STATISTICAL ANALYSIS PLAN
FOR HCV DAA

A PHASE 3 EVALUATION OF A DACLATASVIR/ASUNAPREVIR/BMS-791325
FIXED DOSE COMBINATION (FDC) IN NON-CIRRHOTIC SUBJECTS WITH
GENOTYPE 1 CHRONIC HEPATITIS C

PROTOCOL AI443102

VERSION 1.0
## DOCUMENT HISTORY

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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 regimen or DCV 3DAA fixed dose combination (DCV 3DAA FDC) regimen 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 DCV 3DAA regimen, has demonstrated a high barrier to resistance which provides coverage for GT-1a as well as GT-1b HCV (AI443014).

Study AI443102 will enroll both treatment naïve and treatment experienced non-cirrhotic subjects. Based on favorable response rates to the DCV/ASV/BMS-791325 (DCV 3DAA) regimen in difficult to treat cirrhotic subjects, as well as favorable SVR rates of prior non-responders and prior interferon ineligible naive/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 studies 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 AI443102.

Research Hypothesis:

In HCV GT-1 treatment-naïve non-cirrhotic subjects, treated with 12 weeks of DCV 3DAA FDC can achieve SVR rates significantly higher than the historical threshold of 79%.

2 STUDY DESCRIPTION

2.1 Study Design
AI443102 is a two-cohort, open-label study that will enroll approximately 400 non-cirrhotic GT-1 treatment-naive and treatment-experienced subjects. At least 300 subjects will be treatment-naive and up to 100 subjects will be treatment experienced. All subjects will receive DCV 3DAA regimen for 12 weeks duration. GT 1b subtype will be capped at 40%. At Week 12, subjects will enter the post treatment follow up period and will be followed for 24 weeks post therapy. The primary endpoint, SVR12, will occur at Week 24, and will include SVR12 data for all 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

All subjects will receive DCV 3DAA regimen for 12 weeks duration. At least 300 subjects will be treatment-naive and up to 100 subjects will be treatment experienced. Enrollment will be capped at ~40% for GT-1b.

2.3 Blinding and Unblinding

This study is an open label study.

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.
3  OBJECTIVES

3.1  Primary
To demonstrate the proportion of naive non-cirrhotic subjects enrolled to DCV 3DAA FDC with
SVR12, defined as HCV RNA < LLOQ TD/TND at follow up Week 12 is significantly greater
than a historical threshold of 79%.

3.2  Key Secondary
- To demonstrate the proportion of experienced non-cirrhotic subjects enrolled to DCV 3DAA
  FDC with SVR12, defined as HCV RNA < LLOQ TD/TND at follow up Week 12 is
  significantly greater than a historical threshold of 48%;
- To evaluate the proportion of subjects in each cohort 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 cohort who achieve HCV RNA < LLOQ TND
  at each of the following Weeks: 1, 2, 4, 6, 8, and 12; 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 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 cohort;
- To estimate the rates of selected Grade 3-4 laboratory test result abnormalities (including
  hematologic and liver function, based on DAIDs criteria) in each cohort;
- To evaluate the proportion of subjects achieving SVR12 associated with HCV GT-1a vs.
  GT-1b in each cohort;
- To evaluate the proportion of subjects in each cohort achieving SVR12 associated with
  IL28B rs12979860 SNP status (CC genotype or non-CC genotype);
- To evaluate the proportion of subjects in each cohort achieving SVR12 associated with stage
  of liver fibrosis.

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;
- To describe the pharmacokinetics of DCV 3DAA with stage of liver fibrosis;
• 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 naive cohort 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 subjects in the experienced cohort with SVR12, defined as HCV RNA < LLOQ TD/TND at follow up Week 12 after 12 weeks DCV 3DAA treatment.
• Proportion of subjects in each cohort 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 cohort 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;
• On treatment safety, as measured by frequency of SAEs and discontinuations due to AEs through the end of treatment by cohort;
• Proportion of subjects with anemia defined as Hg < 10 g/dL on-treatment who had Hg ≥ 10 g/dL at baseline in each cohort;
• Rates of selected Grade 3 - 4 laboratory test result abnormalities (hematologic and liver function) in each cohort;
• Proportion of subjects in each cohort achieving SVR12 associated with HCV genotype subtype 1a vs. 1b;
• Proportion of subjects in each cohort achieving SVR12 associated with IL28B rs12979860 SNP status (CC genotype or non-CC genotype).
• Proportion of subjects in each cohort achieving SVR12 associated with stage of liver fibrosis.

