AN OPEN-LABEL PHASE 2A STUDY EVALUATING THE SAFETY AND EFFICACY OF COMBINATION TREATMENT WITH 2 WEEKS OF THE NONNUCLEOSIDE INHIBITOR CDI-31244 PLUS 6 WEEKS OF SOFOSBUVIR/VELPATASVIR IN SUBJECTS WITH CHRONIC HEPATITIS C GENOTYPE 1 INFECTION

PROTOCOL CDI-31244-P2-001

Investigational Drug: CDI-31244

Study Number: HP-00078356

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Statistical Analysis Plan

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TABLE OF CONTENTS

1 PREFACE

The Statistical Analysis Plan (SAP) for the trial "*An Open-Label Phase 2a Study Evaluating the Safety and Efficacy of Combination Treatment with 2 Weeks of the Nonnucleoside Inhibitor CDI-31244 Plus 6 Weeks of Sofosbuvir/Velpatasvir in Subjects with Chronic Hepatitis C Genotype 1 Infection"* describes and expands upon the statistical information presented in the protocol.

This document contains all planned analyses, reasons and justifications for these analyses. It also includes sample tables, listings and figures planned for the Primary and Final analyses. Regarding the Final Analysis and Final Integrated Clinical/Statistical Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

The reader of this SAP is encouraged to also review the clinical protocol for details on conduct of the study and the operational aspects of clinical assessments.

2 PURPOSE OF SAP

During the design and writing phase of the clinical protocol, the principal features of the statistical analysis have been described in the statistical sections of the document. Sample size calculations, along with descriptions of the primary and secondary objectives and appropriate methods, are given. The SAP is a stand-alone document that is created after the completion of the protocol. A more technical and detailed elaboration of the statistical procedures and how they are to be executed is provided. This plan will be reviewed and may be updated prior to database lock.

This SAP also supports the completion of the Clinical Study Report (CSR). The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts, presentations and publications. As a Phase 2a study, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be identified clearly in the CSR.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS

3.1 Study Design

This clinical trial is designed as an open-label, single arm, single stage Phase 2a trial to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of an oral non-nucleoside inhibitor CDI-31244 combined with 6 weeks of SOF/ VEL in adult subjects with chronic HCV genotype 1 virus infection. No dose escalation or de-escalation is planned as part of the trial design.

A total of 12 subjects with treatment-naïve chronic HCV genotype 1 (either 1a or 1b) will be enrolled. The trial will be conducted at the Institute of Human Virology (IHV), University of Maryland School of Medicine, Baltimore, MD. Subjects will be recruited from the clinical practices of the investigator and associate investigator and referring physicians. HCV infection will be diagnosed based on history, physical examination, and laboratory studies. Inclusion criteria for this study include patients (age ≥ 18 years) with chronic HCV genotype 1a or 1b. A maximum of 4 subjects with genotype 1b will be enrolled. For detailed inclusion and exclusion criteria, please refer to sections 5.1 and 5.2 of the trial protocol.

Subjects who have virologic failure (see section 4.2.1) during the 6-week study drug treatment period will be discontinued from study drug treatment and will be scored and analyzed as treatment failures. These patients will cross over to the standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects who complete the 6-week treatment period will be considered to have virologic (treatment) failure if they have detectable HCV RNA at the next study visit and thereafter throughout the study. These subjects will receive additional treatment with standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/ 100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Safety oversight will be under the purview of a Data Safety and Monitoring Board (DSMB) and will operate according to DMID guidelines (http://www.niaid.nih.gov/dmid/clinresearch/).

3.2 Study Objectives

The overall aim of this trial is to evaluate the safety, tolerability, and preliminary efficacy of treatment with 2 weeks of an oral non-nucleoside inhibitor CDI-31244 combined with 6 weeks of SOF/VEL in adult subjects with chronic HCV genotype 1 virus infection. Specific objectives are as follows.

3.2.1 Co-Primary Objectives

1. To assess preliminarily the efficacy of short duration combination treatment with CDI-31244 plus SOF/VEL in adults with chronic HCV genotype 1 infection. Efficacy will be evaluated by HCV RNA levels, with sustained virologic response 12 weeks after completion of treatment (SVR12) as the primary endpoint, see below.

2. To assess the safety and tolerability of short duration combination treatment with CDI-31244 plus SOF/VEL in adults with chronic HCV genotype 1 infection. The safety profile will be assessed by adverse events, physical examination (including vital signs), electrocardiogram (ECG), and clinical laboratory data, see below.

3.2.2 Secondary Objectives

1. To evaluate the proportion of patients with sustained virologic response 24 weeks after completion of treatment (SVR24).

2. To document the pharmacokinetics of the combination therapy by measuring plasma concentrations of CDI-31244, SOF, and VEL as a function of time.

3. To assess the viral kinetics during and after treatment with CDI-31244 combined with SOF/VEL by serial plasma HCV levels.

3.2.3 Exploratory Objectives

1. To evaluate immunologic, virologic, and host genetic/proteomic predictors of response to therapy using stored blood.

2. To evaluate the effect of therapy on peripheral markers of T cell activation.

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoints

1. Proportion of subjects who achieve sustained virologic response 12 weeks after completion of treatment (SVR12).

3.3.2 Secondary Efficacy Endpoints

1. Proportion of subjects who achieve sustained virologic response 24 weeks after completion of treatment (SVR24).
2. Time to achieve HCV RNA levels below the lower limit of quantification (LLOQ).
3. Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14 of CDI-31244 plus SOF/VEL treatment.
4. Proportion of subjects with HCV RNA <LLOQ after Day 7 and Day 14 of CDI-31244 plus SOF/VEL treatment by genotype 1a or 1b.

