Interim Analysis Plan

Study 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)

17 July 2014
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3.0 Introduction

This interim analysis plan (IAP) is created for Part 1a of Study M14-004 based on the study protocol incorporating Administrative Change 1 and Amendment 1.

Study M14-004 is designed to examine the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 co-administered with ribavirin (RBV) for 12 or 24 weeks in adults with genotype 1 (GT 1), chronic hepatitis C virus (HCV) infection and Human Immunodeficiency Virus, Type 1 (HIV-1) coinfection. An interim analysis of all efficacy (including resistance and Patient Reported Outcomes [PRO]) and safety data through Post-Treatment Week 12 from Part 1a of the study 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. For the interim analysis, data will be locked after performing appropriate data cleaning.

The IAP provides details to guide the analyses for baseline, efficacy, and safety variables and describes the populations and variables that will be analyzed and the statistical methods that will be utilized. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) under the UNIX operating system.

Any deviations from the planned statistical analysis will be described and justified in the clinical study report, as appropriate.

4.0 Study Objectives, Design and Procedures

4.1 Objectives of the Interim Analysis

The primary objectives of the interim analysis for 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 in Part 1a of the study and to evaluate the percentage of Part 1a subjects achieving a 12-week sustained virologic response, SVR12 (HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following treatment) within the 12- and 24-week arms.
The secondary objectives 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 post-treatment, and the percentage of subjects with plasma HIV-1 viral suppression at the end of HCV treatment and Post-Treatment Week 12 in each treatment group.

4.2 Design Diagram for Part 1a of the Study

Study M14-004 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 HCV GT 1/HIV-1 coinfection who are HCV treatment-naïve or pegIFN/RBV-experienced with and without compensated cirrhosis.

Part 1a of the study is designed as a Phase 2 pilot cohort to enroll approximately 60 HCV GT 1/HIV-1 coinfected, treatment-naïve and pegIFN/RBV-experienced adults. This part consists of 2 ART-regimen subgroups (atazanavir [ATV] and raltegravir [RAL]), each containing at least 20 subjects. As shown in Figure 1, subjects meeting eligibility criteria will be randomized in a 1:1 ratio to receive 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

* RBV will be administered weight-based 1000 or 1200 mg divided twice daily.
Randomized subjects in Part 1a 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).

The duration of Part 1a of the study will be 60 weeks (for subjects randomized to Arm A) or 72 weeks (for subjects randomized to Arm B), not including a screening period of up to 35 days, consisting of a 12-week Treatment Period for subjects randomized to Arm A and a 24-week Treatment Period for subjects randomized to Arm B, and a 48-week Post-Treatment (PT) Period for all subjects who receive at least one dose of study drug.

**Treatment Period (TP)**

Subjects meeting the eligibility criteria will be randomized to either the 12- or 24-week treatment groups and will receive ABT-450/r/ABT-267 orally once daily and ABT-333 and RBV orally twice daily during the Treatment Period.

Based upon HCV treatment adjustment criteria as described in Section 5.5.1.3 in the protocol, subjects randomized to the 12-week treatment group who are in the Treatment Period at the time the criteria met, may have the duration of their treatment extended to
24 weeks. If a treatment group is terminated from further enrollment due to reaching the HCV treatment adjustment criterion or based on data from ongoing studies, subjects ongoing in either the 12-week or 24-week treatment group may be offered add-on pegIFN/RBV treatment. In this case, the AbbVie regimen will be continued for 12 or 24 weeks as specified while pegIFN at standard doses is added on to continue beyond the end of the AbbVie regimen for a total of 48 weeks.

Post-Treatment Period

All subjects who receive at least one dose of DAA in the Treatment Period and either complete treatment or prematurely discontinue study drug will be monitored in the Post-Treatment Period for safety, HCV RNA, the emergence and persistence of resistant 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.

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

4.3 Sample Size

The statistical power was calculated based on the total sample size to be enrolled for the entire study. Therefore, there is no calculation of power based on the sample size of Part 1a alone. Furthermore, the justification of primary and secondary endpoint success criteria is not applicable for Part 1a.

4.4 Planned Interim Analysis

An interim analysis of all efficacy and safety data from Part 1a of the study 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. For the interim analysis, data will be locked after performing appropriate data cleaning. Analysis will be based on data collected through Post-Treatment Week 12. The data for the interim analysis will be stored in Oracle Clinical, transferred into SAS datasets, and any new data after the interim analysis will be added as a new version of the SAS datasets.
All analyses will be conducted by statisticians at AbbVie according to the methodologies specified in this IAP. There is no intention of shortening the follow-up time of Part 1a subjects based on efficacy findings from the interim analysis. The intention is to follow all Part 1a subjects who receive study drug for 48 weeks following treatment. There will be no statistical adjustment employed due to this interim analysis.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

Part 1a Intent-to-Treat (ITT) Population

All randomized subjects in Part 1a of the study who receive at least one dose of study drug will be included in the Part 1a ITT population. The data from the Part 1a ITT population will be presented by the treatment group assigned at the time of randomization (12-week treatment duration [Arm A] or 24-week treatment duration [Arm B]).

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

Efficacy, PRO and resistance analyses will be performed on the Part 1a ITT population.

Part 1a Safety Population

All randomized subjects in Part 1a of the study who receive at least one dose of study drug will be included in the safety population. Safety analyses will be performed on the safety population according to actual treatment received (Arm A or Arm B) during the majority of the entire Treatment Period even if this differs from the randomized treatment assignment. If all Part 1a subjects take the treatment to which they were randomly assigned, the Part 1a safety population will be the same as the Part 1a ITT population.
Demographic and safety analyses will be performed on the Part 1a safety population.

5.2 Variables Used for Stratification of Randomization

Approximately 60 subjects will be randomized in a 1:1 ratio to Arm A or Arm B in Part 1a of the study. Randomized subjects 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).

6.0 Analysis Conventions

6.1 Definition of Baseline and Final Assessment

Definition of Baseline

The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received. All assessments on Study Day 1 should be performed prior to administering the first dose of study drug per protocol. The baseline value is therefore determined by the last non-missing measurement collected on or before the first day of study drug administration.

If multiple measurements are recorded on the same day, the last measurement recorded prior to dosing will be used as the baseline value. If these multiple measurements occur at the same time or time is not available, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as the baseline value. This same baseline value will be used for the Treatment and PT Periods.

Safety assessments that are related to a serious adverse event that occurred on the first dose day are excluded when applying this algorithm.
Definition of Study Days (Days Relative to the First Dose of Study Drug)

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

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

For all subjects who receive at least one dose of study drug, study drug end days are calculated relative to the last dose of study drug. The last day of study drug is defined as Study Drug End Day 0. Days before it have negative study drug end days and days after it have positive study drug end days.

Definition of Final Treatment Value

The final treatment value for each subject is the last non-missing measurement collected after Study Day 1 and within 2 days of the last dose of study drug (i.e., on or before Study Drug End Day 2).

Definition of Final Post-Treatment Value

The final post-treatment value for each subject is the last non-missing measurement collected after Study Drug End Day 2.

6.2 Definition of Analysis Windows

For efficacy analyses of HCV RNA and resistance, the time windows specified in Table 1 and Table 2 describe how efficacy data are assigned to protocol-specified time points during the Treatment and Post-Treatment Periods, respectively. All time points and corresponding time windows are defined based on the blood sample collection date.

For efficacy analyses of HIV-1 RNA and CD4+ T-cell count and percentage, the time windows specified in Table 3 and Table 4 describe how efficacy data are assigned to
protocol-specified time points during the Treatment and Post-Treatment Periods, respectively. All time points and corresponding time windows are defined based on the blood sample collection date.

*Table 5* will be used for visit windows of analyses of health-related quality of life (QoL) patient reported outcomes (PROs) collected throughout the study.

For laboratory data and vital signs, the time windows specified in *Table 6* and *Table 7* describe how data are assigned to protocol-specified time points during the Treatment and Post-Treatment Periods, respectively.

For HCV efficacy analysis, if more than one assessment is included in a time window, the assessment closest to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. The only exception to this is for the SVR windows (e.g., SVR₄ and SVR₁₂); for these windows, the last value in the window will be used.

For efficacy analysis of HIV-1 RNA and CD₄+ T-cell count and percentage as well as safety analysis of a laboratory parameter or a vital sign parameter, if more than one assessment is included in a time window, the assessment closest to the nominal time will be used. If there are two observations equally distant to the nominal time, the latest one will be used in analyses. The only exception to this is for the analysis of HIV virologic outcomes using the FDA snapshot algorithm at end of treatment (EOT) and Post-Treatment Week 12 (PTW₁₂). For these windows, the last HIV-1 RNA value in the window will be used.

If multiple measurements are made on the same day for a safety laboratory parameter or a vital sign parameter, the average of the values will be used in analyses, unless otherwise noted. For summaries of shifts from baseline and potentially significant values, multiple values on the same day will not be averaged; all values will be considered for these analyses.
Table 1. Analysis Time Windows for HCV RNA and Resistance Endpoints (Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day/Time (Study Day)</th>
<th>Time Window (Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline/Day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤ 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Week 16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td>Week 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td>Week 24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>168</td>
<td>155 to 182</td>
</tr>
<tr>
<td>Final Treatment Visit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Day of first dose of study drug.

<sup>b</sup> Visits at Weeks 16 – 24 are only applicable to subjects assigned to 24 weeks of treatment (e.g., Arm B subjects or Arm A subjects whose treatment was extended).

