Official Title of Study:

Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Safety and Efficacy of Daclatasvir (DCV) in Combination with Sofosbuvir (SOF) in Children from 3 to less than 18 Years of Age with GT-1 to -6 Chronic Hepatitis C (CHC) Infection

NCT Number: NCT03487848

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STATISTICAL ANALYSIS PLAN
FOR CSR

OPEN-LABEL, SINGLE-ARM TRIAL TO EVALUATE THE PHARMACOKINETICS, SAFETY AND EFFICACY OF DACLATASVIR (DCV) IN COMBINATION WITH SOFOSBUVIR (SOF) IN CHILDREN FROM 3 TO LESS THAN 18 YEARS OF AGE WITH GT-1 TO -6 CHRONIC HEPATITIS C (CHC) INFECTION

PROTOCOL AI444423

VERSION # 1.1

REVISION HISTORY

Revision	Date	Revised by	Changes Made -- Reasons for the Change
1.0	28APR2018	[redacted]	Initial version
1.1	18JUL2018	[redacted]	• Cover page: Removed header. • Section 2.1: New section added. Moved all text from Section 2 here, and renumbered Figure 2-1 as 2.1-1. • Section 2.2: New section added. Moved all text from Section 5.2 here. • Section 2.3: New section added to describe blinding and unblinding procedures. • Section 5.2: Moved all text to Section 2.2, and added text to cross-reference Section 2.2. • Few typos corrected.

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2 STUDY DESCRIPTION

2.1 Study Design

The study is an open-label, single-arm, sequential descending age cohort trial evaluating the PK profile, safety, tolerability, and efficacy of DCV+SOF, administered for 12 weeks, to paediatric participants (3 years to < 18 years), monoinfected with the hepatitis C virus (genotypes (GT) -1 to -6), who are non-cirrhotic and either treatment naive or treatment experienced.

The total duration of the study for each participant is approximately 2.5 years:

- Screening Duration: 42 days
- Treatment Duration: 12 weeks
- Post-Treatment Follow-up Duration: 108 weeks. Upon completion of the post-treatment follow-up Week 12 visit, participants are followed for an additional 2 years (96 weeks) as long-term follow-up to assess SVR24, durability of response, long term safety, and the persistence of resistance variants in non-responders.

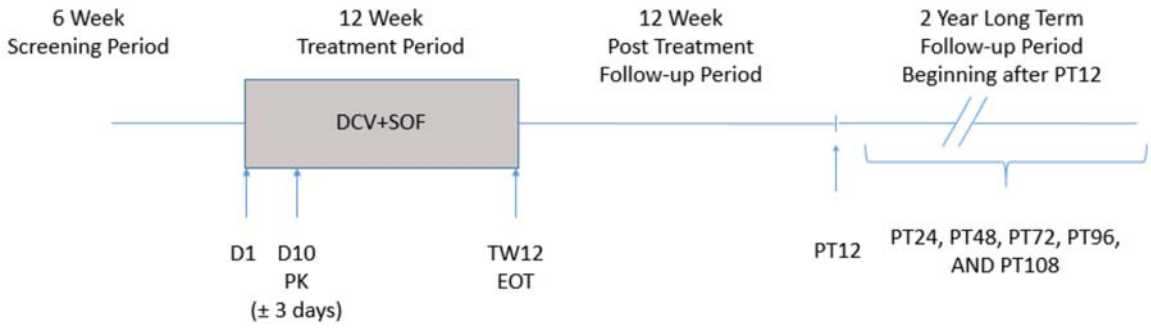
A minimum of 30 participants are evaluated for the primary endpoint, with at least 8 treated per age cohort:

- Cohort 1: 12 to < 18 years old
- Cohort 2: 6 to < 12 years old
- Cohort 3: 3 to < 6 years old

Enrollment begins with Cohort 1, followed by Cohorts 2 and 3. Enrollment in Cohorts 2 and 3 is dependent on the availability of the European Commission approved SOF formulation for the corresponding age cohort.

The study design is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

All participants receive DCV+SOF in Cohort 1 (12 to < 18 years), Cohort 2 (6 to < 12 years), and 3 (3 to < 6 years). Cohorts are determined by age at Day 1 assigned by Interactive Response Technology (IRT), not age at enrollment collected on the Case Report Form (CRF).

2.3 Blinding and Unblinding

This is an open-label study; unblinding procedures are not applicable.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are presented in Table 3-1.

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the PK profile of DCV in combination with SOF in children and adolescents aged 3 to <18 years of age	• PK parameters (Cmin, Cmax, Tmax, AUC (TAU), CLT/F) for DCV derived from plasma concentration versus time data on Day 10 (± 3 days) within a dosing interval. • In Cohort 3, PK parameters from model-based analyses with 5 samples from each participant.
Secondary	
To assess the safety and tolerability of the DCV+SOF regimen in pediatric participants	Frequencies of serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of study therapy, AEs by intensity, and laboratory abnormalities by toxicity grade on treatment and during follow-up
To determine the proportion of participants with SVR12	Proportion of participants with HCV RNA < LLOQ (TD or TND) at post-treatment follow-up Week 12
To evaluate genotypic substitution(s) associated with virologic failure	Frequencies of NS5A and NS5B resistance-associated variants (RAVs) emergent at the time of virologic failure on treatment and during follow-up in non-responders
To assess the acceptability and palatability for the age-appropriate chewable tablet formulation, and acceptability for adult filmcoated tablet	Summary of responses from questionnaire assessing acceptability and palatability at Day 1, Week 4, and Week 12

Table 3-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

LLOQ = lower limit of quantification; TD = target detected; TND = target not detected

4 SAMPLE SIZE AND POWER

A minimum of 30 participants, assigned to 3 age descending cohorts, are evaluated for the primary endpoint (PK) with at least 8 participants assessed in each age cohort.

The primary objective of this study is to evaluate the PK of DCV. The PK profile of DCV has been well characterized in the clinical development program and it has been noted that DCV is associated with predictable pharmacokinetics. The intra-participant variability for DCV Cmax and AUC(INF) was assessed from clinical studies where single oral doses of DCV were administered with or without food and were estimated to be low with a % CV of 18% for Cmax and 10% for AUC(INF). Similarly, the inter-participant variability in DCV Cmax and AUC were assessed from clinical studies where single and multiple oral doses of DCV administered alone, and with or without food in some cases, was identified to be modest with % CV values of 37.5% for Cmax and 35% for AUC. PK is assessed in all participants; however, due to the low observed variability in DCV exposure, assessment of the PK in the initial 5 participants per age cohort provides the necessary information to match DCV exposures between adults and paediatric participants and either allow enrollment to be initiated in the next descending age cohort(s) or indicate that additional participants need to be enrolled in the cohort with a modified dose.

Enrollment will continue in each cohort, after the initial 5 participants have completed their Day 10 assessments, to have a minimum of 8 evaluable participants in each cohort.

