>
</tr>
<tr>
<td>Bands</td>
<td>Serum glutamic-oxaloacetic transaminase (SGOT/AST)</td>
<td>Glucose</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Alkaline phosphatase</td>
<td>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</td>
</tr>
<tr>
<td>Absolute Neutrophil Count (ANC)</td>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Prothrombin Time/International Normalized Ratio (INR)</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 a</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) b, c</td>
<td></td>
</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>Creatinine phosphokinase (CPK)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha fetoprotein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha2-macroglobulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haptoglobin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apolipoprotein A1 b</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg d</td>
<td>Anti-HCV Ab d</td>
<td>Human Chorionic Gonadotropin (hCG) (females)</td>
</tr>
<tr>
<td>HIV Ab d</td>
<td>FSH (females) d</td>
<td>Total insulin</td>
</tr>
<tr>
<td>Opiates d</td>
<td>Barbiturates d</td>
<td>HCV RNA</td>
</tr>
<tr>
<td>Amphetamines d</td>
<td>Cocaine d</td>
<td>Plasma HIV-1 RNA</td>
</tr>
<tr>
<td>Benzodiazepines d</td>
<td>Alcohol d</td>
<td>Hemoglobin A1 C</td>
</tr>
<tr>
<td>Phencyclidine d</td>
<td>Methadone d</td>
<td>IP-10</td>
</tr>
<tr>
<td>Urine and Serum</td>
<td></td>
<td>IL-28B d</td>
</tr>
<tr>
<td>Human Chorionic Gonadotropin (hCG) (females)</td>
<td></td>
<td>HCV genotype and subgenotype d</td>
</tr>
<tr>
<td>Total insulin</td>
<td></td>
<td>CD4, CD4%</td>
</tr>
<tr>
<td>HCV RNA</td>
<td></td>
<td>CD8, CD8%</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA</td>
<td></td>
<td>CD4:CD8</td>
</tr>
<tr>
<td>Hemoglobin A1 C</td>
<td></td>
<td>Pharmacogenetic sample (optional)</td>
</tr>
<tr>
<td>IP-10</td>
<td></td>
<td>mRNA sample (optional)</td>
</tr>
<tr>
<td>IL-28B d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV genotype and subgenotype d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4, CD4%</td>
<td></td>
<td></td>
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<tr>
<td>CD8, CD8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4:CD8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetic sample (optional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA sample (optional)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

b. Also a component of FibroTest.

c. Collected at Study Day 1 and if Creatinine Clearance < 50 mL/min as defined in Section 6.7.6.

d. Performed only at Screening.

e. Only subjects with compensated cirrhosis.
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 serum pregnancy test will be performed at Screening and Study Day 1 for all female subjects and analyzed by the central laboratory. In addition, a urine pregnancy test will be performed for female subjects at all the visits specified in Table 6, Table 7, Table 8 and Table 9. All urine pregnancy tests will be performed on-site during the study visit if there is a scheduled visit, as specified in Table 6, Table 7, Table 8 and Table 9 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 urine pregnancy test will be performed for all female subjects at the Enrollment Day (for subjects in Part 1b only) and Study Day 1. Urine pregnancy tests are not required after Study 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. FSH will be obtained at the Screening Visit for all female subjects. Confirmation of postmenopausal status by history and as measured by FSH will be determined at the Screening Visit only.

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 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 a serum pregnancy test is elected. Serum pregnancy testing will be completed by the central laboratory.

If a urine pregnancy result is positive, a confirmatory serum human chorionic gonadotropin (hCG) test should be collected and sent to the central lab.

**Hepatitis and HIV Screen**

HBsAg (hepatitis B surface antigen), anti-HCVAb and anti-HIV Ab will be performed at Screening. 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.

**Urine Screens for Drugs of Abuse and Alcohol**

Urine specimens will be tested at the Screening Visit for the presence of drugs of abuse and alcohol. The panel for drugs of abuse will minimally include the drugs listed in Table 10. A positive drug screen that in the opinion of the investigator could preclude adherence to the protocol is exclusionary, with the exception of a positive screen associated with medical short-term or chronic stable use of a 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 5.1.2.

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

**Liver Biopsy, FibroScan or Fibrotest**

At Screening, it is recommended that subjects should otherwise meet all of the inclusion criteria and none of the exclusion criteria before undergoing a liver biopsy.

Subjects who have not had a liver biopsy within 24 months prior to screening demonstrating the absence of cirrhosis, but who otherwise meet all of the inclusion criteria and none of the exclusion criteria will undergo either a liver biopsy or a non-invasive test (FibroTest/APRI or FibroScan® [where approved]) prior to enrollment to determine eligibility. Selection of liver biopsy or non-invasive testing should be based on local standard practice.

Subjects with a screening FibroTest result that is ≤ 0.72 and an APRI > 2, or a FibroTest result that is ≥ 0.73 and an APRI ≤ 2 must have a FibroScan or liver biopsy to determine the presence or absence of cirrhosis.

- If the FibroScan result is ≥ 12.5 kPa, then the subject will be considered cirrhotic and will be eligible for study participation. If the FibroScan result is < 12.5 kPa, then the subject will be considered non-cirrhotic and will be eligible for study participation.
- If the liver biopsy demonstrates the presence of cirrhosis, the subject will be considered cirrhotic and will be eligible for study participation. If the liver biopsy does not demonstrate cirrhosis, then the subject will be considered non-cirrhotic and will be eligible for study participation.
For a subject to qualify as a subject with compensated cirrhosis, documentation of cirrhosis by one of the following methods, per local standard practice, is necessary to be eligible for the study:

- Previous histologic diagnosis of cirrhosis on liver biopsy, e.g., Metavir Score of $> 3$ (including $3/4$), Ishak score of $> 4$ or on a liver biopsy conducted during screening, or
- A screening FibroTest result that is $\geq 0.73$ and an APRI $> 2$, or
- A screening FibroScan score $\geq 12.5$ kPa (FibroScan must be approved by the local regulatory agency to qualify for entrance criteria).

**Note:** Genotype 1a, null responders with cirrhosis are not eligible for enrollment in Part 1b.

**Child-Pugh Score and Category**

Subjects with compensated cirrhosis will have Child-Pugh scores assessed. The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) as shown in Table 11. Child-Pugh score will be determined at the visits indicated in Table 6, Table 7, Table 8 and Table 9.
Table 11. 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>(≤ 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>

* 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, inappropiate 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.

** 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

Clinical Assessment of Hepatic Decompensation

A clinical assessment of hepatic encephalopathy and ascites will be performed at Study Day 1 prior to dosing to confirm the subject has not progressed to hepatic decompensation since screening for all subjects who have compensated cirrhosis. Grading system guidelines for ascites are listed above in Table 11.

Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein

In order to monitor for the presence of hepatocellular carcinoma (HCC), a serum alpha fetoprotein will be assayed and an ultrasound of the liver will be performed as indicated below and in Table 6, Table 7, Table 8 and Table 9 for all subjects with compensated cirrhosis.
Subjects who do not have a historical qualifying liver ultrasound will have an ultrasound and alpha fetoprotein performed at the Screening Visit, and the Treatment Period Week 24 Visit (for subjects assigned to Arm B), or upon subject discontinuation as indicated in Table 6 and Table 8. 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.

Additionally, for subjects who do not have a qualifying historical liver ultrasound, an ultrasound and alpha fetoprotein should be performed at PT Week 12 and PT Week 36 for subjects assigned to Arm A, Arm C and Arm D, at PT Week 24 and PT Week 48 for subjects assigned to Arm B, and at unscheduled visits as needed (approximately every 6 months) for subjects in the PT Period who prematurely discontinued study drug as indicated in Table 7 and Table 9.

For subjects who qualify for the study by historical liver ultrasound (within 3 months prior to screening), additional ultrasounds and alpha fetoprotein testing should be obtained every 6 months from the qualifying liver ultrasound throughout the Treatment and Post-Treatment Periods. If additional liver ultrasound testing is required, it should be completed as an unscheduled visit.

Any positive ultrasound result suspicious for HCC will be confirmed with CT scan or MRI.

**Concomitant Medication Assessment**

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements, and any prohibited medications) from the time of signing the informed consent through 30 days after last dose of study drug will be recorded in the eCRF at each study visit as specified in Table 6, Table 7, Table 8 and Table 9. Additional information regarding concomitant medication assessment can be found in Section 5.2.3.
During the Post-Treatment Period, antiviral therapies related to the treatment of HCV, HIV, and medications prescribed in association with an SAE will be recorded in the eCRF at the visits specified in Table 7 and Table 9.

At each scheduled study visit specified in Table 6, Table 7, Table 8 and Table 9, subjects will be provided with an HIV-1 ARV dosing card. Subjects will record doses of their HIV-1 ARV regimen taken (exact dates, times, and number of pills) prior to each scheduled pharmacokinetic sample collection as specified in Table 6, Table 7, Table 8 and Table 9.

**Randomization and Assignment of Subject Numbers**

All screening activities must be completed and reviewed prior to randomization. Subjects in Part 1a and Part 2 who meet the eligibility criteria will proceed to randomization via the IRT system on Study Day 1 (Treatment Period). Subjects in Part 1b who meet the eligibility criteria will proceed to randomization via the IRT system on the Enrollment Day (Pre-Treatment Period).

Screening numbers will be unique 6-digit numbers and will begin with 100901, 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 the Enrollment Day (Part 1b) or Study Day 1 (Part 1a and Part 2) as described in Section 5.1.4 and will receive a separate unique 5-digit randomization number that will be recorded automatically in the eCRF through the IRT system. This randomization number will be used only by AbbVie for loading the treatment schedule into the database.

Subjects that were screened in Part 1 but were unable to enroll in Part 1 before enrollment was complete, will receive a new unique 6-digit screening number if screened for Part 2.
**Patient Reported Outcomes (PRO) Instruments (Questionnaires)**

Subjects will complete the self-administered PRO instruments (where allowed per local regulatory guidelines) on the study days specified in Table 6, Table 7, Table 8 and Table 9. 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, the EQ-5D-5L second, and finally the HCVPRO. PRO instruments should be completed prior to drug administration on Study 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 (SF-36v2)**

The SF-36v2 is a non-disease specific Health related Quality of Life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Scoring is totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36v2 scores indicate a better state of health. Completion of the SF-36v2 should require approximately 10 minutes.

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

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

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

The HCVPRO has been developed specifically to capture the function and wellbeing impact of HCV conditions and treatment. Preliminary validation of the instrument has been substantial and validation in trials 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.

**HIV-1 ARV Regimen Dosing Card**

A dosing card will be provided to subjects at each study visit in order to collect information for the last two doses of their HIV-1 ARV medications taken prior to each scheduled pharmacokinetic sample collection as specified in Table 6, Table 7, Table 8 and Table 9.

The dosing card that is provided to subjects on the Enrollment Day in Part 1b will be used to collect information for all doses of their HIV-1 ARV medications taken beginning at randomization until Study Day –1 and information regarding the last two doses of their HIV-1 ART medications taken prior to the Study Day –1 pharmacokinetic sampling will be entered in the eCRF. The investigator will review the dosing card completed during the Pre-Treatment Period to assess if the subject has been adherent with their HIV-1 ARV regimen during the Pre-Treatment Period and remains a suitable candidate to continue study participation as described in Section 5.1.3. In the event that the dosing card is not available at the Study Day –1 visit, the investigator may obtain dosing information via patient interview in order to assess if the subject remains a suitable candidate to continue study participation. Information regarding the last two doses taken prior to the Study Day
Pharmacokinetic sampling will not be captured on an HIV-1 ARV dosing card since the morning dose and evening dose (if applicable) will be taken on site and information regarding these doses will be recorded in source documents by the site staff and also entered in the eCRF.

In Part 1a, Part 1b and Part 2, information regarding the HIV-1 ARV doses taken on site at the Study Day 1 and Treatment Period Week 4 visit will be recorded in source documents by the site staff and also entered in the eCRF.

The information recorded on the dosing cards may be used to guide HIV-1 ARV treatment compliance discussion and to assess PK collection time relative to HIV-1 ARV dose. If poor adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Site personnel will provide training on its proper use and subjects will be instructed to complete the required information and ensure that entries are up-to-date prior to arrival at the study site on study visit days. In addition, the investigator or designee will contact the subject approximately 2 days prior to the scheduled pharmacokinetic sample collection date to review the importance of proper HIV-1 ARV administration and documentation of dosing times on the dosing card. The date and time of the phone contact will be entered into source documentation. For subject in Part 1b, the contact prior to the scheduled pharmacokinetic sample collection at Study Day 1 will be completed on site at the Study Day –1 visit rather than via phone contact.

Subjects will be required to enter the exact date, time, and number of pills taken for each medication of the ART regimen separately (each nucleoside and nucleotide reverse transcriptase inhibitor, plus the ritonavir-boosted protease inhibitor or the integrase inhibitor). The information recorded will be reviewed by the site staff; then site staff will enter the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling in the source documents and the eCRF. The completed dosing card will be collected by the site personnel on the day of the pharmacokinetic sampling and will be kept as a source record of dosage administration.
In the event that the dosing card is not available at the time of pharmacokinetic sample collection, the site may obtain dosing information via patient interview and record the information for the last 2 doses taken prior to the scheduled pharmacokinetic sampling in the source notes and the eCRF.

**MEMS Caps**

At the Study Day 1 Visit, subjects will be assigned a MEMS cap for their RBV bottle and provided with instructions for use. To ensure that a dosing event is recorded for the first dose of study drug at the site on Study Day 1, the site should place the MEMS cap on the RBV bottle before dispensing the first dose. Additionally, at each visit, site personnel should download the MEMS dosing history data from the MEMS cap, review, and counsel the patient as appropriate regarding compliance. Additional information regarding Treatment Compliance and MEMS can be found in Section 5.6.6 and Section 5.6.7, respectively.

**Study Drug Compliance for Kits**

At each visit noted in Table 6 and Table 8, study drug compliance per the number of tablets of ABT-450/r/ABT-267, ABT-333, and RBV remaining in each kit (blister card for DAAs or bottle for RBV) will be recorded in the source and entered into the IRT system. Additional information regarding treatment compliance can be found in Section 5.6.6.

