STATISTICAL ANALYSIS PLAN
FOR HCV DAA

A PHASE 3 EVALUATION OF A DACLATASVIR/ASUNAPREVIR/BMS-791325
FIXED DOSE COMBINATION IN SUBJECTS WITH GENOTYPE 1 CHRONIC
HEPATITIS C AND COMPENSATED CIRRHOSIS

PROTOCOL AI443113
VERSION 1.0
# TABLE OF CONTENTS

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BACKGROUND AND RATIONALE</td>
</tr>
<tr>
<td>2</td>
<td>STUDY DESCRIPTION</td>
</tr>
<tr>
<td>2.1</td>
<td>Study Design</td>
</tr>
<tr>
<td>2.2</td>
<td>Treatment Assignment</td>
</tr>
<tr>
<td>2.3</td>
<td>Blinding and Unblinding</td>
</tr>
<tr>
<td>2.4</td>
<td>Protocol Amendments</td>
</tr>
<tr>
<td>3</td>
<td>OBJECTIVES</td>
</tr>
<tr>
<td>3.1</td>
<td>Primary</td>
</tr>
<tr>
<td>3.2</td>
<td>Key Secondary</td>
</tr>
<tr>
<td>3.3</td>
<td>Other Secondary</td>
</tr>
<tr>
<td>3.4</td>
<td>Exploratory Objectives</td>
</tr>
<tr>
<td>4</td>
<td>ENDPOINTS</td>
</tr>
<tr>
<td>4.1</td>
<td>Primary Endpoints</td>
</tr>
<tr>
<td>4.2</td>
<td>Secondary Endpoints</td>
</tr>
<tr>
<td>4.3</td>
<td>Exploratory Endpoints</td>
</tr>
<tr>
<td>5</td>
<td>SAMPLE SIZE AND POWER</td>
</tr>
<tr>
<td>6</td>
<td>STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES</td>
</tr>
<tr>
<td>6.1</td>
<td>Study Periods</td>
</tr>
<tr>
<td>6.1.1</td>
<td>Pre-Treatment Period</td>
</tr>
<tr>
<td>6.1.2</td>
<td>On-Treatment Period</td>
</tr>
<tr>
<td>6.1.3</td>
<td>Follow-up Period</td>
</tr>
<tr>
<td>6.2</td>
<td>Treatment Regimens</td>
</tr>
<tr>
<td>6.3</td>
<td>Populations for Analyses</td>
</tr>
<tr>
<td>7</td>
<td>STATISTICAL ANALYSES</td>
</tr>
<tr>
<td>7.1</td>
<td>General Methods</td>
</tr>
<tr>
<td>7.2</td>
<td>Study Conduct</td>
</tr>
<tr>
<td>7.3</td>
<td>Study Population</td>
</tr>
</tbody>
</table>
1 BACKGROUND AND RATIONALE

Daclatasvir (BMS-790052, DCV), asunaprevir (BMS-650032, ASV), and BMS-791325, hereafter referred to as DCV/ASV/BMS-791325, or the DCV 3DAA, or DCV 3DAA fixed dose combination (DCV 3DAA FDC) has the potential to become an important addition to the future anti-HCV treatment. This DCV 3DAA FDC is interferon (IFN)- and possibly Ribavirin (RBV)- sparing, and early clinical data suggest potent in vivo anti-viral activity (AI443014). The non- nucleoside inhibitor BMS-791325, when combined with DCV/ASV in the Triple regimen, has demonstrated a high barrier to resistance which provides coverage for GT-1a as well as GT-1b HCV (AI443014).

Study AI443113 will enroll both treatment naïve and treatment experienced cirrhotic subjects. Based on favorable response rates to the DCV/ASV/BMS-791325 (DCV 3DAA) regimen in difficult-to-treat cirrhotic subjects (AI443014), as well as favorable SVR rates of prior non- responders and prior interferon ineligible naïve/intolerant GT-1b subjects treated with DCV/ASV in a Japanese Phase 3 study (AI447026), it is anticipated that SVR rates for treatment experienced subjects will be comparable to treatment naive subjects. SVR4 data from Phase 2 study (AI443014) of prior null responders to pegIFN/RBV treated with DCV/ASV/BMS-791325 75 mg BID or 150 mg BID for 12 or 24 weeks will be available prior to enrollment of subjects in AI443113.

Research Hypothesis:

In HCV GT-1 treatment-naïve cirrhotic subjects, treated with 12 weeks of DCV 3DAA FDC with or without RBV, at least one of these two arms can achieve SVR rates significantly higher than the historical threshold of 69%.

2 STUDY DESCRIPTION

2.1 Study Design

Research Hypothesis:

In HCV GT-1 treatment-naïve cirrhotic subjects, treated with 12 weeks of DCV 3DAA FDC with or without RBV, at least one of these two arms can achieve SVR rates significantly higher than the historical threshold of 69%.
AI443113 is a two-cohort, four-arm, open-label DCV 3DAA FDC, blinded placebo-controlled (for RBV) study that will randomize approximately 200 GT-1 treatment naive (Cohort 1) and treatment experienced (Cohort 2) subjects with compensated cirrhosis (Metavir 4 based on biopsy, Fibroscan® or Fibrotest®/APRI score). Treatment naive subjects will be randomized [1:1] to 12 weeks of treatment with either DCV 3DAA FDC + placebo for RBV [Arm 1] or DCV 3DAA FDC + RBV [Arm 2]. Treatment experienced subjects will randomize [1:1] to 12 weeks of treatment with either DCV 3DAA FDC + placebo for RBV [Arm 3] or DCV 3DAA FDC + RBV [Arm 4]. At Week 12, all subjects will complete therapy and enter the follow-up period of 24 weeks.

Within each cohort, subjects will be stratified according to GT-1 subtype (1a vs. 1b). Enrollment will be capped at ~ 40% for GT-1b and at 100 for treatment experienced subjects.

Study duration (from first dose) will be 36 weeks for all subjects (12 weeks therapy + 24 weeks follow-up).

The last visit will be considered the date of the last post-treatment visit. The end of the study will be considered the last subject’s last visit date, or the date the last data point required for statistical analysis is received from the last subject.

2.2 Treatment Assignment

Eligible treatment naive subjects will be randomized [1:1] to 12 weeks of treatment with either DCV 3DAA FDC + placebo for RBV [Arm 1] or DCV 3DAA FDC + RBV [Arm 2]. Treatment experienced subjects will randomize [1:1] to 12 weeks of treatment with either DCV 3DAA FDC + placebo for RBV [Arm 3] or DCV 3DAA FDC + RBV [Arm 4].