<sup>c</sup> The last value within the window will be used to define Final Treatment Visit value. The lower and upper bounds of this Final Treatment Visit window are Study Day 2 and Study Drug End Day 2, respectively.

Note: Data must also have Study Drug End Day ≤ 2 for all windows. The result closest to the scheduled time point will be used.
### Table 2. Analysis Time Windows for HCV RNA and Resistance Endpoints (Post-Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit(^a)</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 2</td>
<td>14</td>
<td>3 to 21</td>
</tr>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>22 to 42</td>
</tr>
<tr>
<td>Post-Treatment Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>71 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24(^b)</td>
<td>168</td>
<td>127 to 210</td>
</tr>
<tr>
<td>Post-Treatment Week 36(^b)</td>
<td>252</td>
<td>211 to 294</td>
</tr>
<tr>
<td>Post-Treatment Week 48(^b)</td>
<td>336</td>
<td>295 to 378</td>
</tr>
<tr>
<td>SVR(_4)^c</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>SVR(_{12})^c</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>SVR(_{24})^c</td>
<td>168</td>
<td>127 to 210</td>
</tr>
</tbody>
</table>

---

a. Post-Treatment Visits are applicable for subjects who received at least one dose of study drug.
b. These endpoints will not be analyzed for this interim analysis.
c. For SVR windows, the last value in the window will be used.

Note: Data must have Study Drug End Day > 2 for all windows. Study Drug End Day 0 is defined as the day of the last dose of study drug. The result closest to the scheduled time point will be used, except for SVR\(_4\), SVR\(_{12}\), and SVR\(_{24}\). For SVR endpoints, the last value in the window will be used.
Table 3. **Analysis Time Windows for HIV-1 RNA and CD4+ T-Cell Counts**

(Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day/Time (Study Day)</th>
<th>Time Window (Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1/Baseline(^a)</td>
<td>1</td>
<td>(\leq 1)</td>
</tr>
<tr>
<td>Week 2</td>
<td>14</td>
<td>2 to 21</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>22 to 42</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>71 to 98</td>
</tr>
<tr>
<td>Week 16(^b)</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td>Week 20(^b)</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td>Week 24(^b)</td>
<td>168</td>
<td>155 to 182</td>
</tr>
</tbody>
</table>

\(^a\) Day of first dose of study drug. A value is considered to be Baseline if it is the last non-missing value on or before Study Day 1.

\(^b\) Applicable to subjects with 24 weeks of treatment.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day \(\leq 2\).

Table 4. **Analysis Time Windows for HIV-1 RNA and CD4+ T-Cell Counts**

(Post-Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24(^a)</td>
<td>168</td>
<td>127 to 210</td>
</tr>
<tr>
<td>Post-Treatment Week 36(^a)</td>
<td>252</td>
<td>211 to 294</td>
</tr>
<tr>
<td>Post-Treatment Week 48(^a)</td>
<td>336</td>
<td>295 to 378</td>
</tr>
</tbody>
</table>

\(^a\) These endpoints will not be analyzed for this interim analysis.

Note: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2.
Table 5. **Analysis Time Windows for PRO Instruments**

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

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>3 to 56</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>57 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24&lt;sup&gt;e&lt;/sup&gt;</td>
<td>168</td>
<td>127 to 252</td>
</tr>
<tr>
<td>Post-Treatment Week 48&lt;sup&gt;e&lt;/sup&gt;</td>
<td>336</td>
<td>253 to 378</td>
</tr>
<tr>
<td>Final Post-Treatment Visit&lt;sup&gt;f&lt;/sup&gt;</td>
<td>&gt; 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Day of first dose of study drug. A value is considered to be baseline if it is the last non-missing value on or before Study Day 1.

<sup>b</sup> Applicable to subjects with 24 weeks of treatment.

<sup>c</sup> PRO data was not collected at Weeks 16 and 20. Values in the analysis windows for Weeks 16 and 20 will not be displayed in mean change from baseline summary tables.

<sup>d</sup> The last value within the window will be used to define the final on-treatment value. The upper bound of this final window is Study Drug End Day ≤ 2.

<sup>e</sup> These endpoints will not be analyzed for this interim analysis.

<sup>f</sup> The last value within the Post-Treatment Period window will be used to define the final post-treatment value. The lower bound of this final window is Study Drug End Day 3 with no upper bound.

Note: The result closest to the scheduled time point will be used. For visits through Week 24 of the Treatment Period, data must also be within 2 days of the last dose of study drug. For post-treatment visits, data must also have Study Drug End Day > 2.
### Table 6. Laboratory Data and Vital Sign Visit Windows (Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day/Time (Study Day)</th>
<th>Time Window (Study Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1/Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Week 1</td>
<td>7</td>
<td>2 to 10</td>
</tr>
<tr>
<td>Week 2</td>
<td>14</td>
<td>11 to 21</td>
</tr>
<tr>
<td>Week 4</td>
<td>28</td>
<td>22 to 35</td>
</tr>
<tr>
<td>Week 6</td>
<td>42</td>
<td>36 to 49</td>
</tr>
<tr>
<td>Week 8</td>
<td>56</td>
<td>50 to 63</td>
</tr>
<tr>
<td>Week 10</td>
<td>70</td>
<td>64 to 77</td>
</tr>
<tr>
<td>Week 12</td>
<td>84</td>
<td>78 to 98</td>
</tr>
<tr>
<td>Week 16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td>Week 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td>Week 24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>168</td>
<td>155 to 182</td>
</tr>
<tr>
<td>Final Treatment Visit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 to ≤ 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Day of first dose of study drug.

<sup>b</sup> Applicable to subjects with 24 weeks of treatment.

<sup>c</sup> The last value within the window will be used to define the final on-treatment value. The lower and upper bounds of the Final Treatment Visit window are Study Day 2 and Study Drug End Day 2, respectively.

**Notes:**
- The result closest to the scheduled time point will be used. Data must also have Study Drug End Day ≤ 2.
- IP-10 is measured at baseline, Week 4, Week 8, Week 12, Week 24 (Arm B only), or EOT. Total Insulin is measured at baseline, Week 12, Week 24 (Arm B only), or EOT. Clinical assessments of ascites and hepatic encephalopathy for Child-Pugh classification are collected at Screening, baseline, Week 12, Week 24 (Arm B only), or EOT on subjects with compensated cirrhosis only. FibroTest samples are collected at Screening only.
Table 7. Laboratory Data and Vital Sign Visit Windows (Post-Treatment Period)

<table>
<thead>
<tr>
<th>Scheduled Visit</th>
<th>Nominal Day (Study Drug End Day)</th>
<th>Time Window (Study Drug End Days Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment Week 2</td>
<td>14</td>
<td>3 to 21</td>
</tr>
<tr>
<td>Post-Treatment Week 4</td>
<td>28</td>
<td>22 to 42</td>
</tr>
<tr>
<td>Post-Treatment Week 8</td>
<td>56</td>
<td>43 to 70</td>
</tr>
<tr>
<td>Post-Treatment Week 12</td>
<td>84</td>
<td>71 to 126</td>
</tr>
<tr>
<td>Post-Treatment Week 24a</td>
<td>168</td>
<td>127 to 210</td>
</tr>
<tr>
<td>Post-Treatment Week 36a</td>
<td>252</td>
<td>211 to 294</td>
</tr>
<tr>
<td>Post-Treatment Week 48a</td>
<td>336</td>
<td>295 to 378</td>
</tr>
<tr>
<td>Final Post-Treatment Visit</td>
<td>&gt; 2 days after last dose of study drug</td>
<td></td>
</tr>
</tbody>
</table>

a. These endpoints will not be analyzed for this interim analysis.

Notes: The result closest to the scheduled time point will be used. Data must also have Study Drug End Day > 2.

Vital signs and hematology, chemistry, urinalysis, and coagulation panels are collected at every Post-Treatment Period visit. IP-10 samples are collected at Post-Treatment Weeks 24 and 48 (or upon study discontinuation). Total Insulin is not collected during Post-Treatment Period. Clinical assessments of ascites and hepatic encephalopathy for Child-Pugh classification are collected at Post-Treatment Week 12 and 48 (or upon study discontinuation) for the subjects with cirrhosis at baseline.

6.3 Missing Data Imputation

Data will be imputed for HCV RNA analyses of SVR, for HIV-1 RNA analyses of HIV virologic response, and for analyses of QoL questionnaires.

HCV RNA

HCV RNA values will be selected for analysis based on the analysis windows defined in Section 6.2. If an HCV RNA value is missing within a study visit window, then the missing HCV RNA value will be imputed via a flanking imputation approach. When there is no HCV RNA value in a defined visit window, the HCV RNA values immediately preceding and succeeding the window will be used for the flanking imputation regardless of the values chosen in the preceding and succeeding windows. If a subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and the succeeding value, then the HCV RNA
level will be imputed as undetectable or unquantifiable, respectively, at this visit for this subject. In addition, if a subject has an unquantifiable HCV RNA level at the preceding value and an undetectable HCV RNA level at the succeeding value, or vice versa, the HCV RNA level will be imputed as unquantifiable at this visit for this subject.

If an HCV RNA value is missing within the SVR windows, then a flanking imputation including backward imputation approach will be used. The flanking imputation approach will be used first. If the SVR window is still missing an HCV RNA value, then a backward imputation approach will be carried out where if the nearest HCV RNA value after the SVR window is unquantifiable or undetectable, then it will be used to impute the HCV RNA value in the SVR window.

If a subject starts another treatment for HCV, then all HCV RNA values for this subject measured on or after the start date of the new HCV treatment will be excluded from analyses. The subject will be considered a failure for summaries of viral response at all time points after the start of the new HCV treatment.