**HCV RNA and HCV Resistance Testing Samples**

Plasma samples for HCV RNA levels will be collected as indicated in Table 6, Table 7, Table 8 and Table 9. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. The lower limit of detection (LLOD) is 15 IU/mL and results below LLOD are reported as "HCV RNA not detected;" the LLOQ for this assay is 25 IU/mL and results below LLOQ but detectable are reported as "< 25 IU/mL HCV RNA detected."
A plasma sample for HCV resistance testing will be collected at the study visits indicated in Table 6, Table 7, Table 8 and Table 9. Specific instructions for preparation and storage of HCV RNA and HCV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

**Flow Cytometry, HIV RNA and HIV Resistance Testing Samples**

Samples for plasma HIV-1 RNA levels and flow cytometry (including but not limited to CD4+ T-cell and CD8+ T-cell counts [absolute and percent]) will be obtained at the times specified in Table 6, Table 7, Table 8 and Table 9.

Plasma HIV-1 RNA will be measured by the central laboratory using the Abbott RealTime HIV-1 Assay. Results below the LLOD are reported as: "Not Detected." Subjects will also have blood samples drawn and archived as shown in Table 6, Table 7, Table 8 and Table 9. These samples may be used for other analyses including drug resistance testing. These samples may be tested at the discretion of AbbVie.

If a subject's HIV-1 RNA level was < 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 genotypic resistance testing. If the subject's repeat HIV-1 RNA is ≥ 500 copies/mL, the sample obtained for HIV-1 genotypic resistance testing will be analyzed.

HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assay.

If the subject's repeat HIV-1 RNA is < 40 copies/mL, then the subject will resume routine plasma HIV-1 RNA assessments as shown in Table 6, Table 7, Table 8 and Table 9 and described in Section 5.5.1.2.
Specific instructions for preparation and storage of flow cytometry, plasma HIV-1 RNA, archive and HIV resistance samples will be provided by the central laboratory, AbbVie, or its designee.

**Archive Plasma and Serum Samples**

Archive plasma and serum samples will be collected at the study visits, indicated in Table 6, Table 7, Table 8 and Table 9. Archive plasma and serum samples are being collected for possible additional analyses, including but not limited to, study drug or metabolite measurements, viral load, safety/efficacy assessments, HCV gene sequencing, HCV resistance testing, and other possible predictors of response, as determined by the Sponsor.

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

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

A plasma sample for IP-10 testing will be collected at the study visits indicated in Table 6, Table 7, Table 8 and Table 9. Specific instructions for preparation and storage of IP-10 samples will be provided by the central lab.

**5.3.1.2 Confinement**

Subjects in Part 1b will be confined to the study site and supervised for approximately 12 hours on the Study Day –1 and Treatment Period Week 4 visits. Confinement will begin in the morning prior to the AM dose of the subject's HIV-1 ART regimen and end after the collection of the 12-hour blood samples and completion of all scheduled study procedures. Strenuous activity during confinement will not be permitted.
5.3.1.3 Meals and Dietary Requirement

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.

In Part 1b, subjects will consume only the scheduled meals provided and water to quench thirst at the Study Day –1 and Treatment Period Week 4 visits. These subjects will abstain from all other food and beverage on these days. On Study Day –1 and Treatment Period Week 4, subjects should arrive at the study site in a fasted state (nothing but water by mouth for the 8 hours prior) and will be served breakfast in the morning, lunch approximately 4 hours after dosing, dinner approximately 5 hours after lunch, and a snack approximately 3 hours after dinner. The standardized breakfast should be administered prior to the (pre-dose) blood draw. Site staff will record the approximate percent of the meal ingested and the time the meal was completed on the eCRF and in source documents. It is expected that subjects will complete the whole meal. On Study Day –1, the morning dose of DRV + RTV (with or without TDF/FTC or TDF/3TC) will be administered approximately 30 minutes after the start of a standardized breakfast and the evening dose (if applicable) will be administered approximately 30 minutes after the start of an evening snack. On Treatment Period Week 4, the morning dose of study drugs (ABT-450/r/ABT-267 + ABT-333 + RBV + DRV with or without TDF/FTC or TDF/3TC) will be administered approximately 30 minutes after the start of a standardized breakfast and the evening dose of study drugs (ABT-333, RBV and DRV + RTV [for subjects on DRV BID regimen]) will be administered approximately 30 minutes after the start of an evening snack. The meal content on the intensive pharmacokinetic sampling days for each subject will contain with approximately 40% of the daily calories from fat and up to 45% of the daily calories from carbohydrates (approximately 2200 calories/day).
5.3.1.4 Blood Samples for Pharmacogenetic Analysis

**IL28B Sample**

One (required) whole blood sample for deoxyribonucleic acid (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 Study Day 1 (Treatment Period) from each subject who consents to provide the optional sample for pharmacogenetic (PG) analysis. If the optional pharmacogenetic sample is not collected at Study 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 6, Table 7, Table 8 and Table 9.

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 and DNA testing are considered exploratory and thus results will not be provided to the sites or subjects. In addition, the data obtained may not be included in the Clinical Study Report.
Specific instructions for preparation and storage of DNA and mRNA samples will be provided by the central laboratory, AbbVie, or its designee.

DNA and mRNA 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

Treatment Period Pharmacokinetic Samples

Pharmacokinetic Sparse Sampling of DAAs and HIV-1 ARVs (for subjects in Part 1a and Part 2)

Two blood samples will be collected by venipuncture at each sparse sampling study visit specified in Table 6. One sample for the pharmacokinetic assay of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, ritonavir as well as RBV and a second sample for the assay of HIV-1 ARVs as mentioned below.

Study Day 1: Two blood samples (one for DAAs and RBV, and another for HIV-1 ARVs) for the pharmacokinetic assay will be collected immediately prior to DAA and HIV-1 ART regimen dosing on Study Day 1 such that the time of sample collection is also approximately 24 hours after their HIV-1 ART regimen dosing on the morning of the day prior to DAA dosing.

All other sparse sampling visits: Two blood samples (one for DAAs and RBV, and another for HIV-1 ARVs) will be collected at all other visits as specified in Table 6.
Pharmacokinetic Sparse Sampling of DAAs and DRV/HIV-1 ARVs (for subjects in Part 1b)

Two blood samples will be collected by venipuncture at each sparse sampling study visit specified in Table 8. One sample for the pharmacokinetic assay of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, ritonavir as well as RBV and a second sample for the assay of DRV/HIV-1 ARVs as mentioned below.

Study Day 1: Two blood samples (one for DAAs and RBV, and another for DRV/HIV-1 ARVs) for the pharmacokinetic assay will be collected immediately prior to DAA and HIV-1 ART regimen dosing on Study Day 1 such that the time of sample collection is also approximately 24 hours after their HIV-1 ART regimen dosing on the morning of Study Day –1.

All other sparse sampling visits: Two blood samples (one for DAAs and RBV, and another for DRV/HIV-1 ARVs) will be collected at all other visits as specified in Table 8.

Pharmacokinetic Intensive Sampling of DAAs and HIV-1 ARVs (for subjects in Part 1a and Part 2)

Pharmacokinetic intensive samples will be collected from each subject prior to the morning dose of DAAs/HIV-1 ARVs and at 2 and 4 hours after dosing at the Treatment Period Week 4 visit as specified in Table 6. Two samples will be collected at each of the 3 time points (one for DAAs and RBV, and another for HIV-1 ARVs).

Subjects will be instructed to come to the study sites approximately 24 hours after their last morning dose of the DAAs such that the prior to morning dose samples will be collected approximately 24 hours after the morning dose of DAAs and the HIV-1 ART regimen on the day prior to the study visit.
Pharmacokinetic Intensive Sampling of DAAs and DRV/HIV-1 ARVs (for subjects in Part 1b)

- Study Day –1: Pharmacokinetic intensive samples will be collected from each subject prior to the morning dose of DRV/HIV-1 ARVs and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after dosing as specified in Table 8. Two blood samples will be collected at each of these time points (one for ritonavir and another for DRV/HIV-1 ARVs).

- Treatment Period Week 4: Pharmacokinetic intensive samples will be collected from each subject prior to the morning dose of DAAs and DRV/HIV ARVs and at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after dosing as specified in Table 8. Two samples will be collected at each of these time points (one for DAAs and RBV, and another for DRV/HIV-1 ARVs).

Subjects will be instructed to come to the study sites on Study Day –1 and Treatment Period Week 4 approximately 24 hours after their last morning dose of DRV/HIV-1 ARVs and DAAs + DRV/HIV-1 ARVs, respectively, such that the prior to morning dose samples will be collected approximately 24 hours after the morning dose of these drugs on the day prior to the study visits (Study Day –1 and Treatment Period Week 4).

Post-Treatment Period Pharmacokinetic Samples (for subjects in Part 1a and Part 2)

One blood sample for the assay of HIV-1 ARVs will be collected by venipuncture at Post-Treatment Weeks 2 and 4 as specified in Table 7.

Post-Treatment Period Pharmacokinetic Samples (for subjects in Part 1b)

Two blood samples for the assay of DRV/HIV-1 ARV will be collected by venipuncture at Post-Treatment Weeks 2 and 4 as specified in Table 9 (one for ritonavir and another for DRV/HIV-1 ARVs).
5.3.2.2 Handling/Processing of Samples

Specific instructions for collection, preparation and storage of the blood samples for the pharmacokinetic assays of ABT-267, possible ABT-267 metabolites, ABT-333, ABT-333 M1 metabolite, other possible ABT-333 metabolites, ABT-450, possible ABT-450 metabolites, ritonavir, RBV and HIV ARVs will be provided by the central laboratory, by AbbVie, 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 HIV ARVs 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:
The central laboratory will then ship the HIV ARV and DRV/HIV ARV samples to:

An inventory of the included samples will accompany the package and an electronic copy of the manifests (including subject number, study day, the time of sample collection and barcode) will be sent to AbbVie Sample Receiving or PPD and AbbVie.

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 metabolites of ABT-450 and ABT-267, and other metabolites of ABT-333 may also be determined using non-validated methods.

The samples for HIV ARVs in Part 1a and 2 for individual subjects, a group of subjects or for the whole study will be analyzed based on HCV RNA and plasma HIV-1 RNA results. The samples for darunavir in Part 1b will be analyzed for all subjects. The plasma concentrations of HIV ARVs will be determined at a separate laboratory (PPD) using validated assay methods under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

HCV virologic response will be assessed by HCV RNA in IU/mL.
5.3.3.1  **Primary Variable**

The primary endpoint is the percentage of subjects achieving SVR$_{12}$ (HCV RNA $<$ LLOQ 12 weeks after the last actual dose of study drug) in the 12-week and 24-week treatment groups.

5.3.3.2  **Secondary Variables**

The secondary endpoints are:

- The comparison of the percentage of subjects achieving SVR$_{12}$ between the 12-week and 24-week treatment groups;
- The percentage of subjects in each treatment group with on-treatment virologic failure;
- The percentage of subjects in each treatment group with post-treatment relapse;
- The percentage of subjects in each treatment group with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12.

5.3.3.3  **HCV Resistance Variables**

For subjects who do not achieve SVR$_{12}$: the variants at each amino acid position by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence, the variants at signature resistance-associated amino acid positions at available post-baseline time points by population and/or clonal nucleotide sequencing compared to the appropriate prototypic reference sequence, and the variants at each amino acid position identified by population and/or clonal nucleotide sequencing at available post-baseline time points compared to baseline sequence will be tabulated and summarized.

5.3.3.4  **HIV Resistance Variables**

If any subject develops a confirmed, quantifiable plasma HIV-1 RNA level (HIV-1 RNA $\geq$ 40 copies/mL at one assessment and $\geq$ 500 copies/mL on repeat testing) after starting
the study, the HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN) sequences, as applicable, will be analyzed.

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 test 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.

Individual plasma concentrations of HIV ARVs, if measured, will be tabulated and summarized.

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, RBV and DRV including the $C_{\text{max}}$, $T_{\text{max}}$, $C_{\text{trough}}$, and AUC will be determined by noncompartmental methods using data from subjects who participate in Part 1b. For the DAAs and RBV these parameters will be calculated at Treatment Period Week 4. For DRV and ritonavir, these parameters will be calculated on Study Day –1 (DRV without DAAs) and Treatment Period Week 4 (DRV when administered with DAAs). Additional parameters or summaries may be determined if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Variables

IL28B genotypes are associated with response to pegIFN and 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 Criteria for Initiation of Part 2

If the SVR₄ rates are at least 80%, and there is an acceptable safety profile for subjects in Part 1a, then enrollment of Part 2 may be initiated for subjects on an HIV-1 ART regimen containing ATV and RAL. The characteristics of the subjects experiencing HCV virologic failure or failure to maintain HIV-1 RNA suppression will be reviewed to determine if any changes are needed and whether changes should apply to the entire study population or only to certain HIV-1 ART regimen subgroups.

The inclusion of subjects on a DRV-based HIV-1 ART regimen (DRV QD and/or DRV BID) into Part 2 will be determined based on an evaluation of available efficacy data and
an acceptable safety profile during Part 1b, including the rate of failure to maintain HIV-1 RNA suppression for each DRV treatment strategy during the period of co-administration with study treatment.

5.5 Removal of Subjects from Therapy or Assessment

5.5.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, a subject may be discontinued 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 a subject in Part 1b prematurely discontinues during the Pre-Treatment Period (prior to receiving study drugs), the procedures outlined for the Pre-Treatment Period Premature D/C Visit should be completed as defined in Table 8. Subjects that discontinue during the Pre-Treatment Period will not proceed to the Post-Treatment Period.

If a subject prematurely discontinues during the Treatment Period, the procedures outlined for the applicable Premature D/C Visit should be completed as defined in Table 6 and Table 8. 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 with the exception of add-on pegIFN/RBV for subjects ongoing in a discontinued treatment arm.