5 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

5.1 Study Periods

Study periods are defined as follows:

- Pre-treatment period: Begins at the first screening visit and ends on the start date of study therapy (DCV or SOF).
- On-treatment period: Begins after the start date of study therapy and ends on the last date of study therapy.
- Follow-up period: Begins after the last date of study therapy.

Measurements taken before Day 1 (i.e., the start date of 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, diagnostic procedures, disease history, ECG, human genotyping, laboratory test results (including serology and virology), medical history, physical examination, physical measurements, questionnaires, subject status, viral genotyping, viral phenotyping, and vital signs.

Measurements taken after Day 1 through the last date of study therapy 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, PK concentration, PK parameters, sample collection, sample inform consent and sample reference.

Measurements taken after the last date of study therapy are considered follow-up for all data domains unless otherwise specified.

Refer to Section 7.1 for analysis periods used for analyses and reporting.

5.2 Treatment Regimens

See Section 2.2.

5.3 Populations for Analyses

Populations for analyses are presented in Table 5.3-1.

Table 5.3-1: Populations for Analyses

Population	Description
Enrolled participants	All participants who sign informed consent and are assigned Participant Identification Number. This population is used for all non-PK listings and to summarize study conduct.
Treated participants	Enrolled participants who receive at least 1 dose of study therapy (DCV or SOF). This population is used to summarize pre-treatment characteristics, efficacy and on-treatment safety.
Follow-up participants	Treated participants who continue into the LTFU period, as indicated on the end of treatment subject status CRF. This population is used to summarize follow-up safety and duration of virologic response.

6 STATISTICAL ANALYSES

Statistical analyses are performed using the version of UNIX SAS or S-Plus in production, unless otherwise specified.

6.1 General Methods

All summarizes are presented by cohort and total, unless specified otherwise.

Continuous parameters are summarized using univariate statistics, i.e., number of participants (n), mean, standard deviation (SD), median, quartiles, minimum and maximum. Categorical parameters are summarized using counts and percentages, or counts and proportions depending on the endpoint.

In general, all confidence intervals (CIs) are 2-sided with 95% coverage, unless otherwise specified. CIs for binary endpoints are based on exact binomial distribution. CIs for continuous endpoints are based on the normal distribution.

Longitudinal summaries of efficacy, safety, and questionnaire endpoints use pre-defined analysis visit windows.

Laboratory test endpoints are determined from measurements analyzed at both local and central laboratories, and are summarized using both Système International (SI) and US standard units.

Frequencies and percentages of participants with events are presented for the following: relevant protocol deviations; interruptions of study therapy; non-study medications; AEs; laboratory test and ECG abnormalities. Multiple occurrences of the same event are counted once per participant selecting the worst event to summarize, unless specified otherwise.

By-participant listings are provided for select endpoints, and are sorted by cohort, site identifier, and subject identifier. Listings display all events regardless of study period unless otherwise specified. Select listings (e.g., AEs, laboratory tests) display temporal dosing status according to the GBS standard temporal dosing model.[1]

Participants who move to another investigative site during the study are classified according to their original investigative site, country and geographic region.

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

6.2 Study Conduct

Relevant protocol deviations are summarized for treated participants. Relevant protocol deviations are those that are programmable and could potentially affect the interpretability of the study results, such as:[2]

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

APPENDIX 1 describes the relevant protocol deviations that can be programmed from the database.

6.3 Study Population

6.3.1 Disposition of Participants

6.3.1.1 Pre-Treatment Subject Status, Enrollment, and Accrual

Populations for analyses (see Section 5.3) are summarized with counts only (no percentages) for enrolled participants.

Pre-treatment subject status is summarized for enrolled participants (total only, not by cohort) for the following categories: enrolled, treated, not treated, and the reasons for not being treated (e.g., AE, lost to follow-up, death).

Enrollment at each site by country is summarized for enrolled participants by the following populations (not by cohort): enrolled and treated. Enrollment by age group is summarized analogously. Age group categories are: in utero; preterm newborn (gestational age < 37 weeks); newborns (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); adolescents (12 to 17 years); adults (18 to 64 years); adults (65 to 84 years); adults (≥ 85 years).

Accrual by month and year of initial study therapy is also summarized for treated participants.

6.3.1.2 End of Treatment Subject Status

End of treatment subject status is summarized for treated participants for the following categories: completing the period, not completing the period (including reasons for not completing), continuing to the follow-up period, not continuing to the follow-up period, and not reported (i.e., no subject status data).

A by-participant listing of end of treatment subject status is provided for treated participants.

6.3.1.3 End of Study Subject Status

End of study subject status is summarized for follow-up participants for the following categories: completing the study, not completing the study (including reasons for not completing), and not reported (i.e., no subject status data).

A by-participant listing of end of study subject status is provided for treated participants.

6.3.2 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics are summarized for treated participants.

Summaries of categorical parameters identify the number and percentage of participants with not reported (i.e., missing) measurements, unless specified otherwise.

For treated participants, the baseline value of a parameter (e.g., laboratory test, HCV RNA, ECG, vital sign, physical measurement, questionnaire) is defined as the last, non-missing, valid value collected or measured on or before the start date of study therapy.

6.3.2.1 Demographics

Demographics are presented in Table 6.3.2.1-1.

Table 6.3.2.1-1: Demographic Characteristics

Parameter (Units)	Type	Categories
Age at Day 1 from IRT (years)	Continuous and categorical	3 to < 6, 6 to < 12, 12 to < 18 years
Age at enrollment (years)	Continuous and categorical	3 to < 6, 6 to < 12, 12 to < 18 years
Gender	Categorical	Male, Female
Race	Categorical	White Black or African American Asian, with the following subcategories: • Asian Indian • Asian Other • Chinese • Japanese • Taiwanese American Indian or Alaska Native Native Hawaiian or Other Pacific Islander

Table 6.3.2.1-1: Demographic Characteristics

		Other
Ethnicity	Categorical	Hispanic or Latino Not Hispanic or Latino
Country by Geographic Region	Categorical	Countries within the following regions, as applicable: Asia (Taiwan) Europe (Germany, Poland, Romania, Spain) Pacific Rim/Oceania (Australia)

If sites from other countries are included or excluded in this study, then the associated geographic regions are redefined accordingly.

A by-participant listing of demographics is provided for enrolled participants.

6.3.2.2 HCV Disease Characteristics and Virologic Resistance at Baseline

HCV Disease Characteristics

HCV disease characteristics at baseline are presented in Table 6.3.2.2-1.

Table 6.3.2.2-1: HCV Disease Characteristics at Baseline

Parameter (Units)	Type	Categories
HCV RNA (log_{10} IU/mL)	Continuous and categorical	< 800,000, ≥ 800,000, < 2,000,000, ≥ 2,000,000 IU/mL
HCV genotype	Categorical	1, 1a, 1b, 2, 3, 4, 5, 6 (example; include subtypes)
Cirrhosis status	Categorical	Present, Absent
IL28B rs12979860 host genotype	Categorical	CC, CT, TT
HCV treatment history status	Categorical	Naive, Experienced

Cirrhosis status is derived as per APPENDIX 1.