**HCV RNA < LLOQ Analyses for SVR**

If a subject is missing an HCV RNA value for the visit window associated with the analysis of SVR after performing the imputations described above, then this value will be imputed with an HCV RNA value from a local laboratory if present; otherwise, the HCV RNA value for this visit will be missing. Subjects with missing HCV RNA data in the analysis window, after imputations, will be imputed as a failure.

**HCV RNA Analyses for Relapse and Virologic Failure**

If HCV RNA values from the central laboratory are missing but a local laboratory value is present in the appropriate time period, then the local laboratory value will be used to assess post-treatment relapse and on-treatment virologic failure.
HIV-1 RNA

HIV-1 RNA values will be selected for analysis based on the analysis windows defined in Section 6.2, Table 3 and Table 4. For analyses using HIV-1 RNA levels, only data from the central laboratory will be included in the analyses.

HIV-1 RNA Levels Below the LLOQ (40 Copies/mL)

Imputations for missing data will be as specified for the following analyses of virologic response defined as plasma HIV-1 RNA < 40 copies/mL (LLOQ):

- ITT – Noncompleter = Failure (NC = F): when there is no HIV-1 RNA value in a defined visit window, the HIV-1 RNA values immediately preceding and succeeding the window will be used for the flanking imputation regardless of the values chosen in the preceding and succeeding windows. If a subject has a missing HIV-1 RNA value at a post-baseline visit but with the immediately preceding value and the succeeding HIV-1 RNA values both below LLOQ, then the HIV-1 RNA value will be imputed as below LLOQ at this visit for this subject. Otherwise, the HIV-1 RNA value will be imputed as above the LLOQ at that visit.

- ITT – Missing = Failure (M = F): any subject with a missing value at a visit for any reason will be considered to be above the LLOQ at that visit.

- ITT – Last Observation Carried Forward (LOCF): for each subject, missing values will be replaced by the last available nonmissing value prior to the missing data point.

- Observed Data: missing values will be excluded from the analysis (i.e., no imputation of missing data).

The four imputations above will be utilized for the summary of number and percentage of subjects with HIV-RNA < 40 copies/mL at each applicable post-baseline visit.

Suppression of HIV-1 RNA Level Using the FDA Snapshot Algorithm

The determination of HIV virologic response at EOT and at PTW12 using the FDA snapshot algorithm will utilize different rules for imputation as discussed in Section 10.1.
Quality of Life Questionnaires

If more than 4 items of the 16-item HCV-PRO are missing responses, then the total score is set to missing. When four or fewer items are missing, the mean of the non-missing items will be used to impute the responses for the missing item(s) and a total score will be calculated.

For EQ-5D-5L, no imputation will be performed for missing items.

For SF-36 QoL questionnaires, if a respondent answers at least 50% of the items in a multi-item scale of SF-36, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing. The Mental and Physical Component measure will not be computed if any domain is missing.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

Demographics, baseline characteristics, medical history, and previous/concomitant medications will be summarized by treatment group and overall on the Part 1a safety population.

7.1 Demographic and Baseline Characteristics

Demographics include age, weight, body mass index (BMI), sex, race, ethnicity, age categories (< 55 or ≥ 55 years; < 65 or ≥ 65 years), birth year category (< 1945, 1945 to 1965, > 1965), BMI category (< 30 or ≥ 30 kg/m²), and women of childbearing potential (females between the ages of 18 and 55 years, inclusive).

Baseline characteristics will include prior HCV treatment history (treatment-naive or pegIFN/RBV treatment-experienced (null responder [definition 1 or 2], partial responder, or relapser), HCV genotype 1 subtype (1a, 1b, or other), IL28B genotype (CC, CT, or TT; CC or non-CC), baseline log₁₀ HCV RNA levels (continuous), baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL), baseline HIV-1 RNA levels (< 40 or ≥ 40 copies/mL),
baseline CD4+ T-cell count (continuous), baseline CD4+ T-cell percentage (continuous),
baseline CD4+ T-cell count (< 200, 200 to < 350, 350 to < 500, or ≥ 500 cells/mm³), HIV
ART regimen (ATV or RAL), baseline IP-10 (continuous), baseline IP-10 (< 600 or
≥ 600 ng/L), baseline HOMA-IR (< 3 or ≥ 3 mU × mmol/L²), presence of cirrhosis (yes,
no), baseline fibrosis stage (F0 – F1, F2, F3, or F4), history of diabetes (yes, no), history
of bleeding disorders (yes, no), history of depression or bipolar disorder (yes, no), tobacco
(user, ex-user, or non-user) and alcohol use (drinker, ex-drinker, or non-drinker), and
former injection drug user status (yes, no, unknown). Summary of demographics
variables will be provided on the Part 1a safety population only for each treatment group
and overall across treatment groups.

If the IL28B genotype result is not available from a sample collected during the Screening
period, then a result available from a sample collected at any time during the study will be
used to summarize IL28B genotype.

HOMA-IR is defined as fasting glucose (mmol/L) × fasting insulin (μIU/mL) ÷ 22.5.
Subjects who do not have a fasting glucose value and/or a fasting insulin value at baseline
will be excluded from the summary of baseline HOMA-IR.

Histories of diabetes, depression or bipolar disorder, and bleeding disorders will be based
on the Medical History (MH) eCRF. History of diabetes is defined as presence of
"Metabolic/Diabetes mellitus" on the MH eCRF. History of depression or bipolar
disorder is defined as presence of "Neurologic and Psychiatric System/Depression" or
"Neurologic and Psychiatric System/Bipolar Disorder" on the MH eCRF. All medical
history terms within "Clotting/bleeding problems" or "Other" under the "Blood" body
system on the MH eCRF will be reviewed to identify subjects with a history of bleeding
disorders (e.g., hemophilia). Medical history terms within "Other Body System" or any
condition/diagnosis of "Other" may be reviewed for all baseline characteristics
determined by the MH eCRF.

Baseline fibrosis stage is defined for subjects with non-missing liver biopsy scores,
FibroScan scores, or FibroTest scores. If a subject has more than one score recorded, then
only one score will be used to categorize the subject. If a biopsy score is present, then it will be used to categorize the subject, regardless of the FibroScan/FibroTest score. Similarly, if a FibroScan score is present along with a FibroTest score, while a biopsy score is absent, then the FibroScan score will be used to categorize the subject. If biopsy and FibroScan scores are not present and more than one FibroTest result is available, then the baseline FibroTest result (i.e., last non-missing FibroTest result on or before baseline) and concordant APRI result (i.e., last non-missing APRI result on or before baseline) will be used to categorize the subject.

Subjects will be categorized as F0 – F1, F2, F3, or F4 according to Table 8.

Table 8. Baseline Fibrosis Stage

<table>
<thead>
<tr>
<th>Baseline Fibrosis Stage, Metavir Equivalents</th>
<th>Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score</th>
<th>Liver Biopsy Ishak Score</th>
<th>FibroScan (kPa)</th>
<th>FibroTest</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 – F1</td>
<td>0 or 1</td>
<td>0, 1, or 2</td>
<td>&lt; 8.8</td>
<td>≤ 0.48 with APRI ≤ 2</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>3</td>
<td>≥ 8.8 to &lt; 9.6</td>
<td>0.49 to 0.58 with APRI ≤ 2</td>
</tr>
<tr>
<td>F3</td>
<td>3</td>
<td>4</td>
<td>≥ 9.6 to &lt; 12.5</td>
<td>0.59 to 0.72 with APRI ≤ 2</td>
</tr>
<tr>
<td>F4</td>
<td>4</td>
<td>5 or 6</td>
<td>≥ 12.5</td>
<td>≥ 0.73 with APRI &gt; 2</td>
</tr>
</tbody>
</table>

Summary statistics (N, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g., age and BMI), and a one-way analysis of variance (ANOVA) with treatment group as the factor will be used to compare treatment groups (12 weeks versus 24 weeks). The number and percentage of subjects will be presented for categorical variables (e.g., sex and race), and treatment groups will be compared using a chi-square test.
7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group and overall. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized by treatment group and overall for the Part 1a safety population. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. The number and percentage of subjects taking prior or concomitant medications will be summarized by generic drug name based on the WHO Drug Dictionary. The prior HCV medications (pegIFN and RBV) taken by the treatment experienced subjects will be summarized separately from other prior medications for each treatment group.

Medications related to the treatment of HCV will be collected in the PT Period and will be summarized by generic drug name for each treatment group. A post-treatment medication for the treatment of HCV is defined as any medication taken on or after the last (maximum) dose of study drug and entered as "Post treatment HCV medications" on the eCRF.

A listing of any subject that has erythropoietin usage during the study will be provided with subject number as well as start and end date of erythropoietin usage.
8.0 Patient Disposition

The number of subjects for each of the following categories will be summarized overall and by investigator for each treatment group and overall on the Part 1a safety population.

- Subjects randomized in Part 1a;
- Subjects who took at least one dose of study drug;
- Subjects who completed study drug;
- Subjects who discontinued from study drug;
- Subjects who completed the study;
- Subjects who discontinued from the study;
- Subjects ongoing in the Post-Treatment Period at the time of the interim analysis.

The number and percentage of subjects who discontinued study drug will be summarized by reason (all reasons) and by primary reason (per eCRF) for each treatment group and overall, as described below. Similar summaries will be provided for discontinuations from the study.

The number and percentage of screened subjects who screen failed for Part 1a and the reasons for screen failure (inclusion/exclusion criteria, withdrew consent, lost to follow-up, and/or other) will be summarized in a table. A CSR listing of reason for screen failure will be provided for all subjects who screen failed.