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 dosing dates of the first through last doses of study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC 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, plasma HIV-1 RNA, HIV resistance and PROs.
If a subject discontinues from the Post-Treatment Period, the subject should return for a Post-Treatment Discontinuation Visit as defined in Table 7 and Table 9. The reason for discontinuation from the Post-Treatment Period will also be recorded on the eCRF.

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 continue to be monitored for SVR in the Post-Treatment Period as described in Section 5.1.5. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry.

5.5.1.1 HCV Virologic Failure Criteria for Subject Management

The following criteria will be considered evidence of HCV virologic failure for the purpose of subject management. 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;
- 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.
Subjects should remain on study treatment until the HCV virologic failure has been confirmed.

5.5.1.2 Failure to Maintain HIV Virologic Suppression

Criteria for failure to maintain HIV-1 RNA suppression during the Treatment Period for the purpose of subject management are outlined below.

HIV-1 RNA will be assessed at each scheduled study visit as detailed in Table 6 and Table 8. If a subject's HIV-1 RNA is $\geq 40$ copies/mL, the HIV-1 RNA should be repeated in approximately 2 weeks, and every 2 weeks thereafter until the subject meets criteria for study treatment discontinuation as noted below or the plasma HIV-1 RNA is $< 40$ copies/mL. At the time the repeat HIV-1 RNA is drawn, a sample for HIV genotypic resistance testing should also be obtained. The sample obtained for HIV genotypic resistance testing will be analyzed if the subject's repeat plasma HIV-1 RNA is $\geq 500$ copies/mL.

A subject should remain on HCV study treatment and his/her current ART regimen while the failure to maintain HIV virologic suppression is being confirmed. Results of the resistance testing will be sent to the investigator in order to guide further HIV-1 ART regimen selection.

Subjects should be discontinued from study drug if they meet one of the following failure to maintain HIV virologic suppression criteria during the Treatment Period:

- HIV-1 RNA $\geq 40$ copies/mL followed by a repeat plasma HIV-1 RNA $\geq 200$ copies/mL, or
- 3 consecutive plasma HIV-1 RNA values $\geq 40$ copies/mL.

If an investigator wishes to maintain study treatment for a subject meeting one of the above criteria for failure to maintain plasma HIV-1 RNA suppression, approval must be obtained from the AbbVie Study Designated Physician. Additionally, if the investigator wishes to change the HIV-1 ART regimen for a subject meeting one of the above criteria
for failure to maintain plasma HIV-1 RNA suppression during the Treatment Period, it must be discussed with the AbbVie Study Designated Physician prior to the change being made.

Clinical management of failure to maintain HIV-1 RNA suppression during the Treatment Period will be handled by the investigator according to current HIV treatment guidelines (e.g., DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents) and local standard of care. Possible HIV-1 ART salvage regimens should take into account the results of HIV genotypic resistance testing, the unique characteristics of the subject, and the subject's HIV treatment history as well as known and/or anticipated drug interactions with study drugs. If no reasonable salvage HIV-1 ART regimen compatible with continued study treatment is deemed available for an individual subject meeting a failure to maintain HIV-1 RNA suppression criterion, then the subject must discontinue study treatment.

Since transient, low-level viremia in plasma HIV-1 RNA may be observed in individuals on HIV-1 ART in the absence of HIV-1 virologic failure, a subject with an HIV-1 RNA value ≥ 40 copies/mL followed by a single confirmatory HIV-1 RNA ≥ 40 and < 200 copies/mL may remain on HCV study treatment and his/her current HIV-1 ART regimen at the discretion of the investigator. The investigator will work with the subject to resolve possible adherence issues. If the subject remains on treatment, then the HIV-1 RNA should be repeated in approximately 2 weeks for further confirmation.

During the Post-Treatment Period, HIV-1 RNA will be assessed at each scheduled visit as detailed in Table 7 and Table 9. Clinical management of failure to maintain HIV-1 RNA suppression during the Post-Treatment Period will be managed by the investigator according to current HIV treatment guidelines (e.g., DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents) and local standard of care. The investigator may determine when a repeat HIV-1 RNA sample should be drawn. When a repeat HIV-1 RNA sample is drawn, a sample for HIV genotypic resistance testing should also be obtained and analyzed if the subject's repeat plasma
HIV-1 RNA is ≥ 500 copies/mL. Results of the resistance testing will be sent to the investigator in order to guide further HIV-1 ART regimen selection.

If the investigator wishes to change the HIV-1 ART regimen for a subject during the Post-Treatment Period, the investigator should notify the AbbVie Study Designated Physician prior to the change being made and provide the reason for the HIV-1 ART regimen switch.

### 5.5.1.3 HCV Treatment Adjustment Criteria

AbbVie will evaluate HCV RNA levels throughout the Treatment and Post-Treatment Periods in Part 1 and Part 2 of this open-label study.

The HCV treatment adjustment criteria will be assessed once subjects start to complete study drug. In the 12-week treatment group (i.e., Arms A, C, or D), if ≥ 5 of the first 10 subjects who complete 12 weeks of therapy experience HCV virologic relapse (confirmed HCV RNA ≥ LLOQ after completing treatment for a subject with HCV RNA < LLOQ at the end of treatment), then AbbVie 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. 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), presence of cirrhosis (cirrhotic or non-cirrhotic), IL28B genotype, or prior HCV treatment history (treatment-naïve or pegIFN/RBV-experienced) and/or type of response to previous pegIFN/RBV treatment.

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 (see Appendix E for the 24-week Study Activities table). For groups of subjects whose treatment is not extended to 24 weeks, enrollment in those treatment arms may continue.
Evaluations of HCV relapse as defined above will continue throughout Part 1 of the study until all subjects complete or discontinue study drug.

The evaluation described above will continue once subjects in Arm A of Part 2 complete 12 weeks of treatment. An additional assessment of HCV relapse will be conducted once 50 subjects assigned to the 12-week treatment arm (Arm A) in Part 2 reach Post-Treatment Week 4 or discontinue study drug. If the HCV virologic relapse rate in these 50 subjects is greater than 20%, then AbbVie 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 HCV virologic 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 HCV virologic relapses occur broadly across all subgroups). Similar assessments to extend the 12-week treatment arm may be performed at other time points based on ongoing monitoring of HCV virologic relapse rates.

### 5.5.1.4 HIV Treatment Adjustment Criteria

If ≥ 2 subjects within an HIV-1 ART regimen subgroup (atazanavir, raltegravir, darunavir QD, or darunavir BID) experience failure to maintain HIV-1 virologic suppression as described in Section 5.5.1.2 during Part 1 for any reason, then that HIV-1 ART regimen will have enrollment halted in Part 1 pending further review. Subjects currently within the Treatment Period may be allowed to continue study drug administration at the discretion of the investigator.

### 5.5.2 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.

5.6 **Treatments**

5.6.1 **Treatments Administered**

Each dose of open-label DAA study drug will be dispensed in the form of tablets (ABT-450/r/ABT-267, ABT-333 and RBV) at the visits listed in Table 6 and Table 8.

The doses are as follows:

- ABT-450/r/ABT-267 will be provided by AbbVie as 75 mg/50 mg/12.5 mg tablets. ABT-450/r/ABT-267 will be taken orally as 2 tablets once daily in the morning which corresponds to a 150 mg ABT-450/100 mg ritonavir/25 mg ABT-267 dose QD.

- ABT-333 will be provided by AbbVie 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 AbbVie as 200 mg tablets. RBV has weight-based dosing 1000 or 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, or as 3 tablets in the morning and 2 tablets in the evening, which corresponds to a 1000 mg total daily dose. For subjects weighing 75 kg or more, RBV may be taken orally as 3 tablets in the morning and 3 tablets in the evening which corresponds to a 1200 mg total daily dose). If a subject's weight changes above or below 75 kg during the study, the weight-based RBV daily dose may be changed at the investigator's discretion.

At Study Day 1, subjects will be administered study drugs by the study site personnel and receive instructions for self-administration of all study drugs through the end of the Treatment Period depending on the duration of their assigned treatment. All subjects will be instructed to come to the study site approximately 24 hours after their last morning dose of the HIV-1 ART regimen so that the morning dose of their HIV-1 ART regimen on Study Day 1 can be administered along with the morning dose of study drugs at the study
site. The date and time of dosing will be recorded in source documents and in the eCRF for the study drugs and the HIV-1 ART regimen. Subjects that were taking atazanavir in the evening prior to enrollment or DRV QD in the evening at the time of screening must switch to morning administration beginning at Study Day 1 (Part 1a and Part 2) and the Enrollment Day (Part 1b), respectively, so that the atazanavir and DRV QD is taken together with the morning dose of ABT-450/r/ABT-267 starting on Study Day 1.

On the day of intensive pharmacokinetic sampling at the Study Day –1 (in Part 1b), subjects will be instructed to come to the study site approximately 24 hours after their last morning dose of HIV-1 ARVs. The morning dose and evening dose (if applicable) of the HIV-1 ART regimen will be administered at the study site on the day of intensive pharmacokinetic sampling. The date and time of dosing will be recorded in source documents and in the eCRF for the HIV-1 ART regimen.

On the day of intensive pharmacokinetic sampling at the Treatment Period Week 4 visit (in Parts 1a, 1b and 2), subjects will be instructed to come to the study site approximately 24 hours after their last morning dose of DAAs/HIV-1 ARVs. Study drugs along with the morning dose and evening dose (if applicable for subjects in Part 1b) of the HIV-1 ART regimen will be administered at the study site on the day of intensive pharmacokinetic sampling. The date and time of dosing will be recorded in source documents and in the eCRF for the study drugs and HIV-1 ART regimen.

Subjects will be instructed to take study medication at the same time(s) every day. All study drugs should be taken with food. Subjects will be instructed to bring in all blister cards and bottles at each visit.

Beginning with Study Day 1, the site will use the IRT system to obtain the study drug kit numbers to dispense at the study visits specified in Table 6 and Table 8. 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. The site will also contact the IRT system to provide study drug return information for each kit at the visits specified in Table 6 and Table 8 (see Section 5.6.8).
All subjects who receive at least one dose of DAAs and who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be discontinued from study treatment.

5.6.2 **Identity of Investigational Products**

Information about the study drugs to be used in this study is presented in Table 12.

<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>AbbVie</td>
<td>Oral</td>
<td>Tablet</td>
<td>75 mg/50 mg/12.5 mg</td>
</tr>
<tr>
<td>ABT-333</td>
<td>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>

5.6.2.1 **Packaging and Labeling**

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

The blister cards indicate which drugs on the card should be taken in the morning (both ABT-450/ritonavir/ABT-267 tablets and 1 ABT-333 tablet) with a picture of a sun and which should be taken in the evening (1 ABT-333 tablet) with a picture of a moon. Additional study drug is identified on each blister card as "X."

Ribavirin 200 mg tablets will be supplied to the site in bottles containing 168 tablets each.
All study drugs will be labeled as required per country requirements. The labels must remain affixed to the primary and potential secondary packaging material. All blank spaces should be completed by site staff prior to dispensing to subject.

5.6.2.2 Storage and Disposition of Study Drugs

Table 13. 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 and ABT-333 blistercards</td>
<td>15° to 25°C (59° to 77°F)</td>
</tr>
<tr>
<td></td>
<td>Australia and New Zealand: 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 and New Zealand: 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 AbbVie. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.6.3 Method of Assigning Subjects to Treatment Groups

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

Subjects who 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 for each drug dispensing visit (beginning at Study Day 1) and a unique randomization number (at Study Day 1 for subjects in Part 1a and Part 2, and at the Enrollment Day for subjects in Part 1b). 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.

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

5.6.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.1. Study drug dosing will be initiated at the Study Day 1 Visit.

ABT-450/r/ABT-267 will be dosed QD and ABT-333 will be dosed BID. Thus with normal dosing, 2 ABT-450/r/ABT-267 tablets and 1 ABT-333 tablet should be taken in the morning, and 1 ABT-333 tablet should be taken in the evening.

RBV will be dosed BID, e.g., 2 to 3 tablets taken in the morning, and 3 RBV tablets 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.

All study drugs should be dosed together with the HIV-1 ART regimen, i.e., the AM dose of ABT-450/r/ABT-267, ABT-333 and RBV must be taken together with the AM dose of the subject's HIV-1 ART regimen and the PM dose of ABT-333 and RBV must be taken together with the PM dose of the subject's HIV-1 ART regimen if applicable. Subjects receiving atazanavir or darunavir QD/BID must take the atazanavir, darunavir QD or morning dose of darunavir BID in the morning along with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333) and RBV. Details regarding dosing instructions for HIV-1 ARVs are described in Section 5.2.3.2.

5.6.5 Blinding

This is an open-label study.
5.6.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. All study drugs will be dispensed to 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 along with the morning dose of the HIV-1 ART regimen at the site at the Study Day 1 Visit as well as at the Treatment Period Week 4 Visit. Subjects in Part 1b will administer the morning and evening dose (if applicable) of their HIV-1 ART regimen at the site at the Study Day –1 Visit. The start and stop dates of all study drugs and HIV-1 ARVs will be recorded in the source documents and eCRFs.

The subjects will be instructed to bring all bottles and blister cards of study drug (full, partial or empty) and MEMS caps for RBV to the study site at each study visit. If po or adherence is noted, the subject should be counseled and this should be documented in the subject's source.

Study drug should be returned to the site for IRT reconciliation at the study visits as indicated in Table 6 and Table 8. Study site personnel will inspect the contents of the bottles and blister cards and record the status of each one as well as the exact number of remaining tablets of ABT-450/r/ABT-267 and ABT-333 or tablets of RBV and the date of reconciliation in the IRT system. Returned study drug should not be re-dispensed to the subject. If a study drug dispensation visit occurs early (e.g., due to a planned vacation that will occur at the time of a scheduled drug dispensation visit), the subject should be instructed to keep and finish the remaining study drugs from the previous dispensation visit prior to beginning the newly dispensed bottles and blister cards.
The date of last dose of all study drugs will be recorded in the source documents and the appropriate eCRF.