HCV treatment experienced participants are defined as those who received any prior non-study anti-HCV treatment, while HCV treatment naive participants are defined as those who did not receive any prior non-study anti-HCV treatment (see APPENDIX 1).

A by-participant listings of baseline disease characteristics is provided for treated participants.

Virologic Resistance at Baseline

NS5A resistance testing at baseline is performed on all participants. NS5A key genotypic substitutions at baseline are summarized as categorical parameters for participants with genotypable baseline isolates in the following populations: (1) treated participants; (2) SVR non-responders, which include virologic failures (see Section 6.5.1.2).

NS5B resistance testing at baseline is performed only for virologic failures. Thus, NS5B key genotypic substitutions at baseline are summarized analogously for SVR non-responders with genotypable baseline isolates.

See APPENDIX 2 for key NS5A and NS5B genotypic substitutions.

6.3.2.3 ECGs, Vital Signs, and Physical Measurements at Baseline

ECGs, vital signs, and physical measurements at baseline are summarized as continuous parameters (see Table 6.3.2.3-1).

Table 6.3.2.3-1: ECGs, Vital Signs, and Physical Measurements at Baseline

Parameter (Units)
ECGs (msec): PR interval, QRS width, QT interval, QTC Bazett's (QTcB), QTc Fridericia's (QTcF)
Vital signs: heart rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiration (breaths/min), temperature (°C)
Physical measurements: height (cm), height for age Z score (HAZ), height for age percentile (HAP), weight at Day 1 from IRT (kg), weight (kg), weight for age Z score (WAZ), weight for age percentile (WAP), body mass index (BMI; kg/m^2), BMI for age Z score (BMIAZ), BMI for age percentile (BMIAP)

Physical measurement Z scores and percentiles are calculated using the SAS program for the 2000 Center for Disease Control (CDC) Growth Charts (ages 0 to < 20 years).[3]

6.3.2.4 Laboratory Tests at Baseline

Laboratory test abnormalities at baseline are summarized as categorical parameters using toxicity grades separately for SI and US units. Percentages are based on participants with measurements.

Commonly collected laboratory tests that are graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2004)[4] toxicity grades (Grades 0, 1, 2, 3, 4; Grade 1 to 4; Grade 3 to 4) include the following, as applicable:

- Hematology: hemoglobin, platelets, international normalized ratio (INR), white blood cell count (WBC), lymphocytes (absolute; only for Cohort 1 participants > 13 years old), and neutrophils + bands (absolute; ANC);
- Hepatobiliary enzymes and measures of hepatic synthetic function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and albumin;
- Pancreatic enzymes and renal function tests: lipase (colorimetric or turbidimetric) and creatinine;
- Electrolytes: bicarbonate (low), calcium (high and low), phosphate (low), potassium (high and low), and sodium (high and low).

See Protocol Appendix 5 for DAIDS toxicity grades.

In the absence of DAIDS toxicity grades, the following toxicity grade categories are provided for creatinine clearance using the Schwartz formula:

- SI units (mL/s/ m^2): < 0.25 (Grade 4); 0.25 to < 0.50 (Grade 3); 0.50 to < 1.0 (Grade 2); 1.0 to < 1.5 (Grade 1); ≥ 1.5 (Grade 0);
- US units (mL/min/1.73 m^2): < 15 (Grade 4); 15 to < 30 (Grade 3); 30 to < 60 (Grade 2); 60 to < 90 (Grade 1); ≥ 90 (Grade 0).

General Medical History

A by-participant listing of general medical history is provided for enrolled participants.

6.3.2.5 Prior Non-Study Medications

Prior non-study medications are summarized as categorical parameters alphabetically by anatomic class, therapeutic class, and generic name. Prior non-study medications are defined as those taken before the start of study therapy. These are previous non-study medications (i.e., those taken before informed consent) or current non-study medications (i.e., those taken on or after informed consent to before the start of study therapy).

6.4 Extent of Exposure

Extent of exposure is summarized for treated participants, unless specified otherwise. See Section 7.3 for derived dates and Section 7.4.2 for additional conventions.

6.4.1 Study Therapy and Follow-up

The following time-to-exposure-events (weeks) are summarized as continuous parameters:

- Time on study therapy. Defined as (study therapy end date - study therapy start date + 1)/7.
- Time on each study drug and formulation: DCV (any formulation); DCV tablet; DCV chewable tablet; SOF (any formulation); SOF tablet; SOF pediatric formulation to be determined (TBD). Defined analogously to time on study therapy based on individual start/end dates derived for each drug and formulation.
- Time in follow-up for follow-up participants. Defined as (last contact date - study therapy end date + 1)/7.
- Time on study. Defined as (last contact date - study therapy start date + 1)/7.

6.4.2 Interruption of Study Therapy

Participants with dose interruptions of > 3 consecutive days (including reasons for dose modification) are summarized as categorical parameters for each drug (DCV and SOF).

6.4.3 Concomitant and Post-Treatment Non-Study Medications

Concomitant medications are summarized as categorical parameters alphabetically by anatomic class, therapeutic class and generic name for treated participants. These are non-study medications taken on or after the start date of study therapy and through the last date of study therapy.

Post-treatment medications are summarized analogously for follow-up participants. These are non-study medications taken any time after the last date of study therapy.

A by-participant listing of all non-study medications (i.e., previous, current, concomitant, post-treatment) is provided for enrolled participants.

6.5 Efficacy

All efficacy endpoints in this study are either secondary [redacted], and are assessed for treated participants unless specified otherwise.

Analyses use HCV RNA results from the central laboratory only. Visit windows are constructed around planned visit times for slotting purposes.

For all efficacy analyses, HCV RNA measurements are excluded after the start date of non-study anti-HCV medication on treatment or during follow-up (see Section 7.3).

A by-participant listing of HCV RNA values (in both IU/mL and $\log_{10}$ IU/mL) is provided for enrolled participants. Values meeting the criteria for virologic breakthrough and relapse at any visit are flagged (see Section 6.5.1.2).

The end of treatment (EOT) HCV RNA value is determined from the last HCV RNA value collected during the on-treatment analysis period.

See also Section 7.4.7 for virology conventions.

6.5.1 Primary and Secondary Efficacy Endpoints

6.5.1.1 SVR12

The proportion of treated participants with SVR12, defined as HCV RNA < LLOQ TD or TND at follow-up Week 12, are presented with 2-sided 95% CIs using the following 3 methods:

- Next Value Carried Backwards (NVCB): The numerator is based on participants meeting the response criteria, and the denominator is based on all treated participants. Participants with missing HCV RNA data at follow-up Week 12 have data imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA visit window.
- Modified (mITT): The numerator is based on participants meeting the response criteria, and the denominator is based on all treated participants. Participants with missing follow-up Week 12 HCV RNA are counted as non-responders (i.e., missing data are not imputed).
- Observed values: The numerator is based on participants meeting the response criteria, and the denominator is based on treated participants with an evaluable HCV RNA measurement at follow-up Week 12 (i.e., participants with missing data are excluded).