2.3 Blinding and Unblinding

This study will be open-label for DCV 3DAA therapy, but blinded for RBV/placebo assignment for sites, subjects and the Sponsor. The exceptions are the following staff, who are not directly involved with the conduct of the study: Designated staff of Bristol-Myers Squibb Research and Development, consisting of a pharmacokineticist or designate, a programmer, a PK scientist and two modelers in Discovery Medicine and Clinical Pharmacology will be unblinded to treatment assignment for analysis. In addition, a single member (or designate) of the Bioanalytical Science section and the project manager of the CRO laboratory supporting the bioanalytical work will be unblinded to treatment assignment in order to prioritize the management of PK samples for evaluation. One BMS virologist or designate will also be unblinded to treatment assignment to manage resistance sample testing and analysis.

In the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator.
2.4 Protocol Amendments

Protocol amendment 02, dated April 21, 2014, added an interim database lock after all subjects completed post-treatment Week 4. This interim database lock will support pharmacokinetic modeling and simulations for exposure-response analysis. No hypothesis will be assessed and no summary of efficacy and safety will be done at this lock.

Protocol amendment 03 updated the sustained virologic response (SVR) historical thresholds for naive and experienced cohorts based on more recent data in subjects treated with peg-interferon/ribavirin in combination with either sofosbuvir or simeprevir. It also removed the stepwise sequential procedure for assessing primary and the first secondary objectives.

3 OBJECTIVES

3.1 Primary

To demonstrate the proportion of treatment naive cirrhotic subjects in at least one of DCV 3DAA FDC ± RBV arms with SVR12, defined as HCV RNA < LLOQ target detected or target not detected (LLOQ TD/TND) at follow up Week 12 is significantly greater than a historical threshold of 69%.

3.2 Key Secondary

- To demonstrate the proportion of treatment experienced cirrhotic subjects in at least one of DCV 3DAA FDC +/- RBV arms with SVR12, defined as HCV RNA < LLOQ TD/TND at follow up Week 12 is significantly greater than a historical threshold of 45%;
- To evaluate the proportion of subjects in each arm who achieve HCV RNA < LLOQ TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; post-treatment Weeks 4 (SVR4), 8 (SVR8) and 24 (SVR24);
- To evaluate the proportion of subjects in each arm who achieve HCV RNA < LLOQ TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; and post-treatment Weeks 4, 8, 12 and 24;
- To evaluate on treatment safety, as measured by frequency of SAEs and discontinuations due to AEs through the end of treatment in each arm within each cohort.

3.3 Other Secondary

- To estimate the proportion of subjects with anemia defined as Hg < 10 g/dL on-treatment who had Hg ≥ 10 g/dL at baseline in each arm within each cohort;
- To estimate the differences in rates of selected Grade 3-4 laboratory test result abnormalities (including hematologic and liver function, based on DAIDs criteria) between arms within each cohort;
- To evaluate the proportion of subjects achieving SVR12 associated with HCV GT-1a vs. GT-1b within each arm of each cohort;
- To evaluate the proportion of subjects in each arm achieving SVR12 associated with IL28B rs12979860 SNP status (CC genotype or non-CC genotype).
3.4 Exploratory Objectives

- To describe resistant variants associated with virologic failure for HCV;
- To explore the relationship between endpoints of safety and/or efficacy and exposure to DCV 3DAA when administered with and without RBV;
- To describe the pharmacokinetics of DCV 3DAA when administered with and without RBV in subjects with compensated cirrhosis (Metavir F4);
- To evaluate the potential relationship between SNPs in genes associated with drug metabolism with PK parameters and/or elevations in bilirubin;
- To describe the frequency of relevant special search safety categories potentially including select hematologic, and allergic toxicities.

4 ENDPOINTS

4.1 Primary Endpoints

- Proportion of treated subjects in the treatment naive arm with SVR12, defined as HCV RNA < LLOQ TD/TND at post treatment Week 12. Missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, i.e., missing HCV RNA data in the follow-up Week 12 window will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window.

4.2 Secondary Endpoints

- Proportion of treated subjects in the treatment experienced arm with SVR12, defined as HCV RNA < LLOQ target detected or target not detected (LLOQ TD/TND) at post treatment Week 12.
- Proportion of subjects in each arm who achieve HCV RNA < LLOQ TD/TND at each of the following Weeks: 1, 2, 4, 6, 8, and 12; post treatment Weeks 4 (SVR4), 8 (SVR8) and 24 (SVR24);
- Proportion of subjects in each arm who achieve HCV RNA < LLOQ TD at each of the following Weeks: 1, 2, 4, 6, 8, and 12; and post-treatment Weeks 4, 8, 12 and 24;
- On treatment safety, as measured by frequency of SAEs and discontinuations due to AEs through the end of treatment by each arm within each cohort;
- Proportion of subjects with anemia defined as Hg < 10 g/dL on-treatment who had Hg ≥ 10 g/dL at baseline in each arm within each cohort;
- Differences in rates of selected Grade 3 - 4 laboratory test result abnormalities (hematologic and liver function) between arms within each cohort;
- Proportion of subjects achieving SVR12 associated with HCV geno subtype 1a vs. 1b within each arm of each cohort;
• Proportion of subjects in each arm achieving SVR12 associated with IL28B rs12979860 SNP status (CC genotype or non-CC genotype).

4.3 Exploratory Endpoints

• Frequency of genotypic substitutions at baseline, on treatment, and post-treatment associated with virologic failure in each arm within each cohort;
• Exposure-response analyses will explore the relationship between DCV, ASV or BMS-791325 measures of exposures and endpoints of efficacy and safety within each cohort;
• Trough plasma concentrations of DCV, ASV, BMS-791325 and its metabolite, BMS-794712 with/without RBV within each cohort;
• Potential association between SNPs in genes associated with drug metabolism with PK parameters and/or elevations in bilirubin in each arm within each cohort;
• Frequency of relevant special search safety categories potentially including select hematologic and allergic toxicities in each arm within each cohort.

5 SAMPLE SIZE AND POWER

The primary objective is to determine whether the SVR12 rate in at least one treatment-naive arm is significantly higher than 69% by a confidence interval (CI) approach. Similarly, the first key secondary objective is to determine whether the SVR12 rate in at least one treatment-experienced arm is significantly higher than 45% by the same statistical approach.

Within each cohort, a 97.5% CI will be applied for the CI approach, the type I error rate is set at 0.025 (0.05/2) by Bonferroni multiplicity adjustment for each arm comparing to the historical threshold respectively.