The number and percentage of subjects in Part 1a, as applicable, will be summarized by treatment group and overall for:

- Subjects with interruptions of all study drugs for toxicity management;
- Subjects with any RBV dose modifications;
  - Subjects with RBV dose modification due to decrease in hemoglobin;
  - Subjects with RBV dose modification due to decrease in creatinine clearance;
Subjects with RBV dose modification due to other reasons;

- Subjects with any RBV dose modification to 0 mg (i.e., RBV interruptions).

Reasons for study drug interruptions and RBV dose modifications will be presented in the CSR listings.

9.0 Study Drug Exposure and Compliance

9.1 Exposure

The duration of exposure to study drug will be summarized for each treatment group and overall in the Part 1a safety population. Duration of exposure is defined for each subject as the last study drug dose date minus the first study drug dose date plus 1 day.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented. Study drug duration also will be summarized with frequencies and percentages for both treatment groups using the following categories:

- 1 to 15 days, 16 to 30 days, 31 to 45 days, 46 to 60 days, 61 to 75 days, and > 75 days.
- 1 to 15 days, 16 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 150 days, and > 150 days.

9.2 Compliance

At each protocol-specified visit, the total number of capsules/tablets dispensed and returned is recorded for each type of study drug. The compliance for each study drug (ABT-450/r/ABT-267, ABT-333, and RBV) within the Treatment Period for Part 1a will be calculated as the percentage of capsules or tablets taken relative to the total tablets, respectively, expected to be taken. The total number of tablets prescribed will be equal to the total number of tablets that should have been taken per the protocol for the duration that the subject was in the Treatment Period (date of last dose – date of first dose + 1 day). Study drug interruptions due to an adverse event or other planned interruptions recorded
on the eCRF will be subtracted from the duration. For compliance to RBV, RBV dose modifications due to adverse events, toxicity management, or weight changes as recorded on the RBV Dose Modifications eCRF will be used to modify the total number of tablets that should have been taken. Compliance for each study drug will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum by treatment group and overall. In addition, the percentage of compliant subjects will be calculated by treatment group and overall for each study drug. A subject is considered to be compliant if the percentage is between 80% and 120%.

In addition, adherence to RBV will be assessed by using the Medication Event Monitoring Systems (MEMSTM, AARDEX Group Ltd., Switzerland) throughout the study. The MEMS data will be downloaded from the vendor's web system, and a report of compliance will be supplied to AbbVie by AARDEX. The adherence summary statistics per subject provided in the report from AARDEX are those commonly used in the literature: taking adherence, correct adherence, and timing adherence. The adherence summary statistics will be available for the final CSR at the end of the study.

10.0 Efficacy Analysis

10.1 General Considerations

General Considerations

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 (when rounded to three decimal places). Efficacy analyses will be performed on the ITT population for Part 1. The data from the ITT population will be presented by the treatment group assigned at the time of randomization (12-week arm or 24-week arm).

IL28b rs12979860 will be resulted as C/C, C/T, T/T, or Unable to Assign Genotype by the central laboratory. Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v2.0. For this assay, the lower limit of detection (LLOD) is 15 IU/mL and lower limit of quantification (LLOQ) is 25 IU/mL. HCV RNA
results that are detectable but not quantifiable are reported as "< 25 IU/mL HCV RNA DETECTED" and those that are undetectable are reported as "HCV RNA NOT DETECTED" in the database. The notation "HCV RNA < LLOQ" is used to represent all HCV RNA values < 25 IU/mL, including values reported as "HCV RNA NOT DETECTED" or "< 25 IU/mL HCV RNA DETECTED." HCV RNA ≥ LLOQ are all quantifiable values of 25 IU/mL or greater.

Plasma HIV-1 RNA will be measured by the central laboratory using the Abbott RealTime HIV-1 Assay. The LLOQ for this assay is 40 copies/mL. HIV-1 RNA results below the LLOQ are reported as: "< 40 CP/ML HIV-1 RNA DETECTED" in the database. The notation "HIV-1 RNA < LLOQ" is used to represent all HIV RNA values < 40 copies/mL, including values reported as "NO HIV-1 RNA DETECTED" in the database. HIV-1 RNA ≥ LLOQ are all quantifiable values of 40 copies/mL or greater.

**Definitions for HCV Efficacy Endpoints**

Note that a confirmed quantifiable post-treatment value is defined as any two consecutive post-treatment HCV RNA measurements ≥ LLOQ. During treatment, a confirmed quantifiable value is defined as any two consecutive HCV RNA values ≥ LLOQ, either both during treatment or at the final treatment measurement and the next consecutive post-treatment measurement.

**Rebound** = confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 log10 IU/mL above nadir) at any time point during treatment. A single rebound value (≥ LLOQ or > 1 log10 above nadir) followed by lost to follow-up would be considered a rebound (i.e., will not require confirmation).

**On-treatment virologic failure** = Rebound (see **Rebound** definition) or failure to suppress during treatment (all on-treatment values of HCV RNA ≥ LLOQ) with at least 6 weeks (defined as study drug duration ≥ 36 days) of treatment.
SVR₄ = HCV RNA < LLOQ in the SVR₄ window (4 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

SVR₁₂ = HCV RNA < LLOQ in the SVR₁₂ window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (≥ LLOQ) post-treatment value before or during that SVR window.

Relapse₁₂ = confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of study drug (up to and including the SVR₁₂ assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment.

For relapse analyses, the completion of treatment is defined as a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment (Arm A) or study drug duration ≥ 154 days for subjects assigned to 24 weeks of treatment (Arm B). If the last available post-treatment value is ≥ LLOQ, then the subject will be considered a relapse (i.e., will not require confirmation). Relapse analyses will exclude subjects who do not have any post-treatment HCV RNA values.

Reasons for SVR₁₂ Non-Response

Subjects who do not achieve SVR₁₂ (SVR₁₂ non-responders) will be categorized as having:

1. On-treatment virologic failure (see On-treatment virologic failure definition);
2. Relapse (defined according to the Relapse₁₂ definition for subjects who complete treatment);
3. Prematurely discontinued study drug with no on-treatment virologic failure (defined as any SVR₁₂ non-responder who prematurely discontinued study drug (duration < 77 days for Arm A or duration < 154 days for Arm B) and did not meet the On-treatment virologic failure definition);
4. Missing follow-up data in the SVR\textsubscript{12} window (defined as any subject who completed study drug without data in the SVR\textsubscript{12} window after applying the imputation rules and not meeting the definitions of [1], [2], or [3]);

5. Other (defined as any SVR\textsubscript{12} non-responder not meeting the definitions of [1] – [4], such as a subject with a single quantifiable value within the SVR\textsubscript{12} window followed by an undetectable value beyond the SVR\textsubscript{12} window).

**Definitions for HIV-1 RNA Efficacy Endpoints**

Time windows for HIV-1 RNA efficacy endpoints to be analyzed using the FDA snapshot algorithm are described as follows.

- The time window for HIV virologic outcomes at EOT is the HIV Week 12 window for Arm A (Treatment Day 71 – 98) or HIV Week 24 window (Treatment Day 155 – 182) for Arm B, as described in Table 3.
- The time window for HIV virologic outcomes at PTW12 is the HIV PTW12 window (Post-Treatment Day 57 – 126) for both arms, as described in Table 4, which is the same time window as the HCV SVR\textsubscript{12} window defined in Table 2.

The subject's HIV virologic outcomes at EOT will be determined per the FDA Snapshot Algorithm in the order below. All of the Part 1a ITT population will be included in the analysis except subjects who have not discontinued from study before the upper bound of the EOT window (Day 98 for Arm A; Day 182 for Arm B) and have not reached the upper bound of the EOT window. Vital signs visit dates will be used to determine a subject's study duration.

1. **HIV virologic failure at EOT** = HIV-1 RNA value $\geq 40$ copies/mL at EOT; or if the subject discontinues study drug due to HIV virologic failure with the last HIV-1 RNA value prior to study drug discontinuation $\geq 40$ copies/mL; or if the subject discontinues study for reason(s) other than AE or death on or before the upper bound of the EOT window (Day 98 for Arm A; Day 182 for Arm B) with the last HIV-1 RNA value prior to study discontinuation $\geq 40$ copies/mL; or if the subject
switches the HIV anchor (atazanavir to raltegravir, or raltegravir to atazanavir) on or before the upper bound of the EOT window with the last HIV-1 RNA value on or before the day of the switch ≥ 40 copies/mL.

2. **HIV-1 RNA suppression (or HIV virologic success) at EOT** = HIV-1 RNA value < 40 copies/mL at EOT.

3. **No HIV virologic data at EOT** is defined by subcategories as follows:
   - **Discontinued study due to AE or death** if the subject prematurely discontinues study due to AE or death on or before the upper bound of the EOT window and has no HIV-1 RNA value in that window; or
   - **Discontinued study due to other reason** if the subject prematurely discontinues study due to reason(s) other than AE or death on or before the upper bound of the EOT window and has no HIV-1 RNA value in that window; or
   - **Missing data during window but on study** if the subject has not discontinued from study on or before the upper bound of the EOT window and has no HIV-1 RNA value in that window.

The subject's HIV virologic response at PTW12 will be determined per the FDA Snapshot Algorithm in the order below. All of the Part 1a ITT population will be included in the analysis except subjects who have not discontinued from study before the upper bound of the HIV PTW12 window (Post-Treatment Day 126 for both arms) and have not reached the upper bound of the HIV PTW12 window. Vital signs visit dates will be used to determine a subject's study duration.