NVCB is the principal analysis method, whereas mITT and observed values are sensitivity analysis methods.

SVR12 treatment outcomes are summarized using NVCB in the following categories:

- Responder
- Non-responder
  - Non-responder with HCV RNA < LLOQ TND at EOT
    - Relapser. Defined as HCV RNA < LLOQ TND at EOT and HCV RNA ≥ LLOQ at follow-up Week 12
    - Other non-responder. Defined as HCV RNA < LLOQ TND at EOT and missing HCV RNA at follow-up Week 12 and thereafter.

Percentages for relapse and other non-responders are calculated based on treated participants with HCV RNA < LLOQ TND at EOT.

- On-treatment failure
  - Virologic breakthrough. Defined as either (1) confirmed ≥ 1 $\log_{10}$ IU/mL HCV RNA increase from nadir on treatment, or (2) confirmed HCV RNA ≥ LLOQ on treatment after HCV RNA < LLOQ TD or TND on treatment. Confirmed is defined as ≥ 2 consecutive measurements.
  - Other on-treatment failure
- No post-baseline HCV RNA value

6.5.1.2 Virologic Resistance

Resistance testing is performed post-baseline for participants with HCV RNA ≥ 1,000 IU/mL who have experienced virologic failure, defined as any of the following:

- Virologic breakthrough at any on-treatment visit (see Section 6.5.1.1);
- Relapse at any follow-up visit (see Section 6.5.1.1);
- Other: HCV RNA ≥ LLOQ at any visit not meeting the definition of virologic breakthrough or relapse.

Virologic resistance is assessed for SVR non-responders with paired genotypable isolates, i.e., genotypable at baseline and at least one post-baseline visit. SVR non-responders are those who did not achieve SVR using observed values at a follow-up visit through follow-up Week 108 (see Section 6.5.1.1). The following are summarized as categorical parameters at key amino acid positions defined in APPENDIX 2:

- Emergent NS5A and NS5B genotypic substitutions. An emergent substitution is a post-baseline substitution that was not detected at baseline;
- Replacements of NS5A and NS5B emergent genotypic substitutions. A replacement of an emergent substitution occurs when only the reference or baseline sequence is detected at the last post-baseline genotypable isolate.

A by-participant listing of all NS5A and NS5B genotypic substitutions is provided for enrolled participants. This listing identifies key NS5A and NS5B key substitutions, as well as emergence and replacement of these key substitutions.

6.6 Safety

Safety endpoints include the frequencies of AEs, SAEs, AEs leading to discontinuation of study therapy, deaths and other significant AEs as reported on CRFs. Other safety endpoints include the frequencies of laboratory abnormalities, and changes from baseline in safety parameters (i.e., laboratory tests, ECGs, vital signs, and physical measurements) over time.

Safety endpoints are summarized separately for (1) treated participants during the on-treatment analysis period, and (2) follow-up participants during the follow-up analysis period, unless specified otherwise.

Analyses of safety data are cumulative through the time of database lock.

6.6.1 Deaths

Deaths are identified from two sources of information:

- Subject status CRF: Study discontinuation reason of death;
- AE/SAE CRF: Any of the following parameters: SAE outcome of death; SAE category of death; non-missing character death date.

A by-participant listing of death is provided for enrolled participants, which includes the death date, time to death (weeks), source of information, and cause of death.

Time to death (weeks) is defined as (death date - start date of study therapy + 1)/7.

6.6.2 Adverse Events

An AE is defined per protocol as any new untoward medical occurrence or worsening of a preexisting medical condition in a patient or clinical investigation participant administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant.

Verbatim terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at BMS. Investigators determine the intensity of AEs (mild [Grade 1], moderate [Grade 2], severe [Grade 3], very severe [Grade 4]), and determine the relationship of AEs to study therapy (related, not related).

In order to account for AEs with multiple occurrences in the same participant, AE records are collapsed for each participant and preferred term when records have the same onset date, or when records are contiguous or overlapping[10]. All AE presentations are based on collapsed records.

AEs are summarized as categorical parameters by system organ class (SOC) and preferred term, both in descending order of total frequency. Summaries include both non-SAEs and SAEs, unless otherwise specified.

AE summaries separately by analysis period are presented in Table 6.6.2-1.

Table 6.6.2-1: AE Summaries by Analysis Period

Endpoint	On-Treatment	Follow-up
SAEs	X	X
AEs leading to discontinuation of study therapy	X	
AEs by intensity or relationship: All Grades; Grade 3 to 4; All Grades related to study therapy (on-treatment only)	X	X
Non-SAEs ≥ 5% [a,b]	X	
Exposure-adjusted multiple SAEs[a]	X	
Exposure-adjusted multiple SAEs related to study therapy[a]	X	

Table 6.6.2-1: AE Summaries by Analysis Period

Endpoint	On-Treatment	Follow-up
Exposure-adjusted multiple non-SAEs ≥ 5%[a,b]	X	

[a] ClinicalTrials.gov or EudraCT reporting requirement

[b] Cut-off applies to frequency of participants with preferred terms in any cohort.

A by-participant listing of all AEs is provided for enrolled participants.

6.6.2.1 AEs by Intensity or Relationship to Study Therapy

For graded summaries of AEs (e.g., AEs by intensity, AEs by relationship), AEs with missing intensity are included only in summaries of All Grades events. The greatest intensity during a safety analysis period is presented for each AE.

AEs related to study therapy are those with a "related" or missing relationship to the study therapy. If relatedness to study therapy is unknown, the AE is included in summaries of AEs judged by the investigator to be related to study therapy.

6.6.2.2 Exposure-Adjusted Multiple AEs

Analyses take into account the number of occurrences of an AE reported by individual participants and their cumulative exposure on treatment. These data are presented as the rate per 100 years of patient exposure. For example, if 5 participants report 7 unique episodes of headache and had a combined cumulative exposure of 20 years to study medication, the incidence rate is reported as 7/20 *(100) or 35 cases per 100 patient years of exposure.

Cumulative exposure is defined as (1) time on study therapy for participants who have not discontinued study therapy, and (2) time on study therapy + 7 days for participants who discontinued study therapy to account for on-treatment safety reporting.

6.6.3 Hepatic Disease Progression

Hepatic disease progression is summarized by the categories specified in Table 6.6.3-1 during the on-treatment and follow-up analysis periods combined for treated participants. Hepatic disease progression is identified from the Hepatic Related Diagnoses CRF.

Table 6.6.3-1: Hepatic Disease Progression Diagnoses

Diagnoses
Cirrhosis, non-bleeding esophageal varices, bleeding esophageal varices, hepatic encephalopathy, hepatocellular carcinoma, spontaneous bacterial peritonitis, non-bleeding gastric varices, bleeding gastric varices, hepatorenal syndrome, liver transplant

A by-participant listing of hepatic disease progression is provided for enrolled participants.