For the primary objective, the lower bound of the 97.5% CI of the SVR12 in each treatment naive subjects arm will be used to compare to the historical threshold of 69% respectively; if at least one arm exceeds 69% it can be concluded that the primary objective is achieved and the SVR12 rate of at least one treatment naive arm with DCV 3DAA therapy +/- RBV is significantly higher than the historical threshold of 69%. With 50 treatment naive subjects in each arm it would take a minimum of an observed SVR12 rate of 82% (41/50, 97.5% CI: 69.8%, 94.2%) for the lower bound to exceed 69% and conclude at least one DCV 3DAA-contained regimen (with or without RBV) is significantly higher than the historical threshold of 69% in the treatment-naive subjects. The historical threshold for treatment naive cirrhotic subjects is obtained by subtracting 10% from the non-cirrhotic naïve threshold 79% which was based on NEUTRINO trial data for sofosbuvir. See Appendix 2 for more details.

Similarly, for the first key secondary objective, if the lower bound of the SVR12 97.5% CI in either of the treatment experienced arms exceeds the historical threshold of 45%, it can be concluded that the first key secondary objective is achieved and the SVR12 rate of at least one treatment experienced arm with DCV 3DAA therapy +/- RBV is significantly higher than the
historical threshold of 45%. With 50 treatment experienced subjects it would take a minimum of an observed SVR12 rate of 61% (31/50, 97.5% CI: 45.5%, 76.5%) for the lower bound to exceed 45% and conclude at least one DCV 3DAA-contained regimen (with or without RBV) is significantly higher than the historical threshold of 45% in the treatment-experienced subjects. To calculate the historical threshold for treatment experienced cirrhotic subjects, a composite historical SVR rate of 62.5% for prior virological failures was determined by combining the threshold of 67% for prior relapsers and 58% for non-responders based on studies HPC3007 and C206 for simeprevir. Subjects who did not have sufficient HCV RNA documentation to define response to prior interferon therapy (“indeterminate response”) were also assigned an SVR rate of 62.5%. Subjects who were intolerant to interferon, or who failed prior anti-HCV therapy (ie, DAA or host targeted agents) were assigned an SVR rate of 5%. The final threshold for experienced subjects 45% is calculated assuming 70% subjects with virological failure or indeterminate response, 20% interferon intolerants and 10% DAA failures. See Appendix 2 for more details.

Table 5.1 presents some scenarios of observed response rates and 97.5% confidence intervals for genotype 1 subjects in each arm (N=50):

**Table 5-1: SVR Observed Rates and 97.5% Confidence Intervals* in Each Arm**

<table>
<thead>
<tr>
<th>Observed SVR Rate</th>
<th>Observed Responders</th>
<th>97.5% CI</th>
</tr>
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<tbody>
<tr>
<td>88%</td>
<td>44 of 50</td>
<td>(77.7%, 98.3%)</td>
</tr>
<tr>
<td>85%</td>
<td>43 of 50</td>
<td>(73.7%, 96.3%)</td>
</tr>
<tr>
<td>82%</td>
<td>41 of 50</td>
<td>(69.8%, 94.2%)</td>
</tr>
<tr>
<td>80%</td>
<td>40 of 50</td>
<td>(67.3%, 92.7%)</td>
</tr>
<tr>
<td>75%</td>
<td>38 of 50</td>
<td>(61.3%, 88.7%)</td>
</tr>
<tr>
<td>70%</td>
<td>35 of 50</td>
<td>(55.5%, 84.5%)</td>
</tr>
<tr>
<td>65%</td>
<td>33 of 50</td>
<td>(49.9%, 80.1%)</td>
</tr>
<tr>
<td>61%</td>
<td>31 of 50</td>
<td>(45.5%, 76.5%)</td>
</tr>
<tr>
<td>60%</td>
<td>30 of 50</td>
<td>(44.5%, 75.5%)</td>
</tr>
</tbody>
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*Multiplicity adjustment within each cohort: 1- 0.05/2=97.5% CI

For all other efficacy analyses, approximately 50 genotype 1 subjects in each arm provide 95% confidence that the observed SVR12 rate can be estimated to within 13.6% of the estimates when the observed SVR is 60% or higher (See Table 5.2).
Table 5.2 presents some scenarios of observed response rates and 95% confidence intervals for genotype 1 subjects in each arm (N=50):

### Table 5.2: SVR Observed Rates and 95% Confidence Intervals in Each Arm

<table>
<thead>
<tr>
<th>Observed SVR Rate</th>
<th>Observed Responders</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>88%</td>
<td>44 of 50</td>
<td>(79.0%, 97.0%)</td>
</tr>
<tr>
<td>85%</td>
<td>43 of 50</td>
<td>(75.1%, 94.9%)</td>
</tr>
<tr>
<td>80%</td>
<td>40 of 50</td>
<td>(68.9%, 91.1%)</td>
</tr>
<tr>
<td>75%</td>
<td>38 of 50</td>
<td>(63.0%, 87.0%)</td>
</tr>
<tr>
<td>70%</td>
<td>35 of 50</td>
<td>(57.3%, 82.7%)</td>
</tr>
<tr>
<td>65%</td>
<td>33 of 50</td>
<td>(51.8%, 78.2%)</td>
</tr>
<tr>
<td>60%</td>
<td>30 of 50</td>
<td>(46.4%, 73.6%)</td>
</tr>
</tbody>
</table>

# 6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

## 6.1 Study Periods

### 6.1.1 Pre-Treatment Period

The pre-treatment period begins at the first visit until initiation of active study therapy. Measurements taken before Day 1 (i.e., the first dose of active study therapy) are considered pre-treatment for all data domains. In addition, measurements taken on Day 1 are considered pre-treatment for the following data domains: demography, disease history, ECG, human genotyping, laboratory test results, medical history, physical examination, physical measurements, subject status, viral genotyping, viral phenotyping, virology and vital signs.

### 6.1.2 On-Treatment Period

The on-treatment period for study therapy begins with the first dose of any active study therapy and ends 7 days after last dose of study therapy. The 7-day cut-off reflects the point at which minimal antiviral activity related to study therapy (3DAA) is present. It is also expected that minimal drug exposure and undetectable drug levels will be present beyond 7 days post-dose. Measurements taken after Day 1 (i.e., the first dose of active study therapy) through the last dose of study therapy plus 7 days are considered on-treatment for all data domains. In addition, measurements taken on Day 1 are considered on-treatment for the following data domains: AEs, drug dispensation, exposure, inclusion/exclusion, non-study medications, sample collection, sample inform consent and sample reference.
6.1.3 Follow-up Period

The follow-up period begins on the last dose of study therapy plus 8 days and ends at the last follow-up visit.