1. **HIV virologic failure at PTW12** = HIV-1 RNA value ≥ 40 copies/mL in the HIV PTW12 window, or if the subject discontinues study drug due to HIV virologic failure with the last HIV-1 RNA value prior to study drug discontinuation ≥ 40 copies/mL; or if the subject discontinues study for reason(s) other than AE or death on or before the upper bound of the HIV PTW12 window (Post-Treatment Day 126 for both arms) with the last HIV-1 RNA value prior to study discontinuation ≥ 40 copies/mL; or if the subject switches the HIV anchor
(atazanavir to raltegravir, or raltegravir to atazanavir) on or before the upper bound of the HIV PTW12 window with the last HIV-1 RNA value on or before the day of the switch ≥ 40 copies/mL.

2. **HIV-1 RNA suppression (or HIV virologic success) at PTW12** = HIV-1 RNA value < 40 copies/mL in the HIV PTW12 window.

3. **No HIV virologic data at PTW12** is defined by subcategories as follows:
   - **Discontinued study due to AE or death** if the subject prematurely discontinues study due to AE or death on or before the upper bound of the HIV PTW12 window and has no HIV-1 RNA value in that window; or
   - **Discontinued study due to other reason** if the subject prematurely discontinues study due to reason(s) other than AE or death on or before the upper bound of HIV PTW12 window and has no HIV-1 RNA value in that window; or
   - **Missing data during window but on study** if the subject has not discontinued from study on or before the upper bound of the HIV PTW12 window and has no HIV-1 RNA value in that window.

### 10.2 Analysis of the Efficacy Endpoints

#### 10.2.1 Primary and Secondary Efficacy Analyses

The efficacy endpoints for the interim analysis are listed as follows. HCV RNA values and SVR12 will be imputed as described in Section 6.3.

**Primary Efficacy Endpoint**

- The number and percentage of subjects achieving SVR12 within each treatment group will be calculated, and the 2-sided 95% confidence interval will be presented using the Wilson score method\(^1\) for the binomial proportion.
Secondary Efficacy Endpoints

- The percentage of subjects with SVR$_{12}$ in the 24-week arm will be compared to that of the 12-week arm using Fisher's exact test.
- The number and percentage of subjects in each arm with on-treatment virologic failure during the Treatment Period (defined per On-treatment virologic failure definition) will be calculated.
- The number and percentage of subjects in each arm with post-treatment relapse (defined per Relapse$_{12}$ definition) will be calculated.
- The number and percentage of subjects in each arm with plasma HIV-1 RNA suppression (i.e., HIV virologic success) at EOT and PTW12 using the FDA Snapshot Algorithm as defined in Section 10.1 will be calculated.
- The number and percentage of subjects in each arm with each of the HIV-1 RNA virologic outcomes at EOT and Post-Treatment Week 12 will be summarized by reason using the FDA Snapshot Algorithm as defined in Section 10.1.

The percentages of the subjects with virologic failure during treatment, post-treatment relapse, and HIV-1 RNA suppression at EOT and PTW12 will be calculated for each arm, with the 2-sided 95% confidence intervals presented using the Wilson score method$^1$ for the binomial proportion. Note that the 2-sided 95% confidence intervals for HIV virologic outcomes at EOT and PTW12 will be calculated based on the binomial proportion of HIV virologic success versus other (i.e., virologic failure and no virologic data combined).

The number and percent of subjects who achieve SVR$_{12}$ will be presented along with the number of subjects who do not achieve SVR$_{12}$ by reason for non-response (defined in Section 10.1). The non-responders will be presented in a listing.

Subjects in each arm with each of the HIV-1 RNA virologic outcomes (i.e., virologic failure or no virologic data) at the EOT and Post-Treatment Week 12 will also be presented in a listing.
10.2.2 Additional Efficacy Analyses

The following additional efficacy endpoints will be summarized by treatment group on the Part 1a ITT population.

- The number and percentage of subjects with plasma HIV-1 RNA < 40 copies/mL at each applicable time point;
- Change from baseline in CD4+ T-cell count (absolute and percent) to each applicable post-baseline time point;
- The number and percentage of subjects with unquantifiable HCV RNA at each post-baseline visit throughout the Treatment Period (using data from the central laboratory as observed, i.e., no imputation for missing data);
- The contingency table of number of subjects with HIV-1 RNA < 40 copies/mL or ≥ 40 copies/mL by their CD4+ T-cell counts categorized as < 200 cells/μL or ≥ 200 cells/mm³ at all applicable post-baseline time points;
- The number and percentage of subjects achieving SVR₄.

The analysis of change from baseline in CD4+ T-cell count (absolute and percent) will report the mean and median values at baseline and at each applicable post-baseline visit, as well as N, mean, median, standard deviation (SD), minimum and maximum values for the change from baseline within each treatment arm. The mean change from baseline to each applicable post-baseline visits for the CD4+ T-cell counts and percentages will be compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment group as factor and baseline score as a covariate. For SVR₄, the Wilson score method¹ for the binomial proportion will be used to calculate the 2-sided 95% confidence interval.

Subjects who rebound at any time during treatment and within each protocol-specified visit (defined in Table 1) will be presented through a listing displaying the subject numbers at the first occurrence of rebound.

A listing of completers (defined as study drug duration ≥ 77 days for subjects assigned to Arm A and ≥ 154 days for subjects assigned to Arm B) with final on-treatment HCV
RNA < LLOQ who relapse within the SVR<sub>12</sub> window (defined in Table 2) will be presented displaying the first occurrence of relapse and subject's prior non-response to previous pegIFN/RBV treatment.

10.3 Resistance Analyses

10.3.1 HCV Resistance Analyses

If possible, subjects randomized in Part 1a treated with study drug who do not achieve SVR<sub>12</sub> will have resistance testing conducted if (1) they have on-treatment rebound; (2) if they have post-treatment relapse, with a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment (Arm A) or study drug duration ≥ 154 days for subjects assigned to 24 weeks of treatment (Arm B); or (3) if they have at least 6 weeks of treatment and fail to suppress by Week 6 (i.e., meet virologic stopping criteria). Subjects meeting one of these criteria will be referred to as subjects in the primary virologic failure (PVF) population, and a listing by subject that includes HCV subgenotype, IL28B genotype, reason for SVR<sub>12</sub> non-response, time point(s) sequenced as closest to time of VF, and HCV RNA value at the VF time point(s) will be produced for these subjects. In addition, all listings described below will display HCV subgenotype and reason for SVR<sub>12</sub> non-response in the subject identifier for each subject. A separate listing will delineate all subjects in the PVF population for whom no sequencing was performed (e.g., lost to follow-up while HCV RNA ≤ 1000 IU/mL).

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

Only samples with an HCV RNA level of $\geq 1000$ 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 (VF) is $< 1000$ IU/mL, the sample closest in time after the failure with an HCV RNA level $\geq 1000$ IU/mL will be used if available. Clonal sequencing of a given target will be performed only if no variants are detected at signature resistance-associated amino acid positions by population sequencing in that sample. In addition, clonal sequencing may be performed if there is a complex mixture of amino acids at one or more signature resistance-associated position that cannot be resolved by population sequencing. Neither clonal sequencing nor phenotype analysis will be included in the interim analysis.

Baseline samples will be sequenced by population sequencing as described above. For each subject in the PVF population, at least two SVR$_{12}$-achieving subjects will be matched to the extent possible by HCV subgenotype, baseline HCV RNA level, and IL28B genotype. Baseline samples from these matched SVR$_{12}$-achieving subjects will also be sequenced by population sequencing.

The regions of interest for population sequencing from all evaluated time points in this study are those encoding complete NS3/4A, NS5A, and NS5B, while for clonal sequencing they are those encoding NS3 amino acids 1 – 181, NS5A amino acids 1 – 215, and NS5B amino acids 300 – 591. The regions encoding NS3 1-357, NS5A 1-215, and NS5B 300-591 will be sequenced for analysis of baseline samples from the matched set that will include at least 2 SVR-achieving subjects for every 1 PVF subject. For phenotyping, the regions of interest are those encoding NS3 amino acids 1 – 251, full length NS5A, and full length NS5B. The prototypic reference sequence used for analysis will be H77 for genotype 1a or Con1 for genotype 1b.

For each DAA target, resistance-associated signature amino acid variants will be identified by AbbVie Clinical Virology. Amino acid positions where
resistance-associated variants have been identified in vitro and/or in vivo are 1) for ABT-450: 36, 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 in the subject and is detectable by population sequencing.

- **Post-baseline variant by clonal sequencing:** a variant at a signature resistance-associated amino acid position that was not present in a subject by population sequencing at baseline that is detected in a post-baseline sample from that subject by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).

- **Emerged variant by population sequencing:** a post-baseline variant that is observed in 2 or more subjects of the same subgenotype by population sequencing.

- **Emerged variant by clonal sequencing:** a post-baseline variant that is detected by clonal sequencing in ≥ 20% of the clones in post-baseline samples from 2 or more subjects of the same subgenotype that was not detected at baseline by population sequencing in those subjects.
• Linked variant by population sequencing: 2 or more signature resistance-associated or emerged amino acid variants identified within a target by population sequencing, and no mixture of amino acids is detected at either position.

• Linked variant by clonal sequencing: at least 2 clones from a given sample containing the same 2 or more signature resistance-associated amino acid variants by clonal sequencing.

The following data will be available in the interim analysis:

For those subjects in the PVF population, a listing by subject of all baseline variants relative to prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target (NS3, NS5A and NS5B).