5.6.7 **MEMS Caps**

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

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 Study Day 1 Visit (Treatment Period), subjects will be assigned a MEMS cap that will be placed on the RBV bottle in place of the original cap. The original cap should be saved so it can be placed back on the bottle upon return by the subject in order to store returned study drug.

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

The subjects will be instructed to open the bottle when it is time to take the medicine, to remove the proper amount of medication and promptly close the bottle, then ingest the prescribed dose. The subject should be instructed to transfer the MEMS cap to the next full bottle of study drug at the same time that they take their last dose from the current in-use bottle.
The MEMS cap will be collected from the subject at the completion of study drugs as applicable. If MEMS caps cannot be imported into a participating study country or if other issues preclude the use of MEMS cap at a site(s), dosing histories will not be obtained using the MEMS caps for subjects enrolled at that site(s). Additional instructions for the subject on how to use the MEMS cap will be provided by AbbVie.

5.6.8 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. Final accountability will be performed by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug blister card/bottle, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the blister card/bottles are 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 and an explanation of the reason for the misplaced or damaged study drug will be documented within the IRT system. Study drug start/end dates will be documented in the subject's source documents and recorded on the appropriate eCRF. The status of each blister card/bottle, number of tablets remaining in each one returned, and the date of reconciliation will be documented in the IRT system at the visits specified in Table 6 and Table 8. The monitor will review study drug accountability on an ongoing basis.

Upon completion of or discontinuation from the Treatment Period, all original blister cards and bottles (containing unused study drugs) will be returned to AbbVie (or designee) or destroyed on site. All destruction procedures will be according to
instructions from AbbVie and according to local regulations following completion of drug accountability procedures. The number of tablets of each type of study drug returned in each blister card and each bottle will be noted in the IRT system or on a drug accountability log (if appropriate). Labels must remain attached to the containers.

5.7 Discussion and Justification of Study Design

5.7.1 Discussion of Study Design and Choice of Control Groups

Based upon the results of three Phase 2 studies, Studies M12-267, M12-746, and 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-experienced (null responders, partial responders or relapsers), HCV GT 1-infected adults with HIV coinfection in this multicenter randomized, open-label, duration ranging, Phase 3 study.

Alternative trial designs were considered, including an open-label pegIFN/RBV controlled and placebo controlled study designs.

Global experts in infectious diseases, hepatology and clinical trials were consulted and expressed concerns about enrolling and retaining subjects in a study with an open-label pegIFN/RBV comparator arm. There was general consensus among experts that enrolling subjects in a study with a pegIFN/RBV containing regimen would be a major challenge as many physicians and patients are delaying HCV treatment because of the limited efficacy and significant toxicities associated with pegIFN/RBV in anticipation of better tolerated, and more efficacious pegIFN free regimens. Furthermore, retention of an adequate number of the subjects randomized to an interferon containing regimen for analysis would be difficult. Patients initially attracted to a study evaluating an IFN-free regimen but randomized to the IFN-containing regimen may be inclined to prematurely discontinue treatment or to adhere less strictly to the study regimen and study procedures because of the toxicities associated with and the duration of the regimen. Any premature discontinuation must be counted as a treatment failure and, thus, the SVR rate for the pegIFN-containing comparator arm will likely be inaccurately low. Furthermore,
premature discontinuation of a large portion of those in the comparator arm may give an inaccurate safety profile to compare with the study regimen. Thus, anticipated higher rates of discontinuation and non-compliance in the active comparator arm would affect the quality and validity of the safety and efficacy analyses, and bias the study in favor of the investigational combination DAA regimen.

A placebo-controlled trial was not considered to be appropriate in HCV/HIV-1 coinfected subjects because HCV/HIV-1 coinfected patients have a higher risk of liver disease progression compared to those with HCV alone. Though comparison of active drug to placebo in a blinded fashion would provide an effective method to assess safety and tolerability of the DAA + RBV regimen, the need to double blind for ritonavir which is both a component of the ABT-450/r/ABT-267 co-formulation as well as a component of the HIV-1 ART regimens allowed in this study was not feasible.

In the proposed M14-004 study design, subjects will be randomized to receive either 12 or 24 weeks treatment duration of the AbbVie HCV DAA combination regimen plus ribavirin. Though comparison of the efficacy of this IFN-free regimen to a pegIFN/RBV may be plausible, a comparison of safety profiles would not be fair given that the safety profile of the IFN-containing regimen would be expected to be very different from that of an IFN-free regimen.

A comparative arm with a different duration of therapy (i.e., 24 weeks versus 12 weeks) provides comparative data supporting efficacy of the selected treatment duration. While a 12-week treatment is considered adequate for subjects with HCV monoinfection without cirrhosis, as illustrated by clinical data obtained to date in Study M12-267, Study M12-746, and Study M11-652, HCV/HIV-1 coinfected patients with and without baseline cirrhosis may require longer durations of therapy. Inclusion of a 24-week arm in this study allows assessment of the treatment duration response relationship in this population.

Given the above considerations, the study design will maximize the probability of success in this harder-to-cure population. DMC oversight will ensure the safety of all subjects.
Also, the M14-004 study design will maximize the benefit of an IFN-free treatment for all study subjects while avoiding the limitations of study designs employing pegIFN-based therapy.

5.7.2 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.

5.7.3 Justification of Primary Endpoint Success Criteria

The historical SVR rate, as reported in the peginterferon alfa-2a US Prescribing Information (USPI),31 for pegIFN and RBV in HIV-seropositive adults with HCV genotype 1 infection who were HCV treatment-naïve is 29% (51/176) with a 95% confidence interval of (22.3%, 35.7%).

For a regimen to be considered superior to the historical SVR rate for pegIFN and RBV, the lower bound of the confidence interval for the SVR rate for that regimen must exceed the upper confidence bound of the historical SVR rate for pegIFN and RBV therapy presented above (i.e., 36%).

5.7.4 Suitability of Subject Population

Study M14-004 is planned to enroll both HCV treatment-naïve and treatment-experienced subjects with genotype (GT) 1 HCV infection and HIV-1 coinfection.

Naïve subjects are included to assess the safety and efficacy of the DAA regimen in these subjects with HCV GT 1/HIV-1 co-infection. The optimal treatment duration of a DAA combination regimen in this patient population remains unclear.
Three study populations of HCV genotype 1 treatment-experienced subjects with genotype 1 chronic HCV will be enrolled in this study: null-responders, partial responders, and relapsers. These categories of treatment-experienced subjects are included to gain experience with a 3 DAA regimen in each type of treatment-experienced subjects with HCV GT 1/HIV-1 coinfection. Because other HCV treatments often lead to disparate rates of SVR in the three populations, it is appropriate to include each group in the current study.

The protocol specifically excludes subjects with any prior exposure to DAA HCV protease inhibitors, since prior DAA therapy may have selected mutations which may negatively impact the antiviral response to the DAAs in this study.

The efficacy of the DAA regimen has been evaluated in an HCV-monoinfected, cirrhotic and non-cirrhotic adult population. Because identification of the appropriate treatment duration with the DAA regimen and characterization of the benefit-risk ratio in patients with HCV/HIV-1 coinfection must be clearly understood in a representative population, HCV/HIV-1 coinfected subjects with and without compensated cirrhosis are being included in Study M14-004.

Subjects with decompensated cirrhosis and HCV/HIV-1 coinfection are not being included until safety and efficacy has been described in HCV/HIV-1 coinfected populations with compensated cirrhosis. 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 the additional 12 weeks of treatment.

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 HIV-1 coinfection.
Unanticipated pharmacokinetic or other adverse effects not observed in prior dosing in healthy volunteers or HCV-infected subjects 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. Hence, this protocol will enroll subjects with a BMI up to 38 kg/m².

5.7.5 **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 and RBV and found to be generally safe and well tolerated. The regimen and doses used in this study were administered in Phase 3 studies of HCV genotype 1 mono-infected subjects. These studies included pegIFN/RBV treatment-naïve and treatment-experienced subjects with or without cirrhosis (Child-Pugh A). Among treatment-naïve subjects the SVR₁₂ rates observed across the Phase 3 studies were consistently ≥ 90% with 12 weeks of treatment duration, even among subjects with compensated cirrhosis. As noted in Section 3.0, overall the regimen was associated with high SVR₁₂ rates and was well tolerated.

**ABT-450/r**

ABT-450/r 150/100 mg dose using ABT-450/r/ABT-267 co-formulation tablets were used for Phase 3 studies of ABT-450/r/ABT-267 + ABT-333 with/without RBV in HCV genotype 1 infected subjects, including those with cirrhosis (Child-Pugh A). ABT-450/r dose (150/100 mg QD) and formulation (ABT-450/r/ABT-267 co-formulation tablets) for this study will be the same as used in Phase 3 studies.
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**

ABT-267 at a 25 mg dose using ABT-450/r/ABT-267 co-formulation tablets were used for Phase 3 studies of ABT-450/r/ABT-267 + ABT-333 with/without RBV in HCV genotype 1 infected subjects, including those with cirrhosis (Child-Pugh A). ABT-267 dose (25 mg QD) and formulation (ABT-450/r/ABT-267 co-formulation tablets) for this study will be the same as used in Phase 3 studies.

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-333**

ABT-333 250 mg BID dose using optimized tablets were used for Phase 3 studies of ABT-450/r/ABT-267 + ABT-333 with/without RBV in HCV genotype 1 infected subjects, including those with cirrhosis (Child-Pugh A). ABT-333 dose (250 mg BID) and formulation (ABT-333 optimized tablets) for this study will be the same as used in Phase 3 studies.

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 mg to 1200 mg, divided twice daily, and is 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 as noted in Section 6.7.4.  

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30-32
In addition, this dose was studied in the absence of pegIFN in subjects with chronic hepatitis C infection in multiple Phase 2 (Studies M12-267, M12-746, M12-998 and M11-652) and Phase 3 studies (Studies M11-646, M13-098, M13-099, M14-002, M13-389 and M13-961), and was found to be generally safe and well tolerated.

The recommended dose for ribavirin in combination with pegIFN-alfa-2a in HCV GT 1-infected adults with HIV-1 coinfection is either 800 mg PO total daily dose or a dose based on weight (< 75 kg, 1000 mg total daily dose; ≥ 75 kg, 1200 mg total daily dose). The European AIDS Clinical Society (EACS) 2012 Guidelines recommend initial weight-based dosing of ribavirin for all HCV genotypes in the subjects with HCV/HIV-1 coinfection. In HCV GT 1 monoinfection, patients who receive pegIFN plus weight-based dosing of ribavirin have significantly higher SVR rates than those receiving fixed lower doses of ribavirin.

Early trials evaluating pegIFN/RBV treatment in HCV/HIV-1 coinfected patients used fixed lower doses of ribavirin (800 mg) because of concerns of potential toxicity and drug interactions, in particular, with the nucleoside analogue, AZT (Zidovudine, Retrovir®). These drug interactions are less problematic with current, and commonly used tenofovir-based ART regimens versus older, AZT-inclusive ART regimens.

In each Phase 2 study evaluating AbbVie DAAs in infected subjects in whom RBV was administered, weight-based ribavirin dosing has been employed. Safety analyses from these Phase 2 studies have shown that all of AbbVie DAA regimens in combination with weight-based ribavirin were well tolerated in both treatment-naïve and prior null responder subjects. The efficacy of AbbVie DAAs in combination with a fixed lower dose of ribavirin (800 mg/day) has not been evaluated in Phase 2 studies.

Hence in this study, weight based ribavirin (< 75 kg, 1000 mg total daily dose; ≥ 75 kg, 1200 mg total daily dose) will be administered to HCV GT 1/HIV-1 coinfected adults with appropriate ribavirin dose modifications permitted if significant anemia develops.
The maximum RBV dose administered in this study will not exceed 1200 mg, divided twice daily for 24 weeks.

**Coadministration of DAAs with HIV ART**

Drug-drug interaction studies of the 3-DAA regimen of ABT-450/r, ABT-267 and ABT-333 coadministered with tenofovir DF plus emtricitabine, atazanavir plus ritonavir, darunavir plus ritonavir, and raltegravir have been conducted. Based on the pharmacokinetic and safety data available from these studies, no dose adjustment is needed during coadministration of ABT-450/r, ABT-267 and ABT-333 with tenofovir plus emtricitabine, atazanavir plus ritonavir, and raltegravir. During co-administration of darunavir 800 mg QD or 600 mg BID (with RTV 100 mg administrated with the evening dose of darunavir 600 mg BID) with 3-DAA regimen, darunavir $C_{\text{max}}$ and AUC were not significantly affected, but darunavir $C_{\text{trough}}$ levels were about 43% to 50% lower. However, darunavir exposure ($\text{AUC and } C_{\text{trough}} \left[C_{12} \text{ or } C_{24}\right]$) during co-administration of darunavir 600 mg + ritonavir 100 mg BID with the 3-DAA regimen (morning dose of ritonavir 100 mg was provided by the 3-DAA regimen) were comparable to those achieved with administration of darunavir 800 mg + ritonavir 100 mg QD regimen without DAAs. Thus during co-administration with the 3-DAA regimen, the darunavir 600 mg + ritonavir 100 mg BID regimen could be an alternative to darunavir 800 mg + ritonavir 100 mg QD regimen to provide comparable darunavir exposure. In this study, subjects receiving darunavir QD regimen will be randomized to receive darunavir 800 mg QD or darunavir 600 mg BID to evaluate the beneficial effect of darunavir dose modification in prevention of any potential HIV-1 failures due to drug-drug interaction. Also, due to different elimination pathways of lamivudine and DAAs, no dose adjustment is expected to be needed for lamivudine and DAAs during coadministration. Detail information about these studies can be found in Section 3.0.