Measurements taken on or after the last dose of study therapy plus 8 days are considered follow-up for all data domains unless otherwise specified.

6.2 Treatment Regimens

Treatment regimens are defined as follows:

- As-randomized refers to the treatment regimen assigned at randomization by the Interactive Voice Response System (IVRS). Accrual and efficacy results are presented as-randomized.
- As-treated refers to the actual treatment regimen received. The treatment group “as treated” will be same as the treatment group “as randomized” by IVRS unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject’s treatment group “as treated” will be defined as the study treatment actually received. Results for subject disposition, demographics, baseline characteristics, safety, are presented as-treated.

6.3 Populations for Analyses

Populations are grouped according to treatment regimen as follows:

- Enrolled subjects are those who signed an informed consent form and were assigned a Patient Identification number (PID).
- Randomized subjects are enrolled subjects who received a treatment assignment, as indicated in the IVRS database.
- Treated subjects are enrolled subjects who received at least 1 dose of study therapy.
- Follow-up subjects are treated subjects who continued into the follow-up period, as indicated on the end of treatment subject status Case Report Form (CRF). This cohort is used to assess safety during follow-up.

7 Statistical Analyses

Statistical analyses are performed using the version of SAS in production, unless specified otherwise.

7.1 General Methods

Refer to Section 7.1 of the Core SAP for the general methods of the statistical analyses.

Longitudinal summaries of antiviral activity and safety parameters use pre-defined visit week windows (Refer to Section 8.1).

All analyses are based on IVRS identified cohort (naive and experienced cohorts) at randomization. Cohorts will also be derived using prior anti-HCV medications collected on
CRF. If there are discrepancies between IVRS-identified cohort and CRF-derived cohort, sensitivity analyses using CRF-derived cohort will be done for primary and key secondary efficacy endpoints.

Formats of tables, listings, and graphs are described in the AI443113 Data Presentation Plan.

7.2 Study Conduct

Relevant protocol deviations are summarized by treatment group within cohort and overall for treated subjects. Relevant protocol deviations are those that are programmable and could potentially affect the interpretability of the study results, such as:

- Certain inclusion or exclusion criteria;
- Incorrect dosing or study treatment assignment;
- Use of prohibited concomitant medications;
- Subjects remaining on treatment despite having met specified criteria for withdrawal.

A subject is considered to have a deviation of an inclusion or exclusion criterion only if all pre-treatment measurements fail the criterion. The consent date defines the beginning of enrollment. Appendix 1 describes the relevant protocol deviations that can be programmed from the database.

A listing of subjects with relevant deviations will be also presented.

7.3 Study Population

7.3.1 Disposition of Subjects

Refer to Section 7.3.1 of the Core SAP.

7.3.1.1 Pre-Treatment Subject Status and Accrual

Pre-randomized subject status is summarized for enrolled subjects. This presents the number of subjects enrolled, randomized, not randomized. Reasons for not being randomized are also included (e.g., AE, death, lost to follow-up).

Enrollment by country and investigative site is summarized for enrolled subjects and randomized subjects.

7.3.1.2 End of Treatment Subject Status

Refer to Section 7.3.1.2 of the Core SAP.

7.3.1.3 End of Study Subject Status

Refer to Section 7.3.1.3 of the Core SAP.
7.3.2 Demographics and Other Baseline Characteristics

Summaries are presented by treatment group within cohort and overall for treated subjects unless otherwise specified. Summaries identify the number and percentage of subjects with missing measurements. Baseline values are obtained from the clinical database, unless otherwise specified. Baseline is the last value measured pre-treatment (see Section 6.1.1).

7.3.2.1 Demographics

The following demographics are summarized by treatment group within cohort and overall:

- Age;
- Age categorization (< 65, 65 -< 75, >= 75);
- Gender (male, female);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other);
- Ethnicity (Hispanic/Latino, not Hispanic/Latino);
- Geographic region (Europe, North America, Australia) and country

7.3.2.2 Baseline Disease Characteristics and Prognostic Factors

The following baseline disease characteristics are summarized by treatment group within cohort and overall:

- HCV RNA value (log_{10} IU/mL), HCV RNA categorization (< 400,000 IU/mL and ≥ 400,000 IU/mL; < 600,000 IU/mL and ≥ 600,000 IU/mL; < 800,000 IU/mL, ≥ 800,000 IU/mL);
- Response on prior therapy (Naive; Interferon-based anti-HCV treatment: breakthrough, HCV RNA ever undetectable, HCV RNA never undetectable, indeterminate, intolerance, null responder, partial responder, relapser; Other anti-HCV treatment);
- Cirrhosis status (yes, no, unknown);
- Fibrosis stage (F0, F1, F2, F3, and F4 as defined below);
  - F0: 0 <= baseline Fibrotest score <= 0.27
  - F1: 0.27 < baseline Fibrotest score <= 0.48
  - F2: 0.48 < baseline Fibrotest score <= 0.58
  - F3: 0.58 < baseline Fibrotest score <= 0.74
  - F4: 0.74 < baseline Fibrotest score <= 1.00
- Randomization strata (HCV genotype 1a or 1b) from IVRS;
- HCV Genotype subtype (GT-1a, GT-1b, and any other genotype if present);
- IL28B rs12979860 host genotype (CC, CT, TT, not reported)
- Baseline NS5A-28 resistance (yes, no) for GT-1a and GT-1b subjects separately
- Baseline NS5A-30 resistance (yes, no) for GT-1a and GT-1b subjects separately
• Baseline NS5A-31 resistance (yes, no) for GT-1a and GT-1b subjects separately
• Baseline NS5A-93 resistance (yes, no) for GT-1a and GT-1b subjects separately

7.3.2.3 Other Baseline Characteristics

Physical Measurements at Baseline
Refer to core SAP Section 7.3.2.3. Physical measurements will be listed.

ECG at Baseline
Refer to Section 7.3.1.2 of the Core SAP.

Laboratory Tests at Baseline
Baseline laboratory grades (0, 1, 2, 3, 4) for each test are summarized by treatment group within cohort and overall. Refer to Section 7.3.2.3 for the list of commonly collected laboratory tests with DAIDS toxicity grades.

Prior Treatments
Prior medications are summarized by treatment group within cohort and overall. Refer to core SAP Section 7.3.2.3.