In order to assess the effect of baseline variants on treatment response, the number and percentage of subjects with baseline variants at signature resistance-associated amino acid positions for each DAA target will be compared between the group of subjects in the PVF population and the matched group of subjects who achieved SVR_{12}. The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A or NS5B). The number and percentage of subjects with each baseline variant at a signature resistance-associated amino acid position within each target by HCV subgenotype will be calculated by response (PVF population or SVR_{12}) for each regimen. For each HCV subgenotype and regimen, a comparison of the percentage of subjects with each resistance-associated variant will be made between the PVF population and SVR_{12} subjects using Fisher's exact test.

The following analyses will be performed on the samples from subjects who are in the PVF population and have post-baseline resistance data available. These data will be available in the interim analysis:

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

The number and percentage of subjects with emerged variants by population sequencing, by amino acid position and variant within a DAA target at the time of VF compared to baseline will be summarized, along with the number of subjects within a DAA target and overall. The analyses will be grouped by HCV subgenotype (1a or 1b) and DAA target (NS3, NS5A, or NS5B) and will list the subject numbers of subjects with each variant.

In addition, a listing by subject and time point of all post-baseline variants (by population sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided.

Linkage between emerged or signature variants by population sequencing will also be evaluated. A listing by subject and time point of the linked variants by population sequencing for each target will be provided.

The following analyses will be performed on the samples from subjects who are in the not in the PVF population but have post-baseline sequence data available. These data will be available in the interim analysis:

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.

Resistance datasets will be submitted to the Agency according to the revised template supplied on 25 February 2013 (courtesy copy of Draft Guidance, "Attachment to
Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency; Guidance for Submitting HCV Resistance Data”.

10.3.2 HIV Resistance Analyses

If a subject randomized to Part 1a develops a confirmed, quantifiable plasma HIV-1 RNA level (HIV-1 RNA ≥ 40 copies/mL at one assessment and ≥ 500 copies/mL on repeat testing) after starting Part 1a of 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.2

10.4 Patient Reported Outcomes

The following instruments will be used to collect patient reported outcomes (PROs): HCVPRO, EQ-5D-5L, and SF-36 version 2 (SF-36v2). PROs will be collected at protocol-specified visits for all ITT subjects randomized to Part 1a of the study. The HCVPRO, EQ-5D-5L, and SF-36v2 will be collected at baseline, Weeks 4, 8, and 12, and Post-Treatment Weeks 4, 12, 24 and 48, or upon premature discontinuation of the Treatment or Post-Treatment Periods. The HCVPRO, EQ-5D-5L, and SF-36v2 will also be collected at Week 24 for subjects assigned to 24 weeks of treatment. Missing data for each instrument will be handled as described in Section 6.3.

The following exploratory analyses of PROs will be performed:

- mean change from baseline in HCVPRO total score to each applicable post-baseline time point;
- mean change from baseline in EQ-5D-5L health index score and VAS score to each applicable post-baseline time point;
• mean change from baseline to each applicable post-baseline time point in the SF-36v2 Mental Component Summary (MCS) and Physical Component Summary (PCS) measures;

• continuous plots of the change from baseline to Final Treatment Visit and PT Week 12 in the SF-36v2 PCS and MCS, HCVPRO total score, EQ-5D-5L health index score and VAS on the horizontal axis and the cumulative percent of subjects experiencing up to that change on the vertical axis;

• percentage of subjects without a decrease from baseline to Final Treatment Visit in the SF-36v2 PCS and MCS that is greater than or equal to the minimally important difference (MID) of five points;

• percentage of subjects without a decrease from baseline to Final Treatment Visit in the EQ-5D-5L health index score that is greater than or equal to its study-defined MID;

• percentage of subjects without a decrease from baseline to Final Treatment Visit in the HCVPRO total score that is greater than or equal to its study-defined MID.

The HCVPRO consists of 16 items with 5 response choices (1, 2, 3, 4, or 5) that are recoded to 0, 1, 2, 3, or 4, respectively, when deriving the total score. The total score is the sum of all 16 items and is converted to a score between 0 and 100 by

$$\text{ScaledScore} = \frac{\text{Sum} \times 100}{64}.$$ 

Subject's responses to the self-administered HCVPRO instrument will be assessed for the total score. Subject's responses to the EQ-5D-5L will be combined into a unique health state using a 5-digit code with 1 digit from each of the 5 dimensions. The EQ-5D-5L states will be converted into a single preference-weighted health utility index score by applying country-specific weights (if available) or US weights (if not available). The VAS score will be measured separately. The SF-36v2 measures dimensions of a patient's functional health and well-being in 8 domains and also provides 2 summary scores that characterize a patient's mental (MCS) and physical (PCS) health status. The score for each of the 8 domains ranges from 0 to 100 and will be normalized according to the user manual. The standardization of the normalized scores will provide the norm-based scores with a mean of 50 and a SD of 10. The 2 summary scores are based on the norm-based scores. Per the SF-36v2 instrument manual, score for
any item with multiple responses will be set to "missing." Missing item responses will be handled as described in Section 6.3. Subject's responses to the SF-36v2 will be summarized for the PCS and MCS measures.

Summary statistics (n, mean, SD, median, minimum and maximum) for the mean change from baseline to each applicable visit by treatment group will be provided for the HCVPRO total score, EQ-5D-5L index and VAS scores, and the SF-36v2 PCS and MCS scores.

For HCVPRO total score, SF-36v2 PCS and MCS scores, and EQ-5D-5L health index and VAS scores, the following ANCOVA analyses will be performed for the change from baseline to Final Treatment Visit and the change from baseline to PT Week 12. An ANCOVA analysis will be performed on the change from baseline with treatment group as a factor and baseline score as a covariate. The between group mean change from baseline with the 95% confidence interval, standard error, and \( P \) value will be presented.

An MID of –5 will be used for the change from baseline to Final Treatment Visit in the SF-36v2 PCS and MCS. The percentage of subjects in each treatment group with a change from baseline to Final Treatment Visit > –5 will be presented along with 95% confidence intervals and compared between treatment groups using Fisher's exact test.

To calculate the MID for HCVPRO and EQ-5D-5L, a receiver operating characteristics (ROC) analysis will be performed from PROC LOGISTIC with each of the following anchors for the change from baseline to Final Treatment Visit in the HCVPRO total score and in the EQ-5D-5L health index score:

- Change from baseline to Final Treatment Visit in SF-36 PCS > –5 (yes/no);
- Change from baseline to Final Treatment Visit in SF-36 MCS > –5 (yes/no).

Change from baseline to Final is defined as the Final Score – Baseline Score within the Treatment Period for all subjects in the ITT population. The point on the ROC curve that is closest to the upper left-hand corner (0,1) yields the optimal sensitivity and specificity.
This point will be determined by minimizing \((1 – \text{sensitivity})^2 + (1 – \text{specificity})^2\). The cutoff point corresponding to the sensitivity and specificity values closest to \((0,1)\) for each anchor will be averaged and used as the MID. The MID determined for the HCVPRO total score will be used for the change from baseline to Final Treatment Visit in HCVPRO total score. The MID determined for the EQ-5D-5L health index score will be used for the change from baseline to Final Treatment Visit in EQ-5D-5L health index score. The percentage of subjects in each treatment group with a change from baseline to Final Treatment Visit > MID will be presented along with 95% confidence intervals and compared between treatment groups using Fisher's exact test. If, for example, the MID is determined to be \(-10\) for the HCVPRO total score, then the responders are subjects with an improvement from baseline and subjects with decreases between zero and 10 points in the change from baseline to Final Treatment Visit in HCVPRO total score.

11.0 Safety Analysis

11.1 General Considerations

All subjects from Part 1a of the study who receive at least one dose of study drug will be included in the safety analyses. For safety analyses, data from both treatment groups will be summarized, and comparisons between treatment groups will be performed where specified. All tabulations of safety data also will include a total column combining data from all subjects.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study drug through 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent, unless there is other
evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

HIV-1-infected subjects participating in clinical trials may develop infections typically associated with AIDS. Appendix D of the study protocol contains a list of these known AIDS-associated opportunistic infections (OIs). Adverse events that are identified by the investigators as OIs will not be included in the analyses of other adverse events, but will be summarized separately.

11.2.1.1 Tabulations of Treatment-Emergent Adverse Events

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

Adverse events will be presented by treatment group and overall.

Adverse Event Overview

An overview of adverse events will be presented for each treatment group which consists of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
- Severe treatment-emergent adverse events;
- Serious treatment-emergent adverse events;
Treatment-emergent adverse events leading to discontinuation of study drug;
Treatment-emergent adverse events leading to interruption of study drug;
Treatment-emergent adverse events leading to RBV dose modifications;
Treatment-emergent adverse events leading to death;
Deaths.

For each adverse event presented in the overview, comparisons between treatment groups of the percentage of subjects experiencing an adverse event will be performed using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

**Adverse Event by SOC and PT**

The following summaries of adverse events will be generated:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs;
- Treatment-emergent adverse events with a "reasonable possibility" of being related to RBV;
- Serious treatment-emergent adverse events;
- Moderate or severe treatment-emergent adverse events;
- Severe treatment-emergent adverse events;
- Grade 3 or 4 (see definition below) treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of study drug;
- Treatment-emergent adverse events leading to interruption of study drug;
- Treatment-emergent adverse events leading to RBV dose modifications;
- Treatment-emergent adverse events leading to death;
- Treatment-emergent adverse events leading to concomitant medication use (events with other action taken of "concomitant medication prescribed").