6.6.4 Clinical Laboratory Evaluations

Summaries are based on treated participants with at least one laboratory measurement during the analysis period. All output is presented separately for SI and US units.

EOT toxicity grades and values are determined form the last laboratory test value collected during the on-treatment analysis period.

End of study (EOS) toxicity grades and values are determined form the last laboratory test value collected during the follow-up analysis period.

By-participant listings are provided for enrolled participants for the following laboratory tests:

- Hematology: hematocrit, hemoglobin, platelets, INR, WBC, lymphocytes (absolute), and ANC;
- Hepatobiliary enzymes and measures of hepatic synthetic function: ALT, AST, AST to platelet ratio index (APRI), alkaline phosphatase, total bilirubin, albumin, and alpha fetoprotein;
- Pancreatic enzymes and renal function tests: lipase (colorimetric or turbidimetric), creatinine, and creatinine clearance using the Schwartz formula;
- Electrolytes: bicarbonate, calcium, phosphate, potassium, and sodium.

These listings identify laboratory abnormalities using toxicity grades as specified in Section 6.3.2.4.

6.6.4.1 Laboratory Abnormalities by Toxicity Grade

Laboratory abnormalities are summarized by analysis period (on-treatment and follow-up) in the following toxicity grade categories:

- Worst toxicity grade: 0, 1, 2, 3, 4, 3 to 4, 1 to 4;
- Worst emergent toxicity grade: not emergent, 1, 2, 3, 4, 3 to 4, 1 to 4.

See Section 6.3.2.4 for laboratory tests with toxicity grades. Electrolytes are excluded from summaries due to infrequent post-baseline testing.

Emergent abnormalities on treatment are laboratory tests on treatment that have a higher toxicity grade than the baseline toxicity grade (including missing baseline). The category “not emergent” represents laboratory tests on treatment that have the same or lower toxicity grade than the baseline toxicity grade.

Emergent abnormalities during follow-up are laboratory tests during follow-up that have a higher toxicity grade than the EOT toxicity grade (including missing EOT). The category “not emergent” represents laboratory tests during follow-up that have the same or lower toxicity grade than the EOT toxicity grade.

The laboratory value during the analysis period with the worst (highest) toxicity grade is reported for each laboratory test.

6.6.4.2 Laboratory Tests Changes Over Time

Laboratory test observed values and changes from baseline are summarized as continuous parameters over time at baseline and each scheduled analysis visit on treatment. Laboratory tests may include the following:

- Hematology: hemoglobin, platelets, INR, WBC, lymphocytes (absolute), and ANC;
- Hepatobiliary enzymes and measures of hepatic synthetic function: ALT, AST, and total bilirubin;
- Pancreatic enzymes and renal function tests: lipase colorimetric and creatinine.

Laboratory test observed values and changes from EOT are summarized analogously over time at EOT and each scheduled analysis visit during follow-up.

6.6.4.3 Select Laboratory Test Results

Select laboratory test endpoints are summarized as categorical parameters as follows for treated participants, unless specified otherwise:

- Confirmed creatinine clearance < 1.0 mL/s/m^2 (< 60 mL/min/1.73m^2) using the Schwartz formula on treatment. Confirmed is defined as ≥ 2 consecutive values meeting the criteria on treatment.
- ALT normalization (i.e., ALT ≤ 1 x upper limit of normal [ULN]) at EOT by baseline ALT category (all; ALT ≤ 1 x ULN; ALT > 1 x ULN; not reported) on treatment.
- ALT normalization at EOS by EOT ALT category (all; ALT ≤ 1 x ULN; ALT > 1 x ULN; not reported) during follow-up for follow-up participants.
- AST normalization (i.e., AST ≤ 1 x ULN) at EOT by baseline AST category (all; AST ≤ 1 x ULN; AST > 1 x ULN; not reported) on treatment.
- AST normalization at EOS by EOT AST category (all; AST ≤ 1 x ULN; AST > 1 x ULN; not reported) during follow-up for follow-up participants.
- Potential Drug Induced Liver Injury (PDILI) on treatment or during follow-up, defined as concurrent (1) ALT ≥ 5 x minimum(baseline, nadir), and ALT ≥ 10 x ULN, and (2) total bilirubin ≥ 2 x ULN. Concurrent is defined as the total bilirubin elevation occurring within 30 days after the ALT elevation.

6.6.5 Vital Signs

Vital signs observed values and changes from baseline are summarized as continuous parameters over time at baseline and each scheduled analysis visit on treatment for treated participants. See Section 6.3.2.3 for parameters.

A by-participant listing of vital signs is provided for enrolled participants.

6.6.6 Physical Measurements

Age-adjusted physical measurements (i.e., HAZ, HAP, WAZ, WAP, BMIAZ, BMIAP) observed values and changes from baseline are summarized as continuous parameters over time at baseline

and each scheduled analysis visit on treatment and during follow-up for treated participants. See also Section 6.3.2.3.

A by-participant listing of physical measurements is provided for enrolled participants.

6.6.7 Pregnancy

A by-participant listing of pregnancy test results is provided for enrolled female participants.

6.7 PK Analyses

PK analyses are performed for each cohort separately, and not combined across cohorts.

PK analysis, reporting, and exclusion criteria follow the BMS PK Harmonization Document.[5] Specific guidelines for exclusionary criteria for half-life and how other PK parameters are affected for exclusion are in Section 9 of this document, while conventions for handling concentrations < LLOQ are in Section 11 (i.e., for DCV, LLOQ = 2 ng/mL; for SOF, LLOQ = 5 ng/mL; for SOF metabolite (GS331007), LLOQ = 10 ng/mL).

6.7.1 Intensive PK at Day 10

Intensive PK is assessed for treated PK participants with intensive PK at Day 10.

6.7.1.1 PK Concentration

DCV plasma concentration at Day 10 is summarized over time using univariate statistics (i.e., n, mean, SD) at each nominal collection hour: 0 (pre-dose), 30 min, 1 (Cohorts 1 and 2 only), 2, 4, and 8.

Two graphs are also provided:

- Parallel line plots of individual DCV plasma concentration (linear and semi-log scales) versus actual collection time;
- Longitudinal plot of mean DCV plasma concentration (linear and semi-log scales) versus nominal collection time, with error bars representing ± one SD.

A by-participant listing of DCV plasma concentration is provided. Values excluded from the summary are flagged.

6.7.2 PK Parameters

Individual PK parameter values for DCV (see Table 6.7.2-1) are derived from plasma concentration versus time at Day 10 using non-compartmental methods or model-based approaches as needed. DCV PK parameter values are summarized using univariate statistics (i.e., n, mean, SD, geometric mean, coefficient of variation [%CV], median, quartiles, minimum, and maximum).