7.4 Extent of Exposure
Extent of exposure is presented by as-treated treatment regimen for treated subjects.

7.4.1 Study Therapy
Time on study therapy (in Weeks) is summarized by treatment group within cohort. It is defined as the number of days between the first active dose of any study drug and last dose of any study drug, divided by 7.

Time on therapy (in Weeks) is also summarized for each study drug (DCV 3DAA FDC, RBV) by treatment group within cohort. Time on therapy (in Weeks) for a drug is defined as the number of days between the first dose date and last dose date of the drug, divided by 7.

Average daily dose during the study therapy treatment period is summarized for each drug (DCV 3DAA FDC, RBV) by treatment group within cohort. Average daily dose is the total amount of drug, in dose units divided by time on therapy (in Days). Average daily dose is presented in number of tablets per day for DCV 3DAA FDC and mg per day for RBV.

See Section 8.2.1.1 for additional conventions.

7.4.2 Interruption of Study Therapy
Refer to Section 7.4.2 of the Core SAP.

See Section 8.2.1.2 for additional conventions.
7.4.3   Discontinuation of Study Therapy
Time on study therapy is described by a Kaplan-Meier plot and life table by treatment arm within cohort. Refer to Section 7.4.3 of the Core SAP.

7.4.4   Measurements of Treatment Adherence
Refer to Section 7.4.4 of the Core SAP.

See Section 8.2.1 for additional conventions.

7.4.5   Concomitant Therapy
Refer to Section 7.4.5 of the Core SAP for concomitant medications and post study therapy medications.

7.5   Efficacy
Analyses use HCV RNA results from the central laboratory only. The Roche HCV COBAS® TaqMan® Test v. 2.0 is used to measure HCV RNA levels. Visit windows are constructed around planned visit times for slotting purposes. If there are multiple HCV measurements in a window, the one closest to the planned visit time is used for on-treatment time points and the last one is used for follow-up endpoints, such as SVR12 or SVR24 (See Section 8.1). HCV RNA measurements are excluded after the start of non-study anti-HCV medication on treatment or during follow-up. Results are presented by treatment group within cohort.

Estimates of virologic response rates are computed based on all treated subjects, unless otherwise specified. That is, proportions are defined as the number meeting the response criteria divided by the number treated.

For the proportion of subjects with SVR12 in the primary and the first key secondary objective, response rates and 2-sided 97.5% CIs based on the normal approximation to the binomial distribution will be presented. A Bonferroni multiplicity adjustment of type 1 error (0.05/2) of each arm comparing to the historical control will be applied. Missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach (see Section 4.1).

For all other binary efficacy endpoints, response rates and 2-sided 95% CIs based on the normal approximation to the binomial distribution will be presented. When the sample sizes are small, i.e., < 30, or the proportions are on the edge of the parameter boundary (close to 0 or 100%), CIs are calculated based on exact binomial distribution.

There is an analysis of SVR24 at the time of the primary analysis. It is restricted to the subjects who have HCV RNA measurements at post-treatment follow-up Week 24.
7.5.1 Primary Efficacy Endpoint

Sustained Virologic Response at Post-Treatment Week 12 (SVR12) in Treatment Naive Cirrhotic Subjects

The proportion of subjects with SVR12, defined as HCV RNA < LLOQ TD / TND) at post treatment Week 12, are summarized for subjects in each treatment group in naive cohort. For the primary analysis of SVR12, response rates and two-sided 97.5% CIs will be based on all treated subjects.

Missing HCV RNA data at follow-up Week 12 will be imputed using the Next Value Carried Backwards (NVCB) approach, i.e., missing HCV RNA data in the follow-up Week 12 window will be imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window. The numerator is based on subjects meeting the response criteria and the denominator is based on all treated subjects.

The lower bound of the 97.5% CI of the SVR12 in each treatment naive subjects arm will be used to compare to the historical threshold of 69% respectively; if at least one arm exceeds 69% it can be concluded that the primary objective is achieved and the SVR12 rate of at least one treatment naive arm with DCV 3DAA +/- RBV is significantly higher than the historical threshold of 69%.

Two sensitivity analyses on the SVR12 rate will be conducted using modified ITT approach and observed values as described in Section 7.5.1 of the Core SAP.

7.5.2 First Key Secondary Efficacy

Sustained Virologic Response at Post-treatment Week 12 (SVR12) in Treatment Experienced Subjects

Similarly, the proportion of treatment experienced GT-1 subjects with SVR12, defined as HCV RNA < LLOQ TD/TND at post treatment Week 12, will be summarized for subjects on each treatment group in experienced cohort. Response rate and 2-sided 97.5% CIs will be based on all treated subjects. Missing HCV RNA data at follow-up Week 12 will be imputed using the NVCB approach and the denominator is based on all treated subjects. If the lower bound of the SVR12 97.5%CI in either of the treatment experienced arms exceeds the historical threshold of 45%, it can be concluded that the first key secondary objective is achieved and the SVR12 rate of at least one treatment experienced arm with DCV 3DAA therapy +/- RBV is significantly higher than the historical threshold of 45%.

Sensitivity analyses of this key secondary endpoint will be conducted using both modified ITT approach and observed values.
7.5.3 Other Secondary and Other Efficacy Endpoints

Binary endpoints are estimated using proportions and 95% confidence intervals, based on treated subjects. Analyses are presented by treatment group within cohort.

7.5.3.1 HCV RNA < LLOQ TD or TND Over Time

The proportions of treated subjects with HCV RNA < LLOQ TD / TND are presented at baseline and each scheduled visit on treatment, at weeks 1, 2, 4, 6, 8, and 12; post treatment Weeks 4 (SVR4), 8 (SVR8), 12 (SVR12) and 24 (SVR24).

A longitudinal plot displays the proportions of treated subjects with HCV RNA < LLOQ TD / TND versus week, by treatment group within cohort. The proportions are displayed with error bars represented by 95% confidence intervals.

7.5.3.2 HCV RNA < LLOQ TND Over Time

The proportions of treated subjects with HCV RNA < LLOQ TND are presented at baseline and each scheduled visit on treatment, at weeks 1, 2, 4, 6, 8, and 12; at both weeks 4 and 12, and at EOT; as well as post-treatment Weeks 4, 8, 12 and 24.

A longitudinal plot analogous to the one for HCV RNA < LLOQ TD / TND is produced for HCV RNA < LLOQ TND.

7.5.3.3 HCV RNA Changes from Baseline

Refer to Section 7.5.2.3 of the Core SAP.