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each
treatment group and overall. Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one adverse event will be counted only once in the overall total.

The percentage of subjects experiencing treatment-emergent adverse events, treatment-emergent adverse events with a "reasonable possibility" of being related to study drug (DAA or RBV), moderate or severe treatment-emergent adverse events, and severe treatment-emergent adverse events will be compared between treatment groups using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

A listing by treatment group of treatment-emergent adverse events grouped by SOC and PT with subject numbers will be created.

**Adverse Event by PT**

The number and percentage of subject experiencing treatment-emergent adverse events will be tabulated according to PT and sorted by overall frequency in the total of both treatment groups combined. Similar summaries will be provided for moderate to severe treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs. Percentages will be compared between treatment groups using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented.

**Adverse Events of Special Interest**

Specific treatment-emergent adverse events of special interest, which may be searched using Standardized or Company MedDRA Queries, will be summarized and include hepatic-related events, bilirubin-related events, rash-related events, and anemia. The search criteria for each of the adverse events of interest are as follows:
- Hepatic-related events
  SMQ "Drug related hepatic disorders – severe events only" (broad search)
- Bilirubin-related events
  SMQ "Cholestasis and jaundice of hepatic origin" (broad search)
- Drug induced rashes
  CMQ "Drug induced rash" (version 16.0.2 or later)
- Severe cutaneous reactions
  SMQ "Severe cutaneous adverse reactions" (narrow search)
- Anemia
  SMQ "Haematopoietic erythropenia" (broad search) plus the following preferred terms:
    - Haemolytic anaemia,
    - Coombs negative haemolytic anaemia,
    - Coombs positive haemolytic anaemia.

For each adverse event of interest (hepatic, bilirubin, drug induced rash, severe cutaneous reaction, and anemia), the number and percentage of subjects experiencing at least one treatment-emergent adverse event in the search for the event of interest will be presented for each treatment group and overall and by SOC and PT.

A listing of treatment-emergent adverse events for subjects meeting the search criterion will be provided for each adverse event of special interest.

**Adverse Events by Maximum Severity**

Treatment-emergent adverse events and treatment-emergent adverse events with a "reasonable possibility" of being related to DAAs will be summarized by maximum severity of each PT. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the
subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

**Adverse Events by Maximum Severity Grade Level**

Treatment-emergent adverse events will be summarized by maximum severity grade level of each PT. Each PT will be assigned to a grade level based on severity and seriousness, adapted from the Division of AIDS (DAIDS) table for grading severity of adverse events. All serious adverse events will be categorized as Grade 4. Nonserious adverse events categorized by the investigators as mild, moderate, or severe will be categorized as Grade 1, Grade 2, or Grade 3, respectively. If a subject has a nonserious adverse event with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Grade 3" category. Similarly, if a subject has an adverse event with unknown seriousness, then the subject will be counted in the severity grade level category of "unknown" unless the subject has another occurrence of the same adverse event that is marked serious. In this case, the subject will be counted under the "Grade 4" category.

**Adverse Events by Maximum Relationship**

Treatment-emergent adverse events also will be summarized by maximum relationship of each PT to study drug (DAA or RBV), as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.
**Adverse Events by HIV-1 ART Regimen**

Treatment-emergent adverse events also will be summarized for the subgroups defined by the HIV-1 ART regimen (ATV and RAL) the subjects were receiving at the start of the study. For each HIV-1 ART regimen, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each treatment group and overall. Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one adverse event will be counted only once in the overall total.

**AIDS-Associated Opportunistic Infections Adverse Events**

The number and percentage of subjects experiencing treatment-emergent OIs will be tabulated according to SOC and PT for each treatment group and overall. Subjects reporting more than one OI for a given PT will be counted only once for that term. Subjects reporting more than one OI within a SOC will be counted only once for that SOC. Subjects reporting more than one OI will be counted only once in the overall total.

**11.2.2 Listing of Adverse Events**

Listings of all serious adverse events (from the time the subject signed the study-specific informed consent through the end of the study), treatment-emergent serious adverse events, treatment-emergent adverse events leading to discontinuation of study drug, treatment-emergent adverse events leading to RBV dose modifications, treatment-emergent adverse events leading to study drug interruptions, and treatment-emergent adverse events of special interest will be provided. These listings will include OIs; the OIs will be identified as such in the listings.
11.3 Analysis of Laboratory Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

11.3.1 Variables and Criteria Defining Abnormality

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelet count, absolute neutrophil count (ANC), reticulocyte count, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, direct and indirect bilirubin, serum glutamic pyruvic transaminase (SGPT/ALT), serum glutamic oxaloacetic transaminase (SGOT/AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, albumin, chloride, bicarbonate, magnesium, gamma glutamyl transferase (GGT), creatinine clearance (Cockcroft-Gault calculation), calculation of estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation as defined below, alpha2-macroglobulin, haptoglobin, apolipoprotein A1, and alpha fetoprotein.

Urinalysis variables include: specific gravity, ketones, pH, protein, blood, glucose, urobilinogen, bilirubin, leukocyte esterase, albumin, and microscopic (reflexly performed if other variables are abnormal).

Additional variables include: total insulin and IP-10.

The following calculation is used by the central lab for eGFR by MDRD, where serum creatinine is measured in mg/dL and age is measured in years:

\[
GFR (\text{mL/min/1.73 m}^2) = 175 \times \text{Serum Creatinine (–1.154)} \times \text{Age (–0.203)} \\
\times 1.212 \text{ (if Black)} \times 0.742 \text{ (if Female).}
\]
The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table 9 and Table 10.

### Table 9. Criteria for Potentially Clinically Significant Hematology Values

<table>
<thead>
<tr>
<th>Test/Units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt; 4.9</td>
<td></td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&lt; 8.0</td>
<td></td>
</tr>
<tr>
<td>(g/L)</td>
<td>&lt; 80</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td>&lt; 50,000</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 50 × 10⁹</td>
<td></td>
</tr>
<tr>
<td><strong>White Blood Cell Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td>&lt; 2000</td>
<td>&gt; 20,000</td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 2.0 × 10⁹</td>
<td>&gt; 20 × 10⁹</td>
</tr>
<tr>
<td><strong>Absolute Neutrophil Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td>&lt; 1000</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 1 × 10⁹</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphocyte Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td>&lt; 500</td>
<td></td>
</tr>
<tr>
<td>(cells/L)</td>
<td>&lt; 0.5 × 10⁹</td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophil Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cells/mm³)</td>
<td></td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>(cells/L)</td>
<td></td>
<td>&gt; 5 × 10⁹</td>
</tr>
<tr>
<td><strong>aPTT</strong></td>
<td></td>
<td>&gt; 2 × ULN</td>
</tr>
<tr>
<td><strong>International Normalized Ratio</strong></td>
<td></td>
<td>&gt; 2 × ULN</td>
</tr>
</tbody>
</table>

**Note:** A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.
### Table 10. Criteria for Potentially Clinically Significant Chemistry Values

<table>
<thead>
<tr>
<th>Test/Units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td>$&gt; 5 \times ULN$ and $\geq 2 \times$ baseline</td>
<td></td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>$&gt; 5 \times ULN$ and $\geq 2 \times$ baseline</td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>$&gt; 1.5 \times ULN$</td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>$\geq 2.0 \times ULN$</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mcmol/L)</td>
<td></td>
<td>$\geq 132.605$</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td></td>
<td>$\geq 1.5$</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min)</td>
<td>$&lt; 50$</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td>$&gt; 5 \times ULN$</td>
</tr>
<tr>
<td>Uric Acid (mcmol/L)</td>
<td></td>
<td>$&gt; 713.817$</td>
</tr>
<tr>
<td>Uric Acid (mg/dL)</td>
<td></td>
<td>$&gt; 12.0$</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>$&lt; 0.6$</td>
<td></td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>$&lt; 2.0$</td>
<td></td>
</tr>
<tr>
<td>Calcium, Serum (mmol/L)</td>
<td>$&lt; 1.75$</td>
<td>$&gt; 3.1$</td>
</tr>
<tr>
<td>Calcium, Serum (mg/dL)</td>
<td>$&lt; 7.0$</td>
<td>$&gt; 12.5$</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>$&lt; 130$</td>
<td>$&gt; 155$</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>$&lt; 3.0$</td>
<td>$&gt; 6.0$</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>$&lt; 0.4$</td>
<td>$&gt; 1.23$</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>$&lt; 0.9$</td>
<td>$&gt; 3.0$</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>$&lt; 2.2$</td>
<td>$&gt; 13.9$</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>$&lt; 40$</td>
<td>$&gt; 250$</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>$&lt; 20$</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>$&lt; 2$</td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Criteria for Potentially Clinically Significant Chemistry Values (Continued)

<table>
<thead>
<tr>
<th>Test/Units</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g/L)</td>
<td></td>
<td>&lt; 50</td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&lt; 5.0</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td>&gt; 10.34</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&gt; 400</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&gt; 5.7</td>
<td></td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&gt; 500</td>
<td></td>
</tr>
</tbody>
</table>

Note: A post-baseline value must be more extreme than the baseline value to be considered a PCS finding.

11.3.2 Statistical Methods

Clinical laboratory tests will be summarized by treatment group at each visit during the Treatment Period for Part 1a of the study. The baseline value will be the last measurement on or before the day of the first dose of study drug. This same baseline value will be used for all change from baseline tables in the Treatment Period and Post-Treatment Period.

Mean changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized for each protocol-specified laboratory parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum, maximum, and median.