Table 6.7.2-1: PK Parameters

Parameter (Units)	Definition
Cmax (mg/mL)	Maximum observed plasma concentration

Table 6.7.2-1: PK Parameters

Parameter (Units)	Definition
Tmax (h)	Time of maximum observed plasma concentration
AUC(TAU) (h*ng/mL)	Area under the concentration-time curve in one dosing interval
Cmin (ng/mL)	Minimum (trough) observed plasma concentration
CLT/F (mL/min)	Apparent total body clearance

Concentration at pre-dose on Day 10 is used for C24 (Cmin) solely for the purpose of calculating AUC(TAU).

A by-participant listing of DCV PK parameter values at Day 10 is provided. Values excluded from the summary are flagged.

6.7.3 Trough Concentrations

Trough concentrations of DCV and SOF/metabolites are summarized over time at each scheduled analysis visit (Day 10, Weeks 4, 8, and 12) for treated participants using univariate statistics (i.e., n, mean, SD, geometric mean, %CV, median, quartiles, minimum, and maximum).

Trough concentrations must meet each of the following criteria to be included in the statistical summary:

- Complete sampling and dosing times;
- Collected within 20-28 hours (inclusive) of the previous day's dose;
- Collected before the next dose;

Values that do not meet all the above criteria are excluded from the analysis.

Longitudinal plots display geometric mean of trough concentrations versus visit.

By-participant listings of DCV and SOF/metabolite trough concentrations are provided. Values excluded from summaries are flagged.

6.8 Questionnaires

Questionnaires of DCV palatability and acceptability are assessed for treated participants.

A by-participant listing of DCV palatability and acceptability assessments is provided.

6.8.1 Palatability Assessment of DCV

Palatability of DCV is summarized over time at baseline and each scheduled analysis visit on treatment (Weeks 4 and 12) and by relative time (10 sec, 5 min, 10 min) in the following categories: super bad; bad; maybe good or maybe bad; good; super good; not reported (includes missing and not assessed).

6.8.2 Acceptability Assessment of DCV

Acceptability of DCV is summarized over time at baseline and each scheduled analysis visit on treatment (Weeks 4 and 12) in the following categories:

- Tablet easy to take: yes, no, and not reported. Reasons for "no" include the following subcategories: it was too big; it got stuck on tongue; other.
- Chewable tablet easy to take: yes, no, and not reported. Reasons for "no" include the following subcategories: it was too hard; it took a long time to chew; child had to drink something to help swallow the pieces; at times, the child experiences problems in chewing and swallowing; other.
- Any problems with chewable tablet packaging: yes, no, and not reported. Reasons for "no" include the following subcategories: it was difficult to push out the tablet through the packaging; the tablet broke when pushed out; the package had to be cut open; other.

7 CONVENTIONS

Conventions are followed as per the following BMS documents, unless specified otherwise: Global Biometric Sciences General Requirements for Statistical Outputs[6]; Global Standard Table Reporting Requirements Specification;[7] Global Standard Listing Reporting Requirements Specification.[8]

7.1 Analysis Periods

Analysis periods are defined as follows:

- Pre-treatment period: Begins at the first screening visit and ends on the start date of study therapy (DCV or SOF).
- On-treatment period: Begins after the start date of study therapy and ends on the last date of study therapy plus 7 days. The 7-day cut-off reflects the point at which minimal antiviral activity related to study therapy is present. It is also expected that minimal drug exposure and undetectable drug levels will be present beyond 7 days post-dose.
- Follow-up period: Begins after the last date of study therapy plus 7 days.

Refer to Section 5.1 for slotting Day 1 measurements according to domain.

7.2 Analysis Windows and Multiple Records

Analysis visit windows are defined within analysis periods as follows:

- Select values in the appropriate analysis period.
- Slot observations into analysis visit windows (e.g., "WK 4", "F/U WK 12") defined in Table 7.2-1. Analysis visit windows are generally defined according to mid-points between visits.

Table 7.2-1: Analysis Windows

Abbreviated Analysis Visit Label in Output	Target Visit Day in Analysis Period	Study Days in Analysis Period
PRE-TRT		

Table 7.2-1: Analysis Windows

Abbreviated Analysis Visit Label in Output	Target Visit Day in Analysis Period	Study Days in Analysis Period
B/L[a]	1	≤ 1
ON-TRT		
UNS	4	[2, 6]
DAY 10	10	[7, 13]
WK 4	28	[14, 42]
WK 8	56	[43, 70]
WK 12	84	[71, 98]
WK 16	42	> 98
F/U[b]		
F/U WK 4	21	[7, 49]
F/U WK 12	77	[50, 119]
F/U WK 24	161	[120, 245]
F/U WK 48	329	[246, 413]
F/U WK 72	497	[414, 581]
F/U WK 96	665	[582, 707]
F/U WK 108	749	[708, 791]
F/U WK 120	833	> 791

[a] Baseline in longitudinal summaries

[b] Target visit day and study days reflect 7-day offset that defines follow-up analysis period (see Section 7.1)

For longitudinal analyses [redacted]), if there are multiple values within an analysis window, then select one value for analyses as follows:

- HCV RNA on treatment: Closest value collected relative to the target visit day (as determined by the absolute difference in days between the target visit day and the collection day, and the absolute difference in days between the target visit day and the assay day); if there are ties, then select first value assayed.
- HCV RNA during follow-up: Last value collected; if there are ties, then select first value assayed.
- Other: Last value measured or collected; if there are ties, then select last entered. For questionnaires with multiple items, all items are considered collectively, not individually, for each assessment and entry dates. For other parameters (e.g., laboratory tests, ECGs, vital signs, physical measurements), each parameter is considered individually.

If there are multiple records collected or measured on the same day, then the last value entered is selected, unless specified otherwise in Section 7.4.

7.3 Derived Dates

Derived dates are obtained from full, valid numeric dates. Full dates are those that have non-missing day, month and year. Valid dates are those that are consistent with the calendar (e.g., "31FEB2017" is invalid). No imputation is performed, unless specified otherwise.

- Start date of study therapy is the earliest start date of any drug in the regimen (DCV or SOF) identified from full, valid numeric dates with total dose > 0 from study medication CRFs. This date is used to identify treated participants, define study and analysis periods, and assess time on study therapy. [This is the numeric version of SDTM DM.RFSTDTC, which is the same as DM.RFXSTDTC for this study.]
- End date of study therapy is the latest start or stop date of any drug in the regimen (i.e., DCV or SOF) identified from full, valid numeric dates with total dose > 0 from study medication CRFs. This date is used to assess time on study therapy. [This is the numeric version of SDTM DM.RFXENDTC.]
- Last date of study therapy is the end date of study therapy derived only for participants who completed or did not complete the treatment period based on the end of treatment subject status CRF. This date is used to define study and analysis periods, and assess time on study therapy. [This is the numeric version of SDTM DM.RFENDTC.]
- Last contact date is the death date, if it exists, or the latest of the following numeric dates: randomization; study therapy start or end; AE imputed onset or resolution; diagnostic procedure start; HCV RNA collection; laboratory test (safety, pregnancy) collection; last contact from end of treatment or end of study subject status; medical procedure start or stop; neurologic exam; vital signs; non-study medication imputed start or stop; palatability assessment; acceptability assessment; physical measurement; physical exam; viral genotype collection; vital phenotype collection.
- Start date of anti-HCV therapy on treatment or during follow-up is the earliest imputed concomitant or post-treatment numeric start date among anti-HCV medications (approved antiviral or immunomodulating agent; investigational antiviral or immunomodulating agent; see Section 7.4.5 and APPENDIX 1).