7.5.3.4 Concordance between SVR12 and SVR24

Refer to Section 7.5.2.4 of the Core SAP. This analysis only includes treated subjects with HCV RNA measurements at both weeks 12 and 24 of post-treatment follow-up.

7.5.3.5 Efficacy Results in Subgroups

SVR12 rate with NVCB approach (and SVR24 for final analysis) and 95% CI will be presented by subgroup. These analyses will be conducted by treatment group within cohort.

The following common subgroups are analyzed:

- Gender (male, female);
- Age (< 65 years, ≥ 65 years);
- Race (White, Black or African American, Asian, Other);
- Region (Europe, North America, Australia)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino);
- Baseline HCV RNA ( < 800,000 IU/mL and ≥ 800,000 IU/mL);
- Cirrhosis status (yes, no, unknown, if more than 1 category present);
• Fibrosis stage (F0, F1, F2, F3 and F4, if more than 1 category present);
• BMI (< 20 kg/m², 20-<25 kg/m², 25-<30 kg/m², >=30 kg/m²);
• SNP at rs12979860 of IL28B (CC, and non-CC);
• Randomization strata (HCV genotype 1a or 1b) from IVRS;
• Genotype subtype (GT-1a, GT-1b, other)
• Baseline NS5A-28 resistance (yes, no) for GT-1a and GT-1b subjects separately
• Baseline NS5A-30 resistance (yes, no) for GT-1a and GT-1b subjects separately
• Baseline NS5A-31 resistance (yes, no) for GT-1a and GT-1b subjects separately
• Baseline NS5A-93 resistance (yes, no) for GT-1a and GT-1b subjects separately

In addition, a forest plot displaying the SVR12 (and SVR24 for final analysis) rate and 95% CI for each subgroup will be presented for each treatment group within cohort.

7.5.4 Predictors of Response

Demographic and baseline clinical factors are evaluated as predictors of SVR12 (SVR24 for final analysis) in an exploratory analysis using a logistic regression model. The potential factors to be considered in the model may include cohort, treatment group, age, gender, baseline BMI, baseline viral load, genotype subtype, baseline resistance associated polymorphisms by genotype subtype and IL28B. Other candidate factors for inclusion in the model may also be identified based on the subgroup analysis. The odds ratio and p-value of each predictor will be reported, and a forest plot displaying the odds ratio and 95% CI for each predictor will be presented.

Refer to Section 7.5.3 of the Core SAP for the analyses of SVR12 (SVR24 for final analysis) by positive predictive value (PPV) and negative predictive value (NPV) of various on-treatment time points and by time to first HCV RNA < LLOQ TND.

7.5.5 Association of Dose Compliance and Efficacy

Refer to Section 7.5.4 of the Core SAP.

Duration compliance is computed as 100*min(time on therapy/planned duration of therapy, 1), where planned duration of therapy is 12*7 days for both DCV 3DAA FDC and RBV. Dose compliance to a drug is defined as 100*min(average daily dose/target daily dose, 1), where target daily dose is 2 tablets for DCV 3DAA FDC, and 1000 mg if subject < 75 kg or 1200 mg if subject ≥ 75 kg, for RBV.

7.5.6 Resistance (Viral Genotyping and Phenotyping)

Refer to Section 7.5.5 of the Core SAP.
Summaries of post-baseline resistance substitutions regardless of baseline variants will be presented for treated subjects failing study therapy by treatment group within cohort and overall for each drug combination and will be produced by genotype/subtype separately.

A subject listing of those who have baseline and on-study NS5A or NS3 or NS5B resistance variants will be provided.

A parallel line multi-plot of log10 HCV RNA versus week is presented by treatment within cohort for subjects with virologic failure.

### 7.5.7 Human Genotyping

Blood samples for SNP analysis are collected on Day 1. Frequencies for each SNP -- wild type [common homozygous], mixed [heterozygous], mutant [minor homozygous] -- are summarized, by treatment group within cohort and overall.

Minor allele frequencies and departures from Hardy-Weinberg Equilibrium (HWE) are summarized for each SNP pooled across cohorts. Refer to Section 7.5.6 of the Core SAP for this analysis.

SVR12 is summarized by treatment group within cohort for each IL28B SNP (rs12979860, rs8099917).

In addition, total bilirubin at baseline and Maximum total bilirubin value on treatment will be summarized by treatment group within cohort for each SNP other than IL28B.

### 7.5.8 IP-10

Levels of IP-10 are collected at Day 1. Proportion of subjects with SVR12 by Baseline IP-10 (categories: <150 pg/ml, 150-600 pg/ml, >600 pg/ml) will be presented by treatment within cohort. Baseline IP-10 values will also be summarized for SVR12 responders and non-responders by treatment within cohort.

### 7.6 Safety

Refer to Section 7.6 of the Core SAP. For this study, safety endpoints are assessed by treatment group within each cohort, treatment group combining cohorts and overall.

#### 7.6.1 Deaths

Refer to Section 7.6.1 of the Core SAP.

#### 7.6.2 Other Serious Adverse Events

Refer to Section 7.6.2 of the Core SAP.

#### 7.6.3 Adverse Events Leading to Discontinuation

Refer to Section 7.6.3 of the Core SAP.
7.6.4 **Adverse Events Leading to Interruption**
Refer to Section 7.6.4 of the Core SAP.

7.6.5 **Overall Adverse Events**
Refer to Section 7.6.5 of the Core SAP.

7.6.6 **Multiple Occurrences of Adverse Events**
Refer to Section 7.6.6 of the Core SAP.

7.6.7 **Clinical Laboratory Evaluations**
Summaries are based on subjects with at least one laboratory measurement during the study period and are grouped by treatment group within cohort, treatment group combining cohorts and overall. Analyses of laboratory tests use values from central or local laboratories.

7.6.7.1 **Laboratory Abnormalities**
Refer to Section 7.6.7.1 of the Core SAP.

**Anemia**
Anemia is defined as Hg < 10 g/dL on-treatment who had Hg ≥ 10 g/dL at baseline.

Summary of anemia rate on treatment is produced by treatment group within cohort and overall. Anemia rates will be calculated for treated subjects and also on the subset of treated subjects whose baseline hemoglobin was > 12 g/dL, for women, and >13 g/dL, for men.

**Differences in Rates in Selected Grade 3/4 Laboratory Abnormalities**
Differences between treatment groups within each cohort and across cohort in the rates of selected grade 3-4 laboratory abnormalities (Hematology and liver function including hemoglobin, platelets, lymphocytes (absolute), neutrophils+bands (absolute); ALT, AST, alkaline phosphatase, total bilirubin) on treatment will be estimated and 95% CIs for the differences will be provided based on a normal approximation.