5.8 **Data Monitoring Committee**

An independent Data Monitoring Committee (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 membership, which will include individuals with extensive experience in the management of patients with chronic hepatitis C, and member responsibilities. The DMC will receive interim summaries of safety and virologic data according to a schedule and in a format specified in the charter. 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, meets protocol specific criteria (see Section 6.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

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

### 6.1.2 Serious Adverse Events

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

<table>
<thead>
<tr>
<th>Death of Subject</th>
<th>An event that results in the death of a subject.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-Threatening</td>
<td>An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.</td>
</tr>
<tr>
<td>Hospitalization or Prolongation of Hospitalization</td>
<td>An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.</td>
</tr>
<tr>
<td>Congenital Anomaly</td>
<td>An anomaly detected at or after birth, or any anomaly that results in fetal loss.</td>
</tr>
</tbody>
</table>
**Persistent or Significant Disability/Incapacity**

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

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

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

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

### 6.2 Adverse Event Severity

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

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

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

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

The investigator will use the following definitions to assess the relationship of the adverse event to the use of DAAs (ABT-450/r/ABT-267 and ABT-333), and RBV. The investigator will also use the following definitions to assess the relationship of the adverse event to the use of pegIFN, if applicable:

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

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

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

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for 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 Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

For safety concerns, contact the Antiviral Safety Team at:
For any subject safety concerns, please contact the physician listed below:

Primary Study Designated Physician:

MD, MPH

Telephone Contact Information:

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the 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 Study 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 5.5.1). Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.5. Information regarding a pregnancy occurrence in a study subject and the
outcome of the pregnancy will be collected. 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 AbbVie as having a "reasonable possibility" of being related to the study drug (Section 6.3). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

Study drugs should not be interrupted for toxicity management for more than 7 consecutive days. If study drugs need to be interrupted for more than 7 consecutive days and the investigator believes that permanent discontinuation of study drug is not warranted then the AbbVie Study Designated Physician should be contacted to discuss continued study drug administration and medical management.

If study drugs are stopped or interrupted at any time, subjects who were not receiving the ritonavir portion of their ART regimen (Section 5.2.3.2) while on study drug, should immediately restart the ritonavir as part of the ART regimen. The Investigator should ensure that these subjects are reminded of the need to restart the ritonavir portion of their ART regimen.
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) and the DMC have the data necessary for signal detection at safety data review and DMC meetings. The Investigator should ensure that any study drug interruptions or RBV dose modifications and consequent required adverse events are entered into the appropriate eCRFs.

Safety surveillance, via regular review of safety labs will be performed by AbbVie 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.

If pegIFN and RBV are added to the regimen:

Prior to initiating treatment with add-on pegIFN and RBV, the Investigator must assess if the regimen is appropriate for the subject based on locally approved label and treatment guidelines. Treatment with pegIFN/RBV will be at standard doses based on the locally approved label and will be under the supervision of the Investigator or designee. The Investigator or designee will be responsible for the management of pegIFN/RBV toxicities consistent with their labels.

The toxicity management guidelines below should be followed from the start of study drug administration through completion, or discontinuation, of study drug.

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 6.7.4], ALT parameters [Section 6.7.5], creatinine clearance parameters [Section 6.7.6] and known complications of HIV Infection and AIDS [Section 6.8]) may continue study drugs with follow-up per study protocol.
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 abnormalities of uric acid, phosphorus, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes), if a subject experiences a Grade 3 or greater abnormal laboratory parameter during the Treatment Period, the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically without interruption of study drug, or whether study drugs should be interrupted and the laboratory parameter followed until it improves. If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued.

Decreases in serum hemoglobin or in calculated creatinine clearance or elevations of serum ALT should be managed according to the guidance in Sections 6.7.4, 6.7.5 and 6.7.6 below. Grade 3 or greater abnormalities of uric acid, phosphorus, total cholesterol, triglycerides or glucose (in subjects with a history of diabetes) should be managed medically as appropriate and do not require confirmation or study drug interruption, unless deemed necessary by the investigator.

**Severe Adverse Events or Serious Adverse Events**

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

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

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

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

6.7.3 Management of Elevated Bilirubin

Asymptomatic elevation of indirect (unconjugated) bilirubin is anticipated in this study due to the inhibition of UDP glucuronosyl transferase (UGT) from atazanavir, OAT1B1 from ABT-450 and hemolysis from ribavirin. Based on these mechanisms, elevations in direct bilirubin would be atypical; therefore, elevations in bilirubin which are predominantly direct should be worked up per the investigator's usual management.

Subjects may be maintained on study drug for elevations in total bilirubin which are predominantly indirect bilirubin and are not accompanied by a Grade 3 or higher ALT elevation. These elevations in indirect bilirubin are expected to be transient and asymptomatic. For Grade 3+ total bilirubin levels which are predominantly indirect and the subject is symptomatic, the investigator may manage per his/her discretion or can refer to Section 6.7.2.

6.7.4 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 14. Management will be different for subjects without a history of known cardiac disease and subjects with or without cardiac disease.
If a subject experiences a hemoglobin decrease (as outlined in Table 14), a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 14 should be followed.

Use of hematologic growth factors (such as erythropoietin, filgrastim) or blood transfusions are not recommended; and are permitted only with the prior approval of the AbbVie Study Designated Physician.

Alternate management of hemoglobin decreases requires the prior approval of the AbbVie Study Designated Physician.
### Table 14. 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>&lt; 10.0 g/dL, but ≥ 8.5 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>&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>
</tbody>
</table>

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

| Hemoglobin decrease of ≥ 2 g/dL during a 4-week treatment period (Hb ≥ 10 g/dL) | Study drug may be continued. Reduce RBV dose. Continue to monitor hemoglobin levels per protocol. If 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. |
| < 10.0 g/dL, but ≥ 8.5 g/dL | 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 hemoglobin < 10 g/dL despite 4 weeks at the reduced RBV dose, permanently discontinue all study drugs (if alternative management of study drugs is considered then the SDP should be contacted); manage as medically appropriate. Enter the discontinuation into appropriate eCRFs and create corresponding adverse event. |
| < 8.5 g/dL | Permanently discontinue all study drugs; manage subject as medically appropriate. Enter discontinuation into appropriate eCRFs and create corresponding adverse event (AE). |
6.7.5 Management of Transaminase Elevations

Transient asymptomatic Grade 3 – 4 ALT elevations have been observed in approximately 1% of subjects receiving ABT-450/r-containing regimens.

If a subject experiences a post-baseline increase in ALT to > 5 × ULN that is increased from the previous measurement, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN, the recommendations below should be followed:

- Evaluate for alternative etiology of ALT elevation: Update medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Discontinue study drugs if any of the following is observed at any time:
  - ALT level is ≥ 20 × ULN,
  - Increasing direct bilirubin, increasing INR, or onset of symptoms/signs of hepatitis.

Alternative management of ALT increases requires approval of the AbbVie Study Designated Physician.

6.7.6 Creatinine Clearance

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

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

In addition, the following should occur:

1. Concomitant medication dose reduction based on CrCl should be done (if applicable).

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

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

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

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

If CrCl does not improve by 2 scheduled study visits (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.

6.8 Collection of Data Regarding Known AIDS-Associated Opportunistic Infections

HIV-1 infected subjects participating in clinical trials may develop infections typically associated with AIDS. Appendix D contains a list of these known AIDS-associated opportunistic infections (OI). The events listed in Appendix D will be summarized as HIV-related events, not as adverse events.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol, except when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying the Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie personnel:

Primary Contact:  Alternate Contact:

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

8.1  Statistical Analysis Plans

An interim analysis of all efficacy and safety data from subjects in Part 1a will occur after all randomized subjects in Part 1a have completed the Treatment Period through Post-Treatment Week 12 or have prematurely discontinued from the study. An additional interim analysis of all efficacy and safety data from subjects in Part 1b will occur after all randomized subjects in Part 1b have completed the Treatment Period through Post-Treatment Week 12 or have prematurely discontinued from the study. The primary analysis will occur after all randomized subjects in Part 2 have completed the Treatment Period through Post-Treatment Week 12 or have 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 (Part 1 and Part 2). The Full Analysis Set (FAS) for Part 1 (FAS-1) will consist of all subjects in the ITT population who were randomized in Part 1, and FAS-2 will consist of all subjects in the ITT population who were randomized in Part 2. Efficacy, safety, and demographic interim analyses of Part 1a data will be performed on the Part 1a subjects in FAS-1. Efficacy, safety, and demographic interim analyses of Part 1b data will be performed on the Part 1b subjects in FAS-1. The primary analysis will be performed on the ITT population, combining FAS-1 and FAS-2.

No data will be imputed for any efficacy or safety analyses except for the PRO questionnaires and for analyses of the 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 5 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 SVR endpoints based on the defined visit windows. Backward imputation will be used to impute missing HCV RNA data for SVR analyses.

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

### 8.1.1 Demographics

Demographics and baseline characteristics will be summarized for each treatment group. Demographics include: age, birth year, weight, BMI, sex, race, ethnicity, geographic region, and country. Baseline characteristics will include HCV GT 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 CD4+ T-cell count, HIV ART regimen (ATV, RAL, DRV QD, or DRV BID), baseline IP-10 [(continuous) and (< 600 pg/mL or ≥ 600 pg/mL)], baseline HOMA-IR (< 3 mU × mmol/L² or ≥ 3 mU × mmol/L²), presence of cirrhosis, baseline fibrosis stage (F0-F1, F2, F3, or F4), history of diabetes, history of bleeding disorders, history of depression or bipolar disorder, tobacco (user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker), and injection drug user status. Summary statistics (N, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI) and treatment groups will be compared using a one-way analysis of variance (ANOVA) with treatment group (12-week versus 24-week) as a factor. The number and percentage of subjects will be presented for categorical variables (e.g., sex and race); treatment groups (12-week versus 24-week) will be compared using a chi-square test.
8.1.2 Efficacy

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.

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoints are the percentage of subjects achieving SVR12 (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug) in the 12-week and 24-week treatment groups. The overall 2-sided significance level of 0.05 will be split between the two treatment groups using a Bonferroni correction of 0.025 for each treatment group. The percentage of subjects achieving SVR12 within each treatment group will be calculated and a 2-sided 97.5% confidence interval (CI) of the percentage will be computed using the Wilson score method for the binomial proportion.

A gatekeeping testing procedure will be used to control the Type I error rate at 0.05 and the primary endpoint within the 12-week treatment group will be tested separately from the 24-week treatment group:

- SVR12: Superiority of the 12-week treatment group to the historical SVR rate for pegIFN and RBV therapy; the lower confidence bound (LCB) of the 97.5% CI for the percentage of subjects achieving SVR12 in the 12-week treatment group must exceed 36% to achieve superiority.
• SVR\textsubscript{12}: Superiority of the 24-week treatment group to the historical SVR rate for pegIFN and RBV therapy; the LCB of the 97.5\% CI for the percentage of subjects achieving SVR\textsubscript{12} in the 24-week treatment group must exceed 36\% to achieve superiority.

If success is achieved for both of the primary endpoints, then the first secondary endpoint will be tested; otherwise, statistical testing will stop.

The value of 36\% used in the endpoints as the historical SVR rate for pegIFN and RBV represents the upper confidence bound of the 2-sided 95\% confidence interval of the SVR rate in subjects with chronic hepatitis C coinfected with HIV in PEGASYS Study 7 included in product labeling for peginterferon alfa-2a (Section 5.7.3).

8.1.2.2 Secondary Efficacy Endpoints

The first secondary efficacy endpoint included in the gatekeeping testing procedure is the percentage of subjects achieving SVR\textsubscript{12} in the 24-week treatment group compared to the 12-week treatment group.

If success was demonstrated for both of the primary efficacy endpoints, then the gatekeeping testing procedure will continue to the first secondary efficacy endpoint to compare the percentage of subjects achieving SVR\textsubscript{12} following 12 or 24 weeks of treatment.

Other secondary endpoints not included in the gatekeeping testing procedure are:

• The percentage of subjects in each treatment group with on-treatment virologic failure during the Treatment Period;

• The percentage of subjects in each treatment group with post-treatment relapse.

• The percentage of subjects in each treatment group with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm.
The percentages (with 2-sided 95% confidence intervals using the Wilson score method for the binomial proportion) of the subjects with on-treatment virologic failure during treatment, post-treatment relapse, and plasma HIV-1 RNA suppression will be calculated and summarized for each treatment group. These endpoints will not be part of the gatekeeping testing procedure as no hypothesis is being tested.

### 8.1.2.3 Subgroup Analysis

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

- Treatment-naïve versus previous pegIFN/RBV-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/L$^2$);
- 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 and country (as appropriate);
- BMI (< 30 or ≥ 30 kg/m$^2$);
- Subjects with RBV dose modifications (yes/no);
- History of Diabetes (yes/no);
- History of Bleeding Disorders (yes/no);
- History of Depression or Bipolar Disorder (yes/no);
● Former injection drug user (yes/no);
● Presence of compensated cirrhosis (yes/no);
● Baseline fibrosis stage (F0–F1, F2, F3, or F4);
● Baseline CD4+ Count (< 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm³);
● HIV ART regimen (ATV, RAL, DRV QD, or DRV BID).

8.1.2.4 Additional Efficacy Endpoints

The following additional efficacy endpoints will be summarized and analyzed by treatment group combining both FAS-1 and FAS-2:

● The percentage of subjects with plasma HIV-1 RNA < 40 copies/mL at each applicable time point;
● Mean change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
● The percentage of subjects with unquantifiable HCV RNA at each post-baseline visit in the Treatment Period (using only subjects with data observed in each visit window, i.e., no imputation for missing data);
● The percentage of subjects who complete treatment with HCV RNA < LLOQ at Final Treatment Visit who relapsed at any time post-treatment;
● The percentage of subjects with SVR 4 weeks after the last actual dose of study drug (SVR₄);
● The percentage of subjects with SVR 24 weeks after the last actual dose of study drug (SVR₂₄).

In the above analyses where percentages will be calculated, the number and percentage of responders in each treatment group and 2-sided 95% confidence intervals (using the Wilson score method for the binomial proportion) will be calculated. Analyses of mean change from baseline to end of treatment for the CD4+ T-cell counts will be compared between treatment groups (and study part, if applicable) using an analysis of covariance (ANCOVA) model with treatment group (and possibly study part) as factor(s) and baseline score as a covariate.
8.1.3 Patient Reported Outcomes

The following 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.