4.3 Exploratory Endpoints

• Frequency of genotypic substitutions at baseline, on treatment, and post-treatment associated with virologic failure;
• Exposure-response analyses will explore the relationship between DCV, ASV or BMS-791325 measures of exposures and endpoints of efficacy and safety;
• Trough plasma concentrations of DCV, ASV, BMS-791325 and its metabolite, BMS-794712;
• Potential association between SNPs in genes associated with drug metabolism with PK parameters and/or elevations in bilirubin;
• Frequency of relevant special search safety categories potentially including select hematologic and allergic toxicities.

5 SAMPLE SIZE AND POWER

AI443102 is a two-cohort open-label study, one cohort is for treatment-naive subjects and the other cohort is for treatment-experienced subjects. Overall 400 subjects, including at least 300 treatment-naive and up to 100 treatment-experienced genotype 1 (GT 1) non-cirrhotic subjects will be enrolled to receive DCV 3DAA FDC for the first 12 Weeks in this study. All GT 1 subjects will be included.

The primary objective is to determine whether the SVR12 rate in the treatment-naive subjects treated with DCV 3DAA FDC is significantly higher than 79% by a confidence interval (CI) approach. Similarly, the first key secondary objective is to determine whether the SVR12 rate in the treatment-experienced subjects is significantly higher than 48% by the same statistical approach.

For the primary objective, the lower bound of the SVR12 95% CI in the naive subjects will be used to compare to the historical threshold of 79%, if it exceeds it can be concluded that the primary objective is achieved and the SVR12 rate of DCV 3DAA FDC in the treatment-naive subjects is significantly higher than the historical threshold of 79%. With 300 naive subjects it would take a minimum of an observed SVR12 rate of 84% (252/300; 95% CI: 79.9%, 88.1%)
for the lower bound to exceed 79% and conclude the 3DAA regimen is significantly higher than the historical threshold of 79% in the treatment-naive subjects.

Table 8.1 presents some scenarios of observed response rates and 95% confidence intervals for the genotype 1 naive subjects in 3DAA cohort (N=300):

<table>
<thead>
<tr>
<th>Observed SVR Rate</th>
<th>Observed Responders</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>95%</td>
<td>285 of 300</td>
<td>(92.5%, 97.5%)</td>
</tr>
<tr>
<td>92%</td>
<td>276 of 300</td>
<td>(88.9%, 95.1%)</td>
</tr>
<tr>
<td>90%</td>
<td>270 of 300</td>
<td>(86.6%, 93.4%)</td>
</tr>
<tr>
<td>88%</td>
<td>264 of 300</td>
<td>(84.3%, 91.7%)</td>
</tr>
<tr>
<td>85%</td>
<td>255 of 300</td>
<td>(81.0%, 89.0%)</td>
</tr>
<tr>
<td>84%</td>
<td>252 of 300</td>
<td>(79.9%, 88.1%)</td>
</tr>
</tbody>
</table>

For all the efficacy analyses in naive subjects, approximately 300 genotype 1 subjects treated with DCV 3DAA FDC provide 95% confidence that the observed SVR12 rate can be estimated to within 4.1% of the estimates when the observed SVR is 84% or higher.

For the key secondary objective, if the lower bound of the SVR12 95% CI in the experienced subjects exceeds the historical threshold of 48%, it can further be concluded that the first key secondary objective is achieved and the SVR12 rate of DCV 3DAA FDC in the treatment-experienced subjects is significantly higher than the historical threshold of 48%. With 100 experienced subjects it would take a minimum of an observed SVR12 rate of 58% (58/100; 95% CI: 48.3%, 67.7%) for the lower bound to exceed 48% and conclude the DCV 3DAA FDC regimen is significantly higher than the historical threshold of 48% in the treatment-experienced subjects.