7.6.7.2 **Laboratory Tests over Time**
Laboratory values are summarized at baseline and each scheduled visit week on treatment and at follow-up Week 4 for treated subjects using observed values. This summary is done by treatment group within cohort and overall. A similar analysis is done for change from baseline laboratory values. Commonly collected laboratory tests may include, but are not limited to, the following:

- Hematology: hemoglobin, platelets, INR, WBC, lymphocytes (absolute), neutrophils + bands (absolute), and eosinophils;
- Hepatobiliary enzymes and measures of hepatic synthetic function: ALT, AST, direct bilirubin and total bilirubin;
Pancreatic enzymes and renal function tests: lipase colorimetric and creatinine. Longitudinal plots display median values versus week by treatment group within cohort with error bars representing 1 standard error (SE) for the following laboratory tests: hemoglobin, platelets, absolute lymphocytes, absolute neutrophils + bands, ALT, AST and total bilirubin. See Appendix 2 of the Core SAP for the calculation of the SE estimate of the median.

7.6.7.3 **Select Laboratory Test Results**
Refer to Section 7.6.7.3 of the Core SAP.

7.6.7.4 **Special Search Categories**
Refer to Section 7.6.7.4 of the Core SAP.

7.6.8 **Safety in subgroups**
Select safety tables will be generated for the following subgroups:

- Gender (male, female);
- Age (<65 years, ≥65 years);
- Baseline fibrosis stage (F0, F1, F2, F3 and F4, if more than 1 category present);
- Baseline BMI (< 20 kg/m², 20 - <25 kg/m², 25 - < 30 kg/m², ≥ 30 kg/m²)
- Race (White, Black or African American, Asian, Other)
- Region (Europe, North America, Australia)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino);

The following analyses will be done on all factors listed above, for each regimen:

- On-treatment adverse events in ≥ 5% of Subjects. 5% refers to subjects in any group
- On-treatment serious adverse events
- Worst grade of hematologic, liver, pancreatic and renal function tests on treatment (0, 1, 2, 3, 4, 3-4, 1-4)

7.6.9 **Vital Signs**
Summary statistics for the observed values for each parameter are tabulated by visit for treatment group within cohort and overall.

A listing of vital signs is provided by treatment group for all the cohorts.

7.6.10 **Physical Examination**
All physical examinations data are listed only.

7.6.11 **Pregnancy**
By-subject listing of pregnancy tests results will be provided for randomized female subjects.
7.7 Pharmacokinetic Analyses

Refer to Section 7.7 of the Core SAP.

8 CONVENTIONS

8.1 Visit Definition

Visits are defined below. Subjects receive up to 12 weeks of study therapy and are followed for an additional 24 weeks. Windows are constructed for each visit in order to slot data. Labels for study periods and visits appear in listings and datasets.

<table>
<thead>
<tr>
<th>Study Period Label</th>
<th>Visit Label</th>
<th>Visit Number</th>
<th>Target Day from Start of Study Period</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-TREAT</td>
<td>PRE-TREAT</td>
<td>1</td>
<td>1</td>
<td>&lt; 1 day(^a)</td>
</tr>
<tr>
<td>ON-TREAT</td>
<td>DAY 1</td>
<td>2</td>
<td>1</td>
<td>1 - 4 days(^a)</td>
</tr>
<tr>
<td></td>
<td>WEEK 1</td>
<td>3</td>
<td>7</td>
<td>5 - 10 days</td>
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<td></td>
<td>WEEK 2</td>
<td>4</td>
<td>14</td>
<td>11 days - 3 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 4</td>
<td>5</td>
<td>28</td>
<td>&gt; 3 - 5 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 6</td>
<td>6</td>
<td>42</td>
<td>&gt; 5 - 7 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 8</td>
<td>7</td>
<td>56</td>
<td>&gt; 7 - 10 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 12</td>
<td>8</td>
<td>84</td>
<td>&gt; 10 - 16 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 12 EXT</td>
<td>9</td>
<td>140</td>
<td>&gt; 16 weeks</td>
</tr>
<tr>
<td>FOLLOW-UP</td>
<td>F/U WEEK 4</td>
<td>10</td>
<td>21</td>
<td>&gt; 1 - 6 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 8</td>
<td>11</td>
<td>49</td>
<td>&gt; 6 - 10 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 12</td>
<td>12</td>
<td>77</td>
<td>&gt; 10 - 18 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 24</td>
<td>13</td>
<td>161</td>
<td>&gt; 18 - 30 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 24 EXT</td>
<td>14</td>
<td>245</td>
<td>&gt; 30 weeks</td>
</tr>
</tbody>
</table>

\(^a\) See Section 6.1 for classification of measurements on Day 1 (i.e., the first dose of active study therapy) as pre-treatment or on-treatment depending on the data domain.

Time is measured from the first active dose date of study therapy. For longitudinal summaries of data, windows around planned measurement times are based on the midpoint between planned study visits unless specified otherwise.

Study days are defined as the difference between the measurement date and first active dose date of study therapy.\(^\dagger\) Weeks are study days divided by 7.
8.2 Domain Derivations
Refer to Section 8.2 of the Core SAP.

8.2.1 Exposure
8.2.1.1 Study Therapy
Derived exposure dates and time of therapy that are used commonly in analyses are defined in Section 8.2.1.1 of the Core SAP.

Duration adherence to a study drug is defined as 100 multiplied by the minimum of (time on therapy/planned duration of therapy, 1). The planned duration of therapy for each drug is defined as:

- 12*7 = 84 days.

The exception is in the case of discontinuation for lack of efficacy, in which case planned duration is defined as:

- last dose date of study therapy - first dose date of study therapy + 1

Dose adherence to a study drug is defined as 100 multiplied by the minimum (average daily dose/target daily dose, 1):

- DCV 3DAA FDC: Target daily dose = 2 tablets/day.
- RBV: Target daily dose=1000 mg/day, if subject < 75 kg, or 1200 mg/day, if subject $\geq$ 75 kg.

8.2.1.2 Interruption or Delay of Study Therapy
Interruptions of DCV 3DAA are identified from complete dosing records (i.e., non-missing start date, stop date and drug name) in which the total dose is 0. For subjects who have discontinued study therapy, only records with start dates before the last dose date of DCV 3DAA are selected, and end dates after the last dose date of DCV 3DAA are set to the last dose date of DCV 3DAA. Interruptions of RBV are identified the same way.