7.4 Domain-Specific Conventions

7.4.1 AEs

Missing and partial adverse event onset dates are imputed according to the AE Domain Requirements Specifications[9,10] in place at the start of programming. Imputed dates are used to classify AEs into study and analysis periods. Counting rules for AEs, including those for exposure-adjusted multiple AEs, also follow these specifications.

7.4.2 Exposure

Derivations are based on study medication CRFs.

Start and end dates of individual study drugs (DCV and SOF) and formulations are derived analogously for participants with full, valid numeric dates with total dose > 0 (see Section 7.3).

The following conventions are applied to dosing calculations for each drug/formulation:

- Distinct records with non-missing numeric dose start date, total dose, and generic drug name are selected.
- Missing dose stop dates are imputed. The missing stop date of a dosing record is set to 1 day before the start date of the next available dosing record. If the participant started drug and was lost to follow-up (i.e., has only 1 record), the missing end date is set to the start date, thus crediting the participant with 1 day of dosing.
- Overlapping dose dates are modified. If the start date of a dosing record is equal to or before the end date of the previous dosing record, then the start date is set to 1 day after the previous end date.
- Total dose for a dosing record is calculated as the total dose recorded.
- Duration for a dosing record is calculated as stop date - start date + 1.
- Total amount of drug taken is the sum of total dose x duration across dosing records.

Interruptions of individual study drugs (DCV and SOF) are identified from records with full, valid numeric start and stop dates, and total daily dose of 0. For participants who discontinued study therapy, only records with start dates before the last date of study therapy are selected, and end dates after the last date of study therapy are set to the last date of study therapy.

Dose adherence to a study drug (DCV or DOF) is defined as 100*minimum(average daily dose /target daily dose, 1):

- DCV: Target daily dose = 20 mg if Day 1 weight < 30 kg; 40 mg if 30 ≤ Day 1 weight < 45 kg; 60 mg if Day 1 weight ≥ 45 kg;
- SOF: Target daily dose = 400 mg for Cohort 1; TBD for Cohorts 2 and 3.

Day 1 weight is determined from IRT (see Section 6.3.2.3).

7.4.3 Human Genotyping

SNP genotype is considered missing if either allele is not A, C, G, T, DEL or INS.

7.4.4 Laboratory Test Results

Toxicity grades are based on standard values, standard lower limit of normal (LLN), and standard ULN, as applicable. If a laboratory value that is graded as a multiple of the ULN or LLN falls between 2 toxicity grades, then the higher toxicity grade is assigned (e.g., an ALT value that is 2.53 x ULN is classified as Grade 2, not Grade 1).

7.4.5 Non-Study Medications

Non-study medications are coded using the BMS WHO dictionary. Missing and partial non-study medication start and stop dates (including unknown and continuing) are imputed according to the Non-Study Medication Domain Requirements Specifications in place at the start of

programming.[11] Imputed dates are used to classify medications as previous, current, concomitant or post-treatment.

7.4.6 Viral Genotyping and Phenotyping

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.

7.4.7 Virology

The central laboratory uses the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 to measure HCV RNA level. This assay has limit of detection = 15 IU/mL, LLOQ = 15 IU/mL, and upper limit of quantification (ULOQ) = 1.0 x 10^8 IU/mL.

HCV RNA viral loads are reported by the central laboratory and listed as follows:

- (1) Actual numeric values for detectable virus within LLOQ and ULOQ;
- (2) "> ULOQ" for detectable virus above ULOQ;
- (3) "< LLOQ, HCV RNA detected" for detectable virus below LLOQ;
- (4) "No HCV RNA detected" for undetectable virus.

Analyses of HCV RNA < LLOQ TND use data corresponding to item 4 above. Analyses of HCV RNA < LLOQ TD or TND use data corresponding to items 3 and 4 above.

For analyses of HCV RNA as a continuous parameter, HCV RNA values in the original scale of IU/mL are imputed with a value of 1 more (or 1 less) if an inequality ">" ("<") is present (items 2 and 3 above), and a value of LLOQ - 1 if undetectable (item 4 above). These values are then transformed to the $\log_{10}$ scale.

If there are multiple values on the same collection day, then the first value assayed is selected.

Only records from the central laboratory are used.

8 CONTENT OF REPORTS

The timing of interim analyses will depend on the availability of Day 10 PK results. An interim analysis will be performed when the first 5 participants in each age cohort complete the Day 10 PK sample collection.

If the median plasma exposure in a cohort is outside the predefined therapeutic range, then dose modification will be performed using pediatric formulations of DCV, and an additional 5 participants will be enrolled. Another interim analysis will be performed when these additional participants complete the Day 10 PK sample collection in order to confirm the exposure at the modified dose. All Day 10 PK interim analyses will focus on PK and select safety listings (e.g., AEs, laboratory tests, end of treatment subject status). In each cohort, enrollment will continue in order to achieve at least 8 evaluable participants per cohort.

Additional interim analyses will be performed when all participants in an age cohort complete the Follow-up Week 12 visit and when all participants complete the Follow-up Week 12 visit in order

to assess the primary and secondary endpoints. All endpoints except PK and durability of virologic response will be assessed.

The final analysis will be conducted when all participants complete long-term follow-up to assess long-term efficacy endpoints ([redacted], durability of virologic response, and virologic resistance) and follow-up safety endpoints.

[redacted]

APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

Relevant protocol deviations are summarized as categorical parameters for treated participants.

Eligibility Deviations

Eligibility deviations are based on those occurring during the pre-treatment period for the following categories:

- Inclusion criterion 2a: HCV genotype other than GT-1 to GT-6, including mixtures, during screening;
- Inclusion criterion 2b: HCV RNA < 1,000 IU/mL during screening;
- Inclusion criterion 2e: Presence of cirrhosis as defined in protocol.
  - A participant is considered to be non-cirrhotic if any one of the following criteria is met:
    - Liver biopsy results with F0-F3 stage of fibrosis by Metavir within 3 years before screening. Determined from the Fibrosis Staging CRF;
    - Fibroscan measurement < 12.5 kPa within 1 year before Day 1. Determined from the Fibrosis Staging CRF;
    - APRI ≤ 0.5 during screening. Determined from the laboratory test.
  - A participant is considered to be cirrhotic if any one of the following criteria is met:
    - Liver biopsy results with F4 stage of fibrosis by Metavir at any time before screening. Determined from the Fibrosis Staging CRF;
    - Fibroscan measurement ≥ 12.5 kPa within 1 year before Day 1. Determined from the Fibrosis Staging CRF;
    - APRI > 0.5 during screening. Determined from the laboratory test.