Table 8.2 presents some scenarios of observed response rates and 95% confidence intervals for genotype 1 experienced subjects in 3DAA cohort (N=100):

<table>
<thead>
<tr>
<th>Observed SVR Rate</th>
<th>Observed Responders</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>88%</td>
<td>88 of 100</td>
<td>(81.6%, 94.4%)</td>
</tr>
<tr>
<td>85%</td>
<td>85 of 100</td>
<td>(78.0%, 92.0%)</td>
</tr>
<tr>
<td>80%</td>
<td>80 of 100</td>
<td>(72.2%, 87.8%)</td>
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For all the efficacy analyses in experienced subjects, approximately 100 genotype 1 subjects treated with DCV 3DAA FDC provide 95% confidence that the observed SVR12 rate can be estimated to within 9.7% of the estimates when the observed SVR is 58% or higher.

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, and PK parameters are presented as-treated.
- All subjects will receive 3DAA FDC film-coated tables (30 mg/200 mg/75 mg/ BID for 12 weeks)

6.3 Populations for Analyses

The following populations are used in the analyses:

- Enrolled subjects are those who signed an informed consent form and were assigned a Patient Identification number (PID).
- 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 AI443102 Data Presentation Plan.
7.2 Study Conduct

Relevant protocol deviations are summarized by 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-treatment subject status is summarized for enrolled subjects. This presents the number of subjects enrolled, treated, and not treated. Reasons for not being treated are also included (e.g., AE, death, lost to follow-up, etc.).

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

7.3.1.2 End of Therapy 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 cohort and overall:

- Age;
- Age (< 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, for US subjects only (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 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
- 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 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 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 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 the study drug (DCV 3DAA FDC) by cohort. Time on therapy (in Weeks) 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 the drug by 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.

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 cohort. Refer to Section 7.4.3 of the Core SAP.
7.4.4  **Measurements of Treatment Compliance**

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 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 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 based on exact binomial distribution. Results will be presented for treated subjects. The primary analysis for proportions of subjects with efficacy endpoints will be summarized for all treated subjects. The numerator is based on subjects meeting the response criteria and the denominator is based on all treated subjects. The primary analysis for the efficacy endpoints will include the imputation of missing HCV RNA data at follow-up Week 12. The imputation will be based on the Next Value Carried Backwards (NVCB) approach, where subjects with missing HCV RNA data in the follow-up week 12 window will be imputed as a responder (< LLOQ, TD or TND) if the most recent post follow-up Week 12 HCV RNA value is < LLOQ (TD or TND).

There is an analysis of SVR24 at the time of the primary analysis. It is restricted to the subjects who are evaluable for SVR24.

7.5.1  **Primary Efficacy Endpoint**

**Sustained Virologic Response at Post-Treatment Week 12 (SVR12) in Naïve Cohort**
The proportion of subjects with SVR12, defined as HCV RNA< LLOQ TD /TND at post treatment Week 12, are summarized for subjects in the treatment naive group. For the primary analysis of SVR12, response rates and two-sided 95% 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 95% CI of the SVR12 in the naive subjects cohort will be used to compare to the historical threshold of 79%; if it exceeds 79% it can be concluded that the primary objective is achieved and the SVR12 rate of DCV 3DAA in the treatment-naïve subjects is significantly higher than the historical threshold of 79%.

Refer to Section 7.5.1 of the Core SAP for sensitivity analysis descriptions.

7.5.2 First Key Secondary Efficacy

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

Similarly, the proportion of genotype 1 subjects with SVR12, defined as HCV RNA < LLOQ TD /TND at post treatment Week 12, will be summarized for subjects on the experienced group. Response rate and 2-sided 95% 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 and the denominator is based on all treated subjects.

If the lower bound of the SVR12 95% CI in the experienced subjects exceeds the historical threshold of 48%, it can be concluded that the first key secondary objective is achieved and the SVR12 rate of DCV 3DAA in the treatment-experienced subjects is significantly higher than the historical threshold of 48%.