Dose reduction of RBV is identified from complete dosing records (i.e., non-missing start date, end date, and drug name) in which the total dose is greater than 0 but less than the total dose corresponding to the first dose date of drug.

8.2.2 Human Genotyping
If there are multiple records for a SNP, then the last record collected and entered is selected. SNP genotype is considered missing if either allele is not A, C, G, T, DEL or INS.

8.2.3 Physical Measurements
For each baseline parameter, if there are multiple records on the same measurement day, then the last record entered is selected.
8.2.4 Viral Genotyping and Phenotyping
For baseline HCV subtype, if there are multiple records on the same collection day, then the last record assayed is selected. Only records from the central laboratory are used.

8.2.5 Virology
Refer to Section 8.2.5 of the Core SAP.

In the case of two HCV RNA samples being collected in the same visit window that are equidistant from the planned visit date (absolute difference between the planned visit and the collection date are the same), the latter measurement is used in the analysis.

8.2.6 Laboratory Test Results
Laboratory abnormalities are graded following the Division of AIDS (DAIDS) recommendations. For laboratory values that fall between two DAIDS toxicity ranges, the toxicity grade associated with the higher range is assigned. For example, an ALT value greater than 2.5 x ULN but less than 2.6 x ULN is assigned toxicity Grade 2.

9 CONTENT OF REPORTS

9.1 Planned Analyses
- An interim database lock will occur after all subjects reach post-treatment Week 4 to support modeling and simulations for exposure-response analysis.
- the primary analysis will be conducted after all subjects reach post-treatment Week 12.
- the final analysis will be conducted after all subjects reach post-treatment Week 24 and complete the study.

9.2 Listings
Reports also contain listings described in the DPP. Listings are sorted by cohort and PID, as applicable. Select listings display dosing status according to the GBS standard temporal dosing model.
APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

Relevant protocol deviations that can be programmed from the database are identified below. The list would be updated if, in the course of monitoring the study, additional protocol deviations are found and considered relevant.

- HCV RNA < $10^4$ IU/mL at screening;
- BMI < 18 kg/m² or > 35 kg/m²;
- HCV genotype other than genotype 1 at screening;
- Seropositive for HBsAg at screening;
- Subjects didn’t have compensated cirrhosis as defined in protocol at screening;
- Lab test findings:
  a) Alanine amino transferase (ALT) or aspartate aminotransferase (AST) $\geq 5$ x ULN;
  b) Total Bilirubin $\geq 34$ μmol/L ($\geq 2$ mg/dL),
  c) INR $\geq 1.7$;
  d) Albumin < 3.5 g/dL (35 g/L);
  e) Platelets < 50 x 10⁹ cells/L;
  f) ANC < 0.75 x 10⁹ cells/L;
  g) Hemoglobin < 10 g/dL (100 g/L);
  h) Creatinine Clearance (CrCl) $\leq 50$ mL/min (as estimated by Cockcroft and Gault);
  i) Alpha fetoprotein (AFP): AFP > 100 ng/mL (> 82.6 IU/mL)
  j) QTcF or QTcB > 500 mSec;
  k) Positive HIV-1 or HIV-2 Ab.
- DCV 3DAA average daily dose < 80% of target dose;
- Continuation of study medication after meeting criteria for virologic breakthrough:
  Any confirmed $\geq 1$ log₁₀ IU/mL HCV RNA on-treatment increase from nadir, or
  Any confirmed HCV RNA $\geq$ LLOQ after HCV RNA declined to < LOQ (TD/TND)
  Continuation of study medication means subject is still on study drug after 4 weeks from the time of virologic breakthrough (the first HCV RNA value that met the criteria).
- Use of prohibited concomitant medication, including anti-HCV medications, for more than 1 day;
- Dose interruptions of DCV 3DAA > 7 days from initiation of interruption.

APPENDIX 2 HISTORICAL THRESHOLDS DERIVATION

The historical threshold SVR was derived from a combined analysis in subjects treated with peg-interferon/ribavirin in combination with either sofosbuvir or simeprevir.
The final historical threshold based on these SVR rates is:

Cirrhotic

Treatment-naive 69%
Treatment-experienced 45%

The treatment-naïve data is from the NEUTRINO trial for sofosbuvir, which demonstrated SVR rate of 91% (95% confidence interval 87-94%) in non-cirrhotic subjects [FDA antiviral drugs advisory committee, NDA 204671, 25 October, 2013]. Using a non-inferiority margin of 15% (in consideration for an IFN-free regimen), the threshold for non-cirrhotic subjects was calculated by subtracting the non-inferiority margin from the upper bound of the 95% confidence interval of the point estimate (94% - 15%), which is 79%.

In the NEUTRINO trial, the SVR for cirrhotic subjects was 10% lower than for non-cirrhotic subjects (81% vs. 91%). Therefore, the historical threshold for cirrhotic subjects in AI443113 was determined by subtracting 10% from the historical threshold for non-cirrhotic subjects, which is 79%-10% = 69%.

The prior relapse data is from trial HPC3007 for simeprevir [Forns et al Gastroenterology 2014;146:1669-1679], and the non-responder data is from C206 study for simeprevir [FDA antiviral drugs advisory committee, NDA 205123, 24 October, 2013].

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive</td>
<td>69%</td>
</tr>
<tr>
<td>Prior relapse</td>
<td>67%</td>
</tr>
<tr>
<td>Non-responder (partial, null)</td>
<td>58%</td>
</tr>
</tbody>
</table>

For treatment-experienced subjects, a composite historical threshold will be used, taking into account past treatment response to interferon and RBV as relapse or non-response. Subjects who are intolerant of interferon or who previously failed DAA treatment (if allowed per protocol) have no treatment options so are assigned a historical threshold of 5%.

Virologic failure 62.5% (average of 67% SVR for relapse, 58% for null/partial)
- assumes equal number of relapse and null/partial subjects

Interferon intolerant 5% (no treatment option)
DAA failure 5% (no treatment option)
The final composite threshold for cirrhotic, treatment-experienced subjects, assuming enrollment of 70% virologic failure, 20% interferon-intolerant, and 10% DAA failure, is 45%.

\[ 70\% \times (62.5\% \text{ SVR}) + 20\% \times (5\% \text{ SVR}) + 10\% \times (5\% \text{ SVR}) = 45\% \]

### DOCUMENT HISTORY

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<th>Author(s)</th>
<th>Description</th>
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<tr>
<td>1.0</td>
<td>Rong Yang</td>
<td>Initial version</td>
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### 10 REFERENCES

1. Core SAP AI443 3DAA and AI444 DCV SOF V1.