Summary statistics (n, mean, SD, median, minimum and maximum) at each visit and for change from baseline to each visit by treatment group will be provided for the HCVPRO total score, the EQ-5D-5L health index and VAS scores, and the SF-36v2 PCS and MCS scores, respectively. 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 groups using an ANCOVA model with treatment group (and study part, if applicable) as factors and baseline score as a covariate.

For HCVPRO total score, and for SF-36 PCS and SF-36 MCS, a continuous plot by treatment group 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.

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

8.1.4 Resistance Analyses

8.1.4.1 HCV Drug-Resistance Analyses

Subjects who do not achieve SVR\textsubscript{12} will have resistance testing conducted if (1) they experience on-treatment rebound; or (2) they have post-treatment relapse with a study
drug duration $\geq 77$ days for subjects assigned to 12 weeks of treatment or study drug duration $\geq 154$ days for subjects assigned to 24 weeks of treatment. Subjects meeting one of these criteria will be referred to as subjects in the primary virologic failure (PVF) population and a listing by subject that includes HCV subgenotype, IL28B genotype, reason for SVR$_{12}$ non-response, time point analyzed as closest to VF, and HCV RNA at VF time point will be produced for these subjects. In addition, all listings described below will contain HCV subgenotype and reason for SVR$_{12}$ non-response for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA $\leq 1000$ IU/mL).

Subjects treated with study drug who do not achieve SVR$_{12}$ who do not meet the above criteria for the PVF population (e.g., those with less than 6 weeks of therapy who failed to suppress), but have a time point with HCV RNA $\geq 1000$ IU/mL after treatment discontinuation, will have the sample at that time point and the corresponding baseline sample sequenced. For subjects who are lost to follow-up with less than 6 weeks of therapy while not virally suppressed (e.g., HCV RNA never $<$ LLOQ or have increase in viral load post nadir), the sample at the latest available time point with HCV RNA $\geq 1000$ IU/mL and the corresponding baseline sample will be sequenced. A listing of all subjects not in the PVF population with post-baseline sequencing available will be created that is similar to the listing of subjects in the PVF population with post-baseline sequencing available.

Only samples with an HCV RNA level of $\geq 1000$ 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 or treatment discontinuation is $< 1000$ IU/mL, the first available sample with an HCV RNA level $\geq 1000$ IU/mL after the failure/discontinuation will be used. Clonal sequencing of a given target will be performed 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 a signature resistance-associated position that cannot be resolved by population sequencing.
For each subject in the PVF population, at least two SVR$_{12}$ achieving subjects will be matched to the extent possible by HCV subgenotype, baseline HCV RNA level, IL28B genotype, prior treatment status, and HIV ART regimen. Baseline samples from these matched SVR$_{12}$-achieving subjects will also be sequenced by population sequencing.

For subjects not achieving SVR$_{12}$, the genes of interest for population sequencing in this study are those encoding complete NS3/4A, NS5A, and NS5B, while for clonal sequencing they are those encoding NS3 amino acids 1 to 181, NS5A amino acids 1 to 215, and NS5B amino acids 300 to 591. The regions encoding NS3 1-360, 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$_{12}$-achieving subjects for every 1 PVF subject. For phenotyping, the genes of interest are those encoding NS3 amino acids 1 to 251, full length NS5A, and full length NS5B. The prototypic reference sequences used for analysis will be H77 (NC_004102) for genotype 1a or Con1 (AJ238799) 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, 43, 56, 155, 156, and 168 in NS3 for genotype 1a; 56, 155, 156, and 168 in NS3 for genotype 1b; 2) for ABT-267: 28, 30, 31, 32, 58, and 93 in NS5A for genotype 1a; 28, 29, 30, 31, 32, 58, and 93 in NS5A for genotype 1b; and 3) for ABT-333: 316, 414, 446, 448, 451, 553, 554, 555, 556, 558, 559, and 561 in NS5B for genotype 1a; 316, 368, 411, 414, 445, 448, 553, 556, 558, and 559 in NS5B for genotype 1b. 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.

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 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.
- Linked variant by population sequencing: 2 or more signature resistance-associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at any of the positions.
- 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.

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 SVR12. The analysis 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 SVR₁₂) 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 SVR₁₂ 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.

The HCV amino acid sequence as determined by population sequencing in the sample closest in time after VF with an HCV RNA level of ≥ 1000 IU/mL will be compared with the baseline and appropriate prototypic reference amino acid sequences. A listing by subject of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). 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 sequence will be provided.

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.

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.
The HCV amino acid sequence as determined by population sequencing in the sample closest in time after discontinuation with an HCV RNA level of ≥ 1000 IU/mL will be compared with the baseline sequence. A listing by subject of all post-baseline variants detected by population sequencing relative to the baseline amino acid sequence will be provided for each DAA target (NS3, NS5A, and NS5B). In addition, 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.

For the subset of samples for which clonal sequencing is performed, listings by subject of post-baseline amino acid variants determined by clonal sequencing will be provided for each DAA target. Furthermore, listings of the linked variants by clonal sequencing by subject, DAA target, and time point will be provided.

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 may be introduced into the appropriate 1a-H77 or 1b-Con1 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 including each of these subjects.

### 8.1.4.2 HIV Drug-Resistance Analyses

If a subject develops a confirmed, quantifiable plasma HIV-1 RNA level (HIV-1 RNA $\geq 40$ copies/mL at one assessment and $\geq 500$ copies/mL on repeat testing) after starting the study, the subject's HIV-1 PR, RT, and/or IN sequences, as applicable, will be analyzed by Monogram Biosciences using the GenoSure® Prime drug resistance assays. The number of subjects who demonstrate HIV genotypic resistance and the genotypic resistant mutations detected in the samples obtained from these subjects will be tabulated and summarized. Resistance will be defined as described by the IAS-USA Panel.\(^{36}\)

### 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 group 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 and compared between the treatment groups 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 group 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 for each treatment group and differences between the treatment groups will be analyzed using contrasts within an ANOVA model with treatment group as the factor.

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 group.

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 group. Comparisons will be performed between the treatment groups 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 for each treatment group and will be compared between the treatment groups using a contrast within an ANOVA
model with treatment group as the factor when applicable. 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 groups 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 in the treatment period. Plasma concentrations of HIV ARTs, if measured, will also be summarized.

Values for the pharmacokinetic parameters of ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, RBV and DRV including the $C_{\text{max}}$, $T_{\text{max}}$, $C_{\text{trough}}$, and $AUC$ will be determined by noncompartmental methods using data from subjects who participate in Part 1b. For the DAAs and RBV these parameters will be calculated at Treatment Period Week 4. For DRV and ritonavir, these parameters will be calculated on Study Day –1 (DRV without DAAs) and Treatment Period Week 4 (DRV when administered with DAAs). Additional parameters or summaries may be determined if useful in the interpretation of the data.

Pharmacokinetic exposure parameters of darunavir (such as $C_{\text{max}}$, $AUC$ and $C_{\text{trough}}$) in Part 1b will be compared when HIV-1 ART regimen was administered alone (Study Day –1) with co-administration of HIV-1 ART regimen with DAA regimen (Treatment Period Week 4). To assess the effect of DAA regimen on darunavir, a repeated measures analysis will be performed for the natural logarithms of $C_{\text{max}}$, $AUC$ and $C_{\text{trough}}$ using the SAS® Version 9.2 PROC MIXED utilizing data from the Study Day –1 visit and the Treatment Period Week 4 visit. The model will have visit (Study Day –1 versus Treatment Period Week 4) as a fixed effect. The within-subject variability will be accounted for utilizing the repeated statement for the effect of visit. The relative
bioavailability of the combination regimen (at the Treatment Period Week 4 visit) to that of the darunavir without DAA regimen (at the Study Day –1 visit) will be assessed by a 90% confidence intervals for the difference of the least square means obtained from the repeated measures analyses of the natural logarithms of C\text{max}, AUC and C\text{trough}. The 90% confidence intervals will be obtained for those ratio estimates by taking the anti-logarithm of the upper and lower limits of confidence intervals for the difference of the least squared means on the logarithmic scale obtained within the framework of the repeated measures analysis model. Separate analyses will be done for subjects on darunavir QD and BID regimens. Additional comparisons can be done, if appropriate.

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

Population pharmacokinetic analyses may be performed using the actual sampling time relative to dosing. Population 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. 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.

Relationship between exposure (noncompartmental or population pharmacokinetic model based values of concentrations over time, AUC, C\text{trough} or some other appropriate measure of exposure) and clinical observations (antiviral activity or virologic end points, such as SVR\text{12} response) will be explored, if appropriate. Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may
also be explored. Exposure response relationships will be explored using a logistic regression analysis and/or a semi-mechanistic viral dynamic model.

Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

It is planned to enroll approximately 300 subjects into the study, where approximately 60 subjects will be randomized in a 1:1 ratio to the 12-week treatment group or the 24-week treatment group in Part 1a, approximately 30 additional subjects will be allocated to the 12-week treatment group in Part 1b (randomized in a 1:1 ratio to receive QD or BID DRV), and approximately 210 additional subjects will be randomized in a 1:1 ratio to the 12-week treatment group or the 24-week treatment group in Part 2. The study design will allow for a total of approximately 165 subjects in the 12-week treatment group and a total of approximately 135 subjects in the 24-week treatment group. With a sample size of at least 135 subjects in each treatment group and assuming that 51% of the subjects in each treatment group will achieve SVR12, this study has at least 90% power to demonstrate superiority compared to the historical control rate with a 2-sided 97.5% LCB greater than 36% (based on the normal approximation of a single binomial proportion in a one-sample test for superiority). No adjustment for dropouts is applicable because subjects who do not have data at Post-Treatment Week 12 (after imputing) are counted as failures for SVR12.

8.3 Randomization Methods

Randomization to the 12- and 24-week treatment arms will occur until approximately 60 subjects are enrolled in Part 1a and approximately 210 subjects are enrolled in Part 2. Within Parts 1a and 2, subjects will be randomized in a 1:1 ratio to Arm A and Arm B. In addition, approximately 30 DRV subjects in Part 1b will be randomized in a 1:1 ratio to receive DRV QD (Arm C) or DRV BID (Arm D), coadministered with the 12-week DAA treatment regimen.
Randomized subjects in Arms A and B will be stratified by having received previous pegIFN/RBV treatment versus being treatment-naïve and presence of cirrhosis (cirrhotic or non-cirrhotic). The treatment-naïve subjects will be stratified by IL28B genotype (CC versus non-CC). The treatment-experienced subjects will be stratified by type of previous response to prior pegIFN/RBV treatment (null responder, partial responder, or relapser). Randomized subjects in Part 1b will be stratified by prior HIV treatment history (previously PI-naïve subjects [i.e., no PI exposure other than DRV] and previously PI-experienced subjects [i.e., received non-DRV PI prior to current DRV treatment]).

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

Subjects that were screened in Part 1 but were unable to enroll in Part 1 before enrollment was complete, and are screened for Part 2 must sign a new informed consent form prior to completing screening procedures for Part 2.

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated the pharmacogenetic optional DNA and/or mRNA 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 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 Code of Federal Regulations (CFR) Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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

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

11.0 Data Quality Assurance

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

12.0 Use of Information

Any pharmacogenetic research that may be done using DNA and mRNA 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 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 Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (TURQUOISE-I)

Protocol Date: 17 July 2014

Signature of Principal Investigator

Date

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


15. Sovaldi® (sofosbuvir) [prescribing information]. Foster City, CA; Gilead Sciences, Inc, 2013.

16. Victrelis® (boceprevir) [prescribing information]. Whitehouse Station, NJ; Schering Corporation, 2011.


30. PEGASYS® US Package Insert.

31. COPEGUS® US Package Insert.

32. COPEGUS® Summary of Product Characteristics.

34. Isentress® (Raltegravir) US Prescribing Information. Merck & Co., Inc. April 2012.


40. Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged < 18 Months and for HIV Infection and AIDS Among Children Aged 18 Months to < 13 Years. MMWR. Recommendations and Reports. December 5, 2008/57(RR-10).


Appendix A. Responsibilities of the Clinical Investigator

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

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

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

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

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

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

6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.

7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.