  If fibrosis stage data are available from several sources, then the liver biopsy supersedes Fibroscan, and Fibroscan supersedes APRI.
- Inclusion criterion 2f: Baseline weight < 10 kg;
- Inclusion criterion 3a: Age < 3 or > 18 years at enrollment;
- Exclusion criterion 1a: Positive serological test for HBV or HIV infection during screening. Defined as positive HBsAg, HIV-1 antibody, or HIV-2 antibody.
- Exclusion criterion 1e: Pre-treatment HCC. Identified from general medical history specify details (#) or fibrosis staging finding;
- Exclusion criterion 1i: Confirmed HbA1c ≥ 0.085 or ≥ 8.5% during screening. Confirmed is defined as at least 2 consecutive measurements;
- Exclusion criterion 2a: Use of prohibited prior non-study medication (#). Defined as any of the following:
  - Any HCV NS5A inhibitor or SOF;
  - Any approved anti-HCV therapy < 12 weeks before Day 1;

  Generic drug names are presented alphabetically as subcategories.
- Exclusion criteria 3b to 3i: Laboratory test findings during screening, with the following subcategories:

- Exclusion criterion 3b: ALT or AST > 10 x ULN
- Exclusion criterion 3c: Albumin < 35 g/L or < 3.5 g/dL
- Exclusion criterion 3d: Total bilirubin > 19 µmol/L or > 1.1 mg/dL without history of Gilbert syndrome. Gilbert syndrome is identified from general medical history specify details (#);
- Exclusion criterion 3e: Alpha fetoprotein > 50 ng/mL or > 50 µg/L
- Exclusion criterion 3f: ANC < 1.5 x 10^9 cells/L or < 1.5 x 10^3 cells/µL
- Exclusion criterion 3g: Hemoglobin < 100 g/L or < 10 g/dL
- Exclusion criterion 3h: Platelets < 100 x 10^9 cells/L
- Exclusion criterion 3i: Creatinine clearance < 1 mL/s/m^2 or < 60 mL/min/1.73m^2, using the Schwartz formula.

(#) Non-study medications and medical conditions marked above with # are identified by a BMS physician prior to database lock.

The screening portion of the pre-treatment analysis period begins at informed consent and ends before the start of study therapy (Day 1).

A participant with multiple pre-treatment measurements (e.g., HCV RNA) is considered to have an eligibility deviation only if all pre-treatment measurements meet the deviation criterion.

Participant Management Deviations

Participant management deviations are evaluated during the on-treatment or follow-up analysis period for the following categories:

- At least 2 consecutive missed doses of DCV before Day 10 PK sampling, or at least 1 missed dose of DCV within 2 days before Day 10 PK sampling. Missed doses of DCV are identified from interruptions or gaps between dosing records;
- At least twice of DCV target daily dose taken within 2 days before Day 10 PK sampling;
- DCV or SOF average daily dose < 80% of target daily dose;
- DCV or SOF interruption > 7 consecutive days;
- Continuation of study therapy after having virologic breakthrough;
- Use of prohibited non-study concomitant medication for more than 1 day, including anti-HCV medications (#). Generic drug names are presented alphabetically as subcategories;
- Use of non-study anti-HCV medication during follow-up (#). Generic drug names are presented alphabetically as subcategories;

(#) Non-study medications marked above with # are identified by a BMS physician prior to database lock.

[redacted]

Anti-HCV Medications

Currently, the following non-study generic drugs are approved for HCV treatment: BOCEPREVIR, BROCE/INTA/RIBAV, BROCE/INTAB/RIBAV, DACLATASVIR*, DASABUVIR, DASAB/OMBIT/PARIT/RIBAV/RITON*, DASAB/OMBIT/PARIT/RITON*, ELBASVIR*, ELBVIR/GRAZO*, GLECAPREVIR, GLECA/PIBRE, GRAZOPREVIR, INTERFERON, INTERFERON ALFA, INTERFERON ALFA 1B, INTERFERON ALFA 2A, INTERFERON ALFA 2B, INTERFERON ALFA N1, INTERFERON ALFA N3, INTERFERON ALFACON, INTERFERON ALFACON 1, INTERFERON BETA, INTERFERON BETA 1A, INTERFERON BETA 1B, INTERFERON GAMMA, INTERFERON GAMMA 1B, INTA/RIBAV, INTA/RIBAV/TELAP, INTAA/RIBAV, INTAB/RIBAV, INTFER/RIBAV, LEDIPASVIR*, LEDIP/RIBAV/SOFO*, LEDIP/SOFO*, OMBITASVIR*, OMBIT/PARIT/RITON*, PARITAPREVIR, PIBRENTASVIR*, RIBAVIRIN, RIBAV/SOFO, SIMEPREVIR, SIMPRE/SOFO, SOFOSBUVIR, SOFO/VELPAT*, SOFO/VELPAT/VOXILA*, TELAPREVIR, VELPATASVIR*. The drugs asterisked ("*") are or contain NS5A inhibitors.

Other non-study medications that may be considered to have anti-HCV activity (depending on the reported name) are the following generic drug names: INVESTIGATIONAL ANTIVIRAL, INVESTIGATIONAL IMMUNOMODULATING AGENT, IMMUNOMODULATING AGENT.

APPENDIX 2 NS5A AND NS5B KEY GENOTYPIC SUBSTITUTIONS

All NS5A genotypic substitutions at amino acid positions 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93 are noted if they differ from the reference sequence for each HCV genotype (see table below).

APP 2-1: NS5A Reference Sequence at Key Amino Acid Positions

HCV Genotype	Sequence Accession Number	Reference Strain	Amino Acid Position Reference									
			24	28	29	30	31	32	58	62	92	93
1a	AF009606	H77	K	M	P	Q	L	P	H	E	A	Y
1b	AJ238799	Con1	Q	L	P	R	L	P	P	Q	A	Y
2	AB047639	GT2	T	F	P	K	L	P	P	N	C	Y
3	GU814263	GT3	S	M	P	A	L	P	P	S	E	Y
4	GU814265	GT4	K	L	P	L	M	P	P	D	A	Y
5	AF064490	GT5	Q	L	P	Q	L	P	P	T	A	T
6	Y12083	GT6	Q	F	P	R	L	P	T	V	A	T

The following NS5B key substitutions are noted, regardless of HCV genotype: D61G; A112T; L159F; E237G; S282T or S282R; C316N; L320F, L320I, or L320V; V321A or V321I; S473T.

Mixture substitutions are denoted by Monogram with a slash separating each amino acid in the mixture (e.g., “V321A/I/V”). Each amino acid of the mixture is assessed when determining persistence or replacement of substitutions.