Sensitivity analyses of this key secondary endpoint will be conducted using both modified ITT approach and observed values in a similar manner to the primary endpoint.

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 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 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 or 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.

7.5.3.5 Efficacy Results in Subgroups

SVR12 rate with NVCB approach and 95% CI will be presented by subgroup. These analyses will be conducted by 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, for US subjects only (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);
- 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 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 in an exploratory analysis using a logistic regression model. The potential factors to be considered in the model may include cohort, age, gender, baseline BMI, baseline viral load, genotype subtype, baseline resistance associated polymorphisms (NS5A-28, NS5A-30, NS5A-31, NS5A-93) 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 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 \(100\times\min(\text{time on therapy}/\text{planned duration of therapy}, 1)\), where planned duration of therapy is 12*7 days for DCV 3DAA FDC. Dose compliance to a drug is defined as \(100\times\min(\text{average daily dose}/\text{target daily dose}, 1)\), where target daily dose is 2 tablets.

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 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 cohort for each IL28B SNP.

In addition, total bilirubin at baseline and maximum total bilirubin value on treatment will be summarized by cohort for each non-IL28B SNP.

**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 cohort.

**7.6 Safety**

Refer to Section 7.6 of the Core SAP. For this study, safety endpoints are assessed by cohort 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 cohort and overall.

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 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.

Selected Grade 3/4 Laboratory Abnormalities
Rates of selected grade 3-4 laboratory abnormalities (Hematology and liver function including hemoglobin, platelets, INR, WBC, lymphocytes (absolute), neutrophils+bands (absolute); ALT, AST, alkaline phosphatase, total bilirubin, and albumin) on treatment will be estimated and 95% CIs for the differences will be provided based on a normal approximation by cohort and overall.

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 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 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 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, for US subjects only (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 and change from baseline for each parameter are tabulated by visit cohort and overall.

A listing of vital signs is provided 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 enrolled female subjects.

7.7 Pharmacokinetic Analyses
Refer to Section 7.7 of the Core SAP.
8 CONVENTIONS

Presentations follow BMS general global standards for all data domains. This document is available upon request.

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>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-TREAT</td>
<td>PRE-TREAT</td>
<td>1</td>
<td>&lt; 1 day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ON-TREAT</td>
<td>DAY 1</td>
<td>2</td>
<td>1 - 4 days&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>WEEK 1</td>
<td>3</td>
<td>5 - 10 days</td>
</tr>
<tr>
<td></td>
<td>WEEK 2</td>
<td>4</td>
<td>11 days - 3 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 4</td>
<td>5</td>
<td>&gt; 3 - 5 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 6</td>
<td>6</td>
<td>&gt; 5 - 7 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 8</td>
<td>7</td>
<td>&gt; 7 - 10 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 12</td>
<td>8</td>
<td>&gt; 10 - 16 weeks</td>
</tr>
<tr>
<td></td>
<td>WEEK 12 EXT</td>
<td>9</td>
<td>&gt; 16 weeks</td>
</tr>
<tr>
<td>FOLLOW-UP</td>
<td>F/U WEEK 4</td>
<td>10</td>
<td>&gt; 1 - 6 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 8</td>
<td>11</td>
<td>&gt; 6 - 10 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 12</td>
<td>12</td>
<td>&gt; 10 - 18 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 24</td>
<td>13</td>
<td>&gt; 18 - 30 weeks</td>
</tr>
<tr>
<td></td>
<td>F/U WEEK 24 EXT</td>
<td>14</td>
<td>&gt; 30 weeks</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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.<sup>3</sup> 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:
  - $12 \times 7 = 84$ 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.

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.

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.⁴
REFERENCES

1 Core SAP_AI443 3DAA and AI444 DCV SOF_V1.


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;
- Confirmed Lab test findings:
  a) Alanine amino transferase (ALT) or aspartate aminotransferase (AST) >= 5x ULN;
  b) Total Bilirubin >= 34 mmol/L (>= 2 mg/dL),
  c) INR >= 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) <= 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 HBsAg, 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 $\geq 1 \log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or
  - Any confirmed HCV RNA $\geq$ LLOQ after HCV RNA declined to < LLOQ (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.