8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

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

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<td>Global Drug Supply Management</td>
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</tbody>
</table>
### Appendix C. Clinical Toxicity Grades

<table>
<thead>
<tr>
<th>Clinical Toxicity Grades for HCV Studies¹,²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGY</strong></td>
</tr>
<tr>
<td>Absolute Neutrophil Count Decreased</td>
</tr>
<tr>
<td>&lt; LLN - 1500/mmcu/mL</td>
</tr>
<tr>
<td>&lt; LLN - 1.5 x 10⁹/L</td>
</tr>
<tr>
<td>&lt; 1500 - 1000/mmcu/mL</td>
</tr>
<tr>
<td>&lt; 1.5 - 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>&lt; 1000 - 600/mmcu/mL</td>
</tr>
<tr>
<td>&lt; 1.0 - 0.5 x 10⁹/L</td>
</tr>
<tr>
<td>&lt; 600/mmcu/mL</td>
</tr>
<tr>
<td>&lt; 0.5 x 10⁹/L</td>
</tr>
<tr>
<td>Eosinophil Count Increased</td>
</tr>
<tr>
<td>650-1000 cells/mm³</td>
</tr>
<tr>
<td>1501-2000 cells/mm³</td>
</tr>
<tr>
<td>&gt; 2500 cells/mm³</td>
</tr>
<tr>
<td>Hypereosinophilic</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
</tr>
<tr>
<td>&lt; LLN - 10.0 g/dL</td>
</tr>
<tr>
<td>&lt; LLN - 0.8 - 10g/dL</td>
</tr>
<tr>
<td>&lt; 10.0 - 8.0 g/dL</td>
</tr>
<tr>
<td>&lt; 8.2 - 4.9 mm³</td>
</tr>
<tr>
<td>&lt; 100 - 80g/L</td>
</tr>
<tr>
<td>&lt; 10.0 - 8.0 g/dL</td>
</tr>
<tr>
<td>&lt; 8.0 - 5.5 g/dL</td>
</tr>
<tr>
<td>&lt; 4.9 - 4.0 mm³</td>
</tr>
<tr>
<td>&lt; 8.0 - 85 g/L</td>
</tr>
<tr>
<td>&lt; 65 g/L</td>
</tr>
<tr>
<td>International Normalized Ratio (INR), Increased</td>
</tr>
<tr>
<td>&gt; 1 - 1.5 x ULN</td>
</tr>
<tr>
<td>&gt; 1.5 - 2 x ULN</td>
</tr>
<tr>
<td>&gt; 2 x ULN</td>
</tr>
<tr>
<td>Lymphocyte Count Decreased</td>
</tr>
<tr>
<td>&lt; LLN - 800/mmcu/mL</td>
</tr>
<tr>
<td>&lt; LLN x 0.8 - 10a/L</td>
</tr>
<tr>
<td>&lt; 800 - 500/mmcu/mL</td>
</tr>
<tr>
<td>&lt; 500 - 0.5 x 10a/L</td>
</tr>
<tr>
<td>&lt; 200/mmcu/mL</td>
</tr>
<tr>
<td>Platelets Decreased</td>
</tr>
<tr>
<td>&lt; LLN - 75,000/mm³</td>
</tr>
<tr>
<td>&lt; LLN - 50,000/mm³</td>
</tr>
<tr>
<td>&lt; 75,000 - 50,000/mm³</td>
</tr>
<tr>
<td>&lt; 75,000 - 25,000/mm³</td>
</tr>
<tr>
<td>&lt; 25,000/mm³</td>
</tr>
<tr>
<td>PTT</td>
</tr>
<tr>
<td>&gt; 1 - 1.5 x ULN</td>
</tr>
<tr>
<td>&gt; 1.5 - 2 x ULN</td>
</tr>
<tr>
<td>&gt; 2 x ULN</td>
</tr>
<tr>
<td>White Blood Cell Count Decreased</td>
</tr>
<tr>
<td>&lt; LLN - 3000/mmcu/mL</td>
</tr>
<tr>
<td>&lt; LLN - 2.0 x 10⁹/L</td>
</tr>
<tr>
<td>&lt; 3000 - 2000/mmcu/mL</td>
</tr>
<tr>
<td>&lt; 2000 - 0.5 x 10⁹/L</td>
</tr>
<tr>
<td>&lt; 1000/mmcu/mL</td>
</tr>
<tr>
<td>White Blood Cell Count Increased</td>
</tr>
<tr>
<td>&lt; 10,000 - 15,000 cells/mm³</td>
</tr>
<tr>
<td>&lt; 20,000 - 25,000 cells/mm³</td>
</tr>
<tr>
<td>&gt; 20,000 - 25,000 cells/mm³</td>
</tr>
<tr>
<td>&gt; 25,000 cells/mm³</td>
</tr>
<tr>
<td>CHEMESTRIES</td>
</tr>
<tr>
<td>Albumin, Serum, Low</td>
</tr>
<tr>
<td>&lt; LLN - 3 g/dL</td>
</tr>
<tr>
<td>&lt; LLN - 0.8 - 10a/L</td>
</tr>
<tr>
<td>&lt; 3 - 2 g/dL</td>
</tr>
<tr>
<td>&lt; 30 - 20 g/L</td>
</tr>
<tr>
<td>&gt; 2 g/dL</td>
</tr>
<tr>
<td>&gt; 20 g/L</td>
</tr>
<tr>
<td>Bilirubin, High</td>
</tr>
<tr>
<td>&gt; ULN - 1.5 x ULN</td>
</tr>
<tr>
<td>&gt; 1.5 - 3.0 x ULN</td>
</tr>
<tr>
<td>&gt; 3.0 - 10.0 x ULN</td>
</tr>
<tr>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>BUN</td>
</tr>
<tr>
<td>&gt; 1.25 - 2.5 x ULN</td>
</tr>
<tr>
<td>&gt; 2.5 - 5.0 x ULN</td>
</tr>
<tr>
<td>&gt; 5 - 10.0 x ULN</td>
</tr>
<tr>
<td>&gt; 10 x ULN</td>
</tr>
<tr>
<td>Calcium, Serum Low</td>
</tr>
<tr>
<td>&lt; LLN - 0.8 mg/dL</td>
</tr>
<tr>
<td>&lt; LLN - 0.2 mmol/L</td>
</tr>
<tr>
<td>&lt; 8.0 - 7.0 mg/dL</td>
</tr>
<tr>
<td>&lt; 2.0 - 1.5 mmol/L</td>
</tr>
<tr>
<td>&lt; 1.75 - 1.5 mmol/L</td>
</tr>
<tr>
<td>&lt; 1.5 mmol/L</td>
</tr>
<tr>
<td>Calcium, Serum High</td>
</tr>
<tr>
<td>&gt; ULN - 1.5 mg/dL</td>
</tr>
<tr>
<td>&gt; 2.9 - 3.1 mmol/L</td>
</tr>
<tr>
<td>&gt; 11.5 - 12.5 mg/dL</td>
</tr>
<tr>
<td>&gt; 12.5 - 13.5 mg/dL</td>
</tr>
<tr>
<td>&gt; 13.5 mg/dL</td>
</tr>
<tr>
<td>Calcium, Ionized, Low</td>
</tr>
<tr>
<td>&lt; ULN - 0.8 mmol/L</td>
</tr>
<tr>
<td>&lt; 0.9 - 0.8 mmol/L</td>
</tr>
<tr>
<td>&lt; 0.9 - 0.8 mmol/L</td>
</tr>
<tr>
<td>&gt; 0.8 mmol/L</td>
</tr>
<tr>
<td>Calcium, Ionized, High</td>
</tr>
<tr>
<td>&gt; ULN - 1.5 mmol/L</td>
</tr>
<tr>
<td>&gt; 1.5 - 1.8 mmol/L</td>
</tr>
<tr>
<td>&gt; 1.6 - 1.8 mmol/L</td>
</tr>
<tr>
<td>&gt; 1.8 mmol/L</td>
</tr>
</tbody>
</table>

Clinical Toxicity Grades for HCV Studies
v1.1; 08 Aug 2009
### Clinical Toxicity Grades for HCV Studies (Continued)

<table>
<thead>
<tr>
<th>Grade 1 Toxicity</th>
<th>Grade 2 Toxicity</th>
<th>Grade 3 Toxicity</th>
<th>Grade 4 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol High</strong></td>
<td>ULN = 300 mg/dL</td>
<td>&gt;300 – 400 mg/dL</td>
<td>&gt;400 – 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>ULN = 7.75 mmol/L</td>
<td>&gt;7.75 – 10.34 mmol/L</td>
<td>&gt;10.34 – 12.92 mmol/L</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>1.5 – 1.7 mg/dL</td>
<td>1.8 – 2.0 mg/dL</td>
<td>2.1 – 2.5 mg/dL</td>
</tr>
<tr>
<td><strong>Glucose, Serum, Low</strong></td>
<td>&lt;ULN – 55 mg/dL</td>
<td>&lt;55 – 40 mg/dL</td>
<td>&lt;40 – 30 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;ULN – 3.0 mmol/L</td>
<td>&lt;3.0 – 2.2 mmol/L</td>
<td>&lt;2.2 – 1.7 mmol/L</td>
</tr>
<tr>
<td><strong>Glucose, Serum, High (Fasting)</strong></td>
<td>&gt;ULN – 100 mg/dL</td>
<td>&gt;100 – 250 mg/dL</td>
<td>&gt;250 – 500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt;ULN – 8.9 mmol/L</td>
<td>&gt;8.9 – 13.9 mmol/L</td>
<td>&gt;13.9 – 27.8 mmol/L</td>
</tr>
<tr>
<td><strong>Magnesium, Serum, Low</strong></td>
<td>&lt;ULN – 1.2 mg/dL</td>
<td>&lt;1.2 – 0.9 mg/dL</td>
<td>&lt;0.9 – 0.7 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;ULN – 0.5 mmol/L</td>
<td>&lt;0.5 – 0.4 mmol/L</td>
<td>&lt;0.4 – 0.3 mmol/L</td>
</tr>
<tr>
<td><strong>Magnesium, Serum, High</strong></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>
</tr>
<tr>
<td></td>
<td>&gt;ULN – 1.25 mmol/L</td>
<td>&gt;1.25 – 3.0 mmol/L</td>
<td>&gt;3.30 mmol/L</td>
</tr>
<tr>
<td><strong>Phosphorus, Serum, Low</strong></td>
<td>&lt;ULN – 2.5 mg/dL</td>
<td>&lt;2.5 – 2.0 mg/dL</td>
<td>&lt;2.0 – 1.0 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;ULN – 0.8 mmol/L</td>
<td>&lt;0.8 – 0.6 mmol/L</td>
<td>&lt;0.6 – 0.3 mmol/L</td>
</tr>
<tr>
<td><strong>Potassium, Serum, Low</strong></td>
<td>&lt;ULN – 3.0 mmol/L</td>
<td>&lt;3.0 – 2.5 mmol/L</td>
<td>&lt;2.5 mmol/L</td>
</tr>
<tr>
<td><strong>Potassium, Serum, High</strong></td>
<td>&gt;ULN – 5.5 mmol/L</td>
<td>&gt;5.5 – 7.0 mmol/L</td>
<td>&gt;7.0 mmol/L</td>
</tr>
<tr>
<td><strong>Protein, Serum, Low</strong></td>
<td>5.5 – 6.0 g/dL</td>
<td>&lt;5.5 – 5.0 g/dL</td>
<td>&lt;5.0 g/dL</td>
</tr>
<tr>
<td><strong>Sodium, Serum, Low</strong></td>
<td>&lt;ULN – 130 mmol/L</td>
<td>&lt;130 – 120 mmol/L</td>
<td>&lt;120 mmol/L</td>
</tr>
<tr>
<td><strong>Sodium, Serum, High</strong></td>
<td>&gt;ULN – 150 mmol/L</td>
<td>&gt;150 – 155 mmol/L</td>
<td>&gt;155 – 160 mmol/L</td>
</tr>
<tr>
<td></td>
<td>&gt;160 mmol/L</td>
<td>&gt;160 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>Triglycerides High (Fasting)</strong></td>
<td>160–300 mg/dL</td>
<td>&gt;300–500 mg/dL</td>
<td>&gt;500–1000 mg/dL</td>
</tr>
<tr>
<td></td>
<td>171–3.42 mmol/L</td>
<td>&gt;3.42–6.7 mmol/L</td>
<td>&gt;6.7–11.4 mmol/L</td>
</tr>
<tr>
<td><strong>Uric Acid, Serum, High</strong></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>
</tr>
</tbody>
</table>

Clinical Toxicity Grades for HCV Studies
v1.1, 08 June 2009
<table>
<thead>
<tr>
<th>Clinical Toxicity Grades for HCV Studies (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENZYMES</td>
</tr>
<tr>
<td>ALT/SGPT</td>
</tr>
<tr>
<td>AST/SGOT</td>
</tr>
<tr>
<td>ALKALINE PHOSPHATASE</td>
</tr>
<tr>
<td>AMYLASE</td>
</tr>
<tr>
<td>LIPIASE</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. List of AIDS-Associated Opportunistic Infections

Collection of data regarding known AIDS-associated opportunistic infections is covered in Section 6.8.

- Aspergillosis
- Bartonellosis
- Candidiasis (*Bronchi; *Esophagus; *Lungs; Oropharyngeal [Thrush]; *Trachea; Vulvovaginal [Persistent, Frequent, or Poorly Responsive to Therapy])
- *Coccidioidomycosis
- *Cryptococcosis
- *Cryptosporidiosis
- Cytomegalovirus (*Retinitis; *Cytomegalovirus Disease [other than liver, spleen or nodes])
- Enteric infections, Recurrent (Bacterial)
- Herpes Simplex Virus (*Bronchitis; *Esophagitis; *Pneumonitis; *Chronic Ulcer(s) [> 1 month in duration])
- *Histoplasmosis
- Human Herpesvirus-8 Disease (Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease)
- Human Papilloma Virus Infections
- *Isosporiasis (Cystoisosporiasis)
- Microsporidiosis
- *Mycobacterium avium – Complex Disease (Disseminated)
- *Mycobacterium tuberculosis – Infection and Disease
- *Pneumonia
- *Pneumonia, recurrent bacterial (and/or other respiratory infections including sinusitis, bronchitis, otitis)
- *Progressive multifocal leukoencephalopathy (JC Virus Infection)
- Syphilis
- *Toxoplasma Gondii Encephalitis*
- *Varicella Zoster Virus Diseases*

* AIDS-defining event as described by CDC Surveillance Case Definition of 1993.
## Appendix E. Study Activities – Treatment Extension

<table>
<thead>
<tr>
<th>Activity</th>
<th>Treatment Extension Visits (24-Week Arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 16</td>
</tr>
<tr>
<td>Dispense/Review HIV-1 ART Dosing Card</td>
<td>X</td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
</tr>
<tr>
<td>Vital Signs, Weight, Heightc</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>Hematology/Chemistry/Urinalysis/Coagulation Panel</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test [serum (s) urine (u)]d</td>
<td>X (u)</td>
</tr>
<tr>
<td>Total Insulin</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Scorec</td>
<td></td>
</tr>
<tr>
<td>HCC Screening: Liver Ultrasound &amp; Alpha Fetoprotein</td>
<td></td>
</tr>
<tr>
<td>Concomitant Medication Assessment</td>
<td>X</td>
</tr>
<tr>
<td>Patient Reported Outcomes Instruments (PROs)f</td>
<td></td>
</tr>
<tr>
<td>Adverse Event Assessment</td>
<td>X</td>
</tr>
<tr>
<td>Study Drugs Dispensed</td>
<td>X</td>
</tr>
<tr>
<td>Study Drug Returned for IRT Reconciliation</td>
<td>X</td>
</tr>
<tr>
<td>MEMS Downloaded/Review Compliance/Collect MEMS Capsg</td>
<td>X</td>
</tr>
<tr>
<td>HCV RNA Samples</td>
<td>X</td>
</tr>
<tr>
<td>HIV-1 RNAh</td>
<td>X</td>
</tr>
<tr>
<td>HCV Resistance Sample</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetic Sparse Samplesl</td>
<td>X</td>
</tr>
<tr>
<td>Flow Cytometry Sample</td>
<td></td>
</tr>
<tr>
<td>Archive Plasma Sample</td>
<td>X</td>
</tr>
<tr>
<td>Interferon gamma-induced protein 10 (IP-10) Sample</td>
<td></td>
</tr>
<tr>
<td>Messenger RNA (mRNA) Sample (optional)</td>
<td></td>
</tr>
</tbody>
</table>

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

a. Treatment visits:
   - Subjects randomized to a 12-week treatment arm that are extended to 24-weeks of treatment will complete the screening through Week 12 study visit procedures as detailed in Table 6 and Table 8, and continue with Week 16 through Week 24 visit procedures. Week 24 will be the final visit in the Treatment Period.
• Subjects who prematurely discontinue during the Treatment Extension Period should return to the site to complete the Premature D/C Visit Procedures (preferably prior to the initiation of any other anti-HCV therapy) as detailed in Table 6 and Table 8.