During the Treatment Period, laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline to minimum value, maximum value, and final values during the Treatment Period (Study Drug End Day ≤ 2) will be created. The shift tables will cross tabulate the
frequency of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

The number and percentage of subjects with post-baseline values during the Treatment Period meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values (defined in Table 9 and Table 10) will be summarized by treatment group. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. Comparisons between treatment groups will be performed on the percentage of subjects with PCS laboratory values for each parameter using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented. A separate listing will be provided that presents all of the lab values for the subjects meeting PCS criteria during treatment.

For hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin, the number and percentage of subjects in each treatment group with a maximum CTCAE of 1, 2, 3, or 4 (see definitions in Table 11) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. All LFT tables will include summary rows for the number and percentage of subjects with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of subjects with at least a Grade 2 laboratory abnormality. Treatment group comparisons of the percentage of subjects experiencing a value meeting at least Grade 2 and at least Grade 3 (as reported in the summary row[s]) will be performed using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented. Accompanying listings of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase will be created for any subject who had at least a Grade 2 ALT, AST, alkaline phosphatase, or total bilirubin, including HIV-1 ART regimen (ATV or RAL) at study start. A listing of hematology results will be provided for subjects with hemoglobin abnormalities.
The hemoglobin by maximum CTCAE grade table, described above, also will be summarized for subjects with and without treatment-emergent adverse events of dyspnea (defined by preferred terms of "dyspnoea" or "dyspnoea exertional").

The LFTs of ALT, AST, alkaline phosphatase, and total bilirubin by maximum CTCAE grade table, described above, will also be generated for the subgroups defined by the HIV-1 ART regimen (ATV and RAL) the subjects were receiving at the start of the study. A separate listing of subjects with LFTs of at least Grade 2 is not needed for the subgroups based on HIV-1 ART regimen.

For subjects with a Grade 3 or higher total bilirubin elevation, a listing of treatment-emergent adverse events (defined as preferred terms within the "Cholestasis and jaundice of hepatic origin" [broad search] SMQ, excluding preferred terms within the "Investigations" SOC) will be provided.

**Table 11. Definitions of CTCAE Grades 1, 2, 3, and 4**

<table>
<thead>
<tr>
<th>Test</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>&gt; ULN – 3 × ULN</td>
<td>&gt; 3 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>&gt; ULN – 2.5 × ULN</td>
<td>&gt; 2.5 – 5 × ULN</td>
<td>&gt; 5 – 20 × ULN</td>
<td>&gt; 20 × ULN</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>&gt; ULN – 1.5 × ULN</td>
<td>&gt; 1.5 – 3 × ULN</td>
<td>&gt; 3 – 10 × ULN</td>
<td>&gt; 10 × ULN</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>&lt; LLN – 100 g/L</td>
<td>&lt; 100 – 80 g/L</td>
<td>&lt; 80 – 65 g/L</td>
<td>&lt; 65 g/L</td>
</tr>
</tbody>
</table>

The number and percentage of subjects in each treatment group meeting the following criteria during treatment will be summarized:

- ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN;
- ALT ≥ 3 × ULN and total bilirubin value < 2 × ULN;
- ALT > 5 × ULN (equivalent to Grade 3 or higher) and total bilirubin value < 2 × ULN;
- ALT < 3 × ULN and total bilirubin ≥ 2 × ULN.
A subject or event will be counted if the post-baseline laboratory values meet the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value). The maximum ratio relative to the ULN will be used to determine if subjects meet the criteria listed above. For subjects meeting the ALT ≥ 3 × ULN and total bilirubin value ≥ 2 × ULN criterion during the Treatment Period, a corresponding listing of all ALT, AST, alkaline phosphatase, and total, direct, and indirect bilirubin values will be provided.

For subjects meeting the criterion of ALT < 3 × ULN and total bilirubin ≥ 2 × ULN, the number and percentage of subjects with a total bilirubin value in the categories of ≤ ULN, > ULN – < 2 × ULN, and ≥ 2 × ULN at the Final Treatment Visit will be summarized. A similar summary will be provided for Post-Treatment Week 4.

In addition, for subjects meeting the criterion of ALT < 3 × ULN and total bilirubin ≥ 2 × ULN (based on the maximum ratio relative to the ULN), the ratio of indirect bilirubin to total bilirubin will be calculated. The following summary statistics will be presented for each treatment group for the ratio at baseline and for the ratio associated with the peak total bilirubin value during the Treatment Period: sample size, mean, standard deviation, minimum, maximum, and median. In addition, the number and percentage of subjects with a ratio < 0.75 and < 0.50 will be presented for baseline and peak.

11.4 Analysis of Vital Signs and Weight

11.4.1 Variables and Criteria Defining Abnormality

Vital sign variables are body temperature, sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate, and body weight.

The Criteria for Potentially Clinically Significant Vital Sign Findings are presented in Table 12.
Table 12. Criteria for Potentially Clinically Significant Vital Sign Values

<table>
<thead>
<tr>
<th>Test/Measurement</th>
<th>Very Low (VL)</th>
<th>Very High (VH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>≤ 90 mmHg AND A decrease of ≥ 20 mmHg from baseline</td>
<td>≥ 180 mmHg AND An increase of ≥ 20 mmHg from baseline</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>≤ 50 mmHg AND A decrease of ≥ 15 mmHg from baseline</td>
<td>≥ 105 mmHg AND An increase of ≥ 15 mmHg from baseline</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>≤ 50 bpm AND A decrease of ≥ 15 bpm from baseline</td>
<td>≥ 120 bpm AND An increase of ≥ 15 bpm from baseline</td>
</tr>
<tr>
<td>Weight</td>
<td>A decrease of ≥ 15% from baseline</td>
<td>An increase of ≥ 15% from baseline</td>
</tr>
<tr>
<td>Temperature</td>
<td>A decrease of ≥ 15% from baseline</td>
<td>&gt; 38.3°C AND An increase of ≥ 1.1°C from baseline</td>
</tr>
</tbody>
</table>

11.4.2 Statistical Methods

Vital signs will be summarized by treatment group at each visit during the Treatment Period for Part 1a of the study. The baseline value will be the last measurement on or before the day of the first dose of study drug. This same baseline value will be used for all change from baseline tables in the Treatment and Post-Treatment Periods.

Mean changes from baseline to each post-baseline visit, including applicable post-treatment visits, will be summarized for each vital sign parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum, maximum, and median.

The number and percentage of subjects with post-baseline values during the Treatment Period meeting Criteria for Potentially Clinically Significant Vital Signs values (Table 12) will be summarized by treatment group. A post-baseline value must be more extreme than the baseline value to be considered as a PCS finding. Comparisons between treatment groups of the percentage of subjects experiencing a value meeting the criteria in the Treatment Period will be performed using Fisher's exact tests. Only $P$ values $\leq 0.100$ when rounded to three digits will be presented. A separate listing will be provided that presents all of the vital sign values for the subjects meeting the PCS vital sign criteria during treatment.
12.0 Additional Interim Analysis

An additional interim analysis will be conducted after all randomized subjects in Part 1a have completed the Treatment Period through Post-Treatment Week 4 or have prematurely discontinued from the study. The purpose of this additional interim analysis is to provide the Food and Drug Administration with results from Part 1a of the study that include data through at least Post-Treatment Week 4 for all subjects. For the additional interim analysis, data will be locked after performing appropriate data cleaning. Analysis will be based on data collected through Post-Treatment Week 12.

The objectives of the additional interim analysis are the same as those of the planned interim analysis.

The data for the additional interim analysis will be stored in Oracle Clinical, transferred into SAS datasets, and any new data after the interim analysis will be added as a new version of the SAS datasets. All analyses will be conducted by statisticians at AbbVie according to the methodologies specified in this IAP. There is no intention of shortening the follow-up time of Part 1a subjects based on efficacy findings from the interim analysis. The intention is to follow all Part 1a subjects who receive study drug for 48 weeks following treatment. There will be no statistical adjustment employed due to this interim analysis.

The following variables will be analyzed for the additional interim analysis using the methods previously specified in this IAP except that no statistical tests will be performed to compare the two treatment groups:

- Demographics and baseline characteristics of sex, race, ethnicity, age, weight, HCV genotype/subtype, IL289B genotype, prior HCV treatment status, HIV-1 RNA level, presence of cirrhosis, CD4+ T-cell count, and HIV-1 PI or INSTI therapy at baseline
• Efficacy variables of EOTR, SVR4, and SVR12, including reasons for not achieving SVR4 and SVR12. For SVR12, all Arm A subjects and only Arm B subjects who have an HCV RNA result within the SVR12 visit window will be included; 95% CIs will only be calculated for SVR12
• Plasma HIV-1 RNA suppression using the FDA Snapshot Algorithm
• Change from baseline in CD4+ T-cell count and CD4+ T-cell %
• Available HCV resistance data
• Results of HIV-1 resistance testing for any subject with plasma HIV-1 RNA ≥ 40 copies/mL and confirmatory plasma HIV-1 RNA ≥ 500 copies/mL
• Incidence of the following types of treatment-emergent adverse events: any, with a reasonable possibility of being related to DAAAs, with a reasonable possibility of being related to RBV, severe, serious, leading to study drug discontinuation, leading to RBV dose modification, leading to death, any death (note that for this additional interim analysis OIs will be included as adverse events; i.e., there will be no separate summary of the OIs)
• Incidence of treatment-emergent adverse events by MedDRA SOC and PT
• Incidence of RBV dose modifications and reasons for RBV dose modification
• Potentially clinically significant laboratory values
• Clinical toxicity (CTCAE) grading of hemoglobin and liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin)

13.0 References