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

c. Height will be measured at Screening only. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes.

d. Urine pregnancy testing is not required after the Study 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.

e. Child-Pugh Score, Clinical Assessment of Hepatic Decompensation, Liver Ultrasound and Alpha Fetoprotein are only performed on subjects with compensated cirrhosis as described in Section 5.3.1.1, Study Procedures.

f. Short Form 36, version 2 (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 following order: SF-36v2, EQ-5D-5L, HCVPRO.

g. MEMS caps will be collected upon completion of study drug (Week 24 or Premature D/C from Treatment).

h. If a subject's plasma HIV-1 RNA level was < 40 copies/mL at the previous time point and is ≥ 40 copies/mL at the next assessment, the subject's HIV-1 RNA is to be repeated as noted in Section 5.5.1.2. At the time the repeat plasma HIV-1 RNA is drawn, a sample should be obtained for HIV-1 resistance testing at an unscheduled visit for confirmation of plasma HIV-1 RNA as detailed in Section 5.5.1.2.

i. Blood samples for DAA and HIV-1 ARV pharmacokinetic assay will be collected as described in Section 5.3.2.
Appendix F.  Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Changes:

Section 1.1 Synopsis
Subsection "Methodology:
Fifth paragraph, second sentence previously read:

Subjects meeting eligibility criteria will be randomized in a 1:1 ratio to either maintain
DRV QD (Arm C) or switch to DRV twice daily (BID) administration (Arm D) for a
minimum of 14 days prior to starting study treatment.

Has been changed to read:

Subjects meeting eligibility criteria will be randomized in a 1:1 ratio to either receive
DRV 800 mg QD (Arm C) or switch to DRV 600 mg twice daily (BID) administration
(Arm D) for a minimum of 14 days prior to starting study treatment.

Section 1.1 Synopsis
Subsection "Methodology:
Eighth paragraph
Add: new last sentence

A minimum of 10 but no more than 20 subjects that are previously HIV-1 PI-naive will be
allowed to enroll in Part 1b of the study.

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

In Part 1b, approximately 30 eligible subjects on a stable once-daily (QD) DRV
containing HIV-1 ART regimen will be randomized in a 1:1 ratio to either maintain DRV
QD (Arm C) or to switch to DRV BID (Arm D) administration beginning on the
Enrollment Day as detailed in Section 5.6.1. Beginning on Study Day 1, subjects in Part
1b will also receive ABT 450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID +
RBV* for 12 weeks.
Has been changed to read:

In Part 1b, approximately 30 eligible subjects on a stable once-daily (QD) DRV-containing HIV-1 ART regimen will be randomized in a 1:1 ratio on the Enrollment Day to either receive DRV QD (Arm C) or to switch to DRV BID (Arm D) administration. Beginning on Study Day 1, subjects in Part 1b will also receive ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV* for 12 weeks as detailed in Section 5.6.1.

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph
Add: new last sentence

A minimum of 10 but no more than 20 subjects that are previously HIV-1 PI-naïve will be allowed to enroll in Part 1b of the study.

Section 5.1.3 Pre-Treatment Period (Part 1b only)
First paragraph, first sentence previously read:

After meeting the eligibility criteria, subjects in Part 1b will be randomized via IRT at the Enrollment Day to either maintain DRV dosing QD or begin dosing DRV BID for at least 14 days prior to initiating study drugs.

Has been changed to read:

After meeting the eligibility criteria, subjects in Part 1b will be randomized via IRT at the Enrollment Day to either receive DRV dosing 800 mg QD or begin dosing DRV 600 mg BID for at least 14 days prior to initiating study drugs.

Section 5.2.1 Inclusion Criteria
Criterion 2, fourth bullet point
Add: new last sentence

(Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment.)
Section 5.2.1 Inclusion Criteria
Criterion 13 previously read:

13. Plasma HIV-1 RNA < 40 copies/mL during screening using Abbott RealTime HIV-1 assay.

Has been changed to read:

13. Plasma HIV-1 RNA < 40 copies/mL during screening using Abbott RealTime HIV-1 assay, and plasma HIV-1 RNA below LLOQ by an approved plasma HIV-1 RNA quantitative assay (including but not limited to: COBAS® Ampliprep/COBAS® Taqman® HIV-1 Test, v 2.0 or Abbott RealTime HIV-1 assay) at least twice during the 24 weeks prior to screening including one qualifying result at least 8 weeks prior to screening.

Subjects with a solitary (unconfirmed) plasma HIV-1 RNA above LLOQ and < 200 copies/mL within 24 weeks of screening may be eligible for enrollment with approval of the AbbVie Study Designated Physician.

Table 4. Medications Contraindicated for Use with the Study Dug Regimen
Previously read:

<table>
<thead>
<tr>
<th>Alfuzosin</th>
<th>Lovastatin</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>Methylergonovine</td>
<td>Salmetrol</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Methylergometrine</td>
<td>Sildenafil**</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Midazolam (oral)</td>
<td>Simvastatin</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>Phenobarbital</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Phenytoin</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>ErgonovineFusidic Acid</td>
<td>Pimozone</td>
<td>Triazolam</td>
</tr>
</tbody>
</table>

Not all medications contraindicated with HIV-1 antiretroviral agents (ARVs) and ribavirin are listed above. Refer to the most current package inserts or product labeling for a complete list of contraindicated medications.

* Subjects receiving Atripla® (TDF/FTC/efavirenz) or an HIV-1 ART regimen containing efavirenz are not eligible for enrollment.

** When used for the treatment of pulmonary arterial hypertension.
Has been changed to read:

<table>
<thead>
<tr>
<th>Alfuzosin</th>
<th>Lovastatin</th>
<th>Rifampin</th>
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<tbody>
<tr>
<td>Astemizole</td>
<td>Methylergonovine</td>
<td>Salmeterol</td>
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<tr>
<td>Carbamazepine</td>
<td>Methylergometrine</td>
<td>Sildenafil**</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Midazolam (oral)</td>
<td>Simvastatin</td>
</tr>
<tr>
<td><strong>Efavirenz</strong>*</td>
<td>Phenobarbital</td>
<td>St. John's Wort</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Phenytoin</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Ergonovine</td>
<td>Pimozide</td>
<td>Triazolam</td>
</tr>
</tbody>
</table>
| Fusidic Acid | Gemfibrozil | **Estrogen-containing Medications for Systemic Use***

Not all medications contraindicated with HIV-1 antiretroviral agents (ARVs) and ribavirin are listed above. Refer to the most current package inserts or product labeling for a complete list of contraindicated medications.

* Subjects receiving Atripla® (TDF/FTC/efavirenz) or an HIV-1 ART regimen containing efavirenz are not eligible for enrollment.

** Progestin-only hormonal contraceptive agents are allowed for use with the study drug regimen

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

Section 5.2.3.2 Prior and Concomitant HIV-1 Therapy

Sixth paragraph, second bullet and two sub-bullets following previously read:

- Darunavir PO QD coadministered with ritonavir PO QD will be randomized approximately 14 days prior to starting the study DAA regimen to either maintain DRV PO QD coadministered with ritonavir PO QD or switch to DRV PO BID coadministered with ritonavir PO BID during the Pre-Treatment Period. Subjects on darunavir QD regimen that were taking the darunavir component of their HIV-1 ART regimen in the evening prior to enrollment must change to morning administration of darunavir at randomization.
  - Subjects that are randomized to maintain DRV PO QD administration will stop the ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen on Study Day 1. The darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333).
  - Subjects that are randomized to switch to DRV PO BID administration will stop the AM ritonavir component of their HIV-1 ART regimen upon
initiating the study DAA regimen on Study Day 1. The AM dose of darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333). Subjects will administer their PM dose of ritonavir with the PM dose of darunavir and the PM dose of ABT-333.

**Has been changed to read:**

- Darunavir PO QD coadministered with ritonavir PO QD will be randomized approximately 14 days prior to starting the study DAA regimen to either receive DRV 800 mg PO QD coadministered with ritonavir 100 mg PO QD or switch to DRV 600 mg PO BID coadministered with ritonavir 100 mg PO BID during the Pre-Treatment Period. Subjects on a darunavir QD regimen that were taking the darunavir component of their HIV-1 ART regimen in the evening prior to enrollment must change to morning administration of darunavir at randomization.

  - Subjects that are randomized to receive DRV 800 mg PO QD administration will stop the ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen on Study Day 1. The darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333).

  - Subjects that are randomized to switch to DRV 600 mg PO BID administration will stop the AM ritonavir component of their HIV-1 ART regimen upon initiating the study DAA regimen on Study Day 1. The AM dose of darunavir must be coadministered with the AM dose of DAAs (ABT-450/r/ABT-267 and ABT-333). Subjects will administer their PM dose of ritonavir with the PM dose of darunavir and the PM dose of ABT-333.
Section 5.2.3.3 Other Concomitant Therapy

First paragraph, first sentence previously read:

Subjects must be able to safely discontinue any prohibited medications or herbal supplements within 2 weeks prior to initial study drug administration through 2 weeks after completion of the Treatment Period

Has been changed to read:

Subjects must be able to safely discontinue any prohibited medications or herbal supplements at least 2 weeks prior to initial study drug administration through 2 weeks after completion of the Treatment Period

Section 5.2.3.3 Other Concomitant Therapy

Subsection Contraceptives

Previously read:

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. Subjects using systemic estrogen-containing contraceptive therapy (including estrogen-containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications should consider discontinuing them or replacing them with an alternate type of medication as described in Section 6.7.

Has been changed to read:

Prior to enrollment, subjects should agree to practice two effective methods of birth control while receiving study drugs starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. Subjects using systemic estrogen-containing contraceptive therapy (including estrogen-containing oral contraceptives) have a higher risk for elevated ALT levels. Subjects using these medications must discontinue them at least 2 weeks prior to study drug administration or 10 half-lives (if known), whichever is longer. Subjects may replace the systemic estrogen-containing contraceptive with a progestin-only hormonal contraceptive method.
Table 9. Part 1b: Study Activities – Post-Treatment (PT) Period*

Note: *A new last sentence:

If a 12-week treatment arm is extended to 24-weeks treatment, HCC screening will be performed during the Post-Treatment Period at PT Wk 24 and PT Wk 48 for subjects who did not have a qualifying historical liver ultrasound.

Table 9. Part 1b: Study Activities – Post-Treatment (PT) Period*
Row "HCC Screening: Liver Ultrasound and Alpha Fetoprotein" previously read:

<table>
<thead>
<tr>
<th>Activity</th>
<th>PT Wk 2</th>
<th>PT Wk 4</th>
<th>PT Wk 8</th>
<th>PT Wk 12</th>
<th>PT Wk 24</th>
<th>PT Wk 36</th>
<th>PT Wk 48 or PT D/C*</th>
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Has been changed to read:

<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>
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Footnote "d." Add: new last sentence
Section 5.3.1.1  Study Procedures
Subsection Concomitant Medication Assessment
First paragraph, first sentence previously read:

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements, and any prohibited medications) 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 as specified in Table 6, Table 7, Table 8 and Table 9.

Has been changed to read:

Use of medications (prescription or over-the-counter, including vitamins and herbal supplements, and any prohibited medications) from the time of signing the informed consent through 30 days after last dose of study drug will be recorded in the eCRF at each study visit as specified in Table 6, Table 7, Table 8 and Table 9.

Section 5.3.1.1  Study Procedures
Subsection HIV-1 ARV Regimen Dosing Card
Delete: second sentence in second paragraph

Additionally, subjects randomized to Arm D will be required to record the date of switch from DRV QD to DRV BID on the HIV-1 ARV dosing card and this information will be recorded in the eCRF.

Section 5.7.5  Selection of Doses in the Study
Subsection Coadministration of DAAs with HIV ART
Sixth sentence previously read:

In this study, subjects receiving darunavir QD regimen will be randomized to receive darunavir QD (no dose modification) or darunavir BID (dose modification) to evaluate the beneficial effect of darunavir dose modification in prevention of any potential HIV-1 failures due to drug-drug interaction.
Has been changed to read:

In this study, subjects receiving darunavir QD regimen will be randomized to receive darunavir 800 mg QD or darunavir 600 mg BID to evaluate the beneficial effect of darunavir dose modification in prevention of any potential HIV-1 failures due to drug-drug interaction.

Section 6.7.5 Management of Transaminase Elevations
Delete: first bullet point

- If using a systemic estrogen-containing product: Immediately discontinue the systemic estrogen-containing product.

Section 15.0 Reference List
References 20, 21, and 22 previously read:


Has been changed to read:


### Appendix B. List of Protocol Signatories

**Previously read:**

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Document Approval

Study M14004 - 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 Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection (TURQUOISE-I) - Amendment 2 - EudraCT 2012-005143-24 - 17Jul2014

Version: 2.0  Date: 21-Jul-2014 10:16:05 PM  Abbott ID: 07212014-00F9F680991BE8-00002-en

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<th>Date:</th>
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