3.3.3 Primary Safety Endpoints

1. Occurrence of related Grade 3 adverse events (AEs) and SAEs for the 28 days following administration.

2. Occurrence of SAEs for the duration of the study

3.3.4. Exploratory Endpoints

1. Pharmacokinetic parameters will be analyzed in relation to efficacy and toxicity metrics

2. Further exploratory endpoints related to stored blood for immunologic, virologic, and host genetic/proteomic predictors of therapy and effect of therapy on peripheral markers of T cell activation will be reported but without a formal statistical analysis due to limited statistical power.

4 STUDY METHODS

4.1 Overall Study Design and Plan

- Open-label, single stage, single arm Phase 2a study with the overall aim of assessing early efficacy and safety data of 2 weeks of CDI-31244 treatment concurrent with 6 weeks of SOF/VEL treatment.
- Study population includes 12 adults with treatment-naïve chronic HCV genotype 1a or 1b.
- One study center: Institute of Human Virology, University of Maryland.
- Safety oversight from a 5-person data and safety monitoring committee (DSMB) with planned biannual meetings. First meeting is planned for January 2019.
- Screening will be performed between 7 and 42 days before initial study drug administration.
- Day 1 is the day of baseline (pre-study drug) assessments and the first day of study drug administration. Clinic visits will occur at screening and baseline and through week 30 (i.e., 24 weeks after completion of treatment) for all subjects.
- Safety evaluations will consist of vital signs, physical examination, electrocardiogram (ECG), and additional clinical and laboratory data. Adverse events will be collected through 4 weeks after completion of treatment for all subjects.
- The primary and secondary efficacy outcomes will be measured throughout the study period by plasma HCV RNA.
- Pharmacokinetic (PK) parameters will be assessed through plasma CDI-31244, sofosbuvir, GS-331007 (sofosbuvir metabolite), and velpatasvir concentrations at Day 1 (pre-dose) and at 0 (pre-dose), 1, 2, 4, 6, 8, 12, and 24 hours after day 14 dosing.
- Viral kinetics (VK) will be assessed through plasma HCV RNA levels obtained at 2, 4, and 6 hours after Day 1 dosing.
- The total study duration is 30 weeks.
- Surveillance for serious adverse events for the duration of the study follow-up period.

- Follow-up of serious adverse events (SAEs) until resolution or stability; follow-up of AEs until resolution or stability or until the end of the trial.

- Electronic and paper case report forms (CRFs) will serve as source documents. Only information that cannot be collected initially onto CRFs (namely, clinical laboratory test results and adverse event medical records) will first be collected onto separate source documents prior to transcription into the Internet data system.

- Participants will be asked to return to clinic at study days 2, 3, 7, 10, 14, 15 as well as week 3, 6, 8, 10, 14, 18, and 30. See section 3.2.2. in the Protocol for a detailed list of study evaluations and tests at each visit. Additional visits are scheduled in patients receiving retreatment.

4.2 Selection of Study Population

Subjects will be recruited from the clinical practice of the investigator/associate investigator and referring physicians and will have a diagnosis of HCV based on history, physical examination, and laboratory studies. Inclusion criteria for this study include patients (age ≥ 18 years) with chronic HCV genotype 1a or 1b. A maximum of 4 subjects with genotype 1b will be enrolled.

Participation in this study is voluntary. The nature of the study will be fully explained to each subject during the informed consent process. The subjects will have the opportunity to ask questions. An informed consent document will then be signed by the subject and the person obtaining the consent. A copy of the signed informed consent will be retained by the investigator according to Good Clinical Practice (GCP) with a copy given to the research subject as well.

4.2.1 Modified Intention to Treat Population

The Modified Intention to Treat (MITT) Population comprises all patients enrolled on the study who received at least one dose of CDI-31244 and who either:

(i) prematurely fails efficacy ("virologic failure") based on any of the two following criteria, which must be confirmed by a repeat test within 7 days:
  - HCV RNA > LLOQ after 2 prior consecutive HCV RNA values < LLOQ.
  - Greater than 10-fold increase in HCV RNA from nadir.

(ii) have a Week 18 visit with assessment of SVR12.

(iii) patients who withdraw from the study because of toxicity will be retained in the MITT and assessed as treatment failures for the efficacy analysis according to the ITT principle.

Patients who prematurely discontinue the study for any other reason than the above will be replaced in the MITT.

4.2.2 Safety Population

The Safety Population comprises all patients enrolled on the study who received at least one dose of CDI-31244. Patients who withdraw from the study for any reason except toxicity will be replaced.

4.2.3 Completer Population

The Completer Population will include all patients who receive the full planned course of 2 weeks of an oral NNI CDI-31244 combined with 6 weeks of SOF/VEL and who completed all study procedures at Baseline, at Week 18 and at Week 30 as a minimum.

4.2.4 Pharmacokinetic Population

The Pharmacokinetic (PK) Population will include all patients who receive CDI-31244 and had all Day 14 PK plasma samples collected.

4.3 Assignment of Treatment

This study is a single-arm, open-label trial and research subjects and investigators will be unblinded. There is no dose escalation in the design.

4.4 Re-treatment

Subjects who have virologic (treatment) failure *during the 6-week study drug treatment period*, defined as in 4.2.1. (i) above, will be discontinued from study drug treatment. These subjects will receive retreatment with standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects *who complete the 6-week treatment period* will be considered to have virologic failure if they have detectable HCV RNA at the next study visit or at any time after completion of treatment. These subjects will receive retreatment with standard of care regimen using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) 400 mg/ 100 mg/100 mg once daily for 12 weeks with additional follow-up through 12 weeks after cessation of treatment (SVR12).

Subjects receiving retreatment will have study visits at 4-weeks after initiation of retreatment, at the end of the 12-week retreatment period, at 4 weeks after completion of treatment (SVR4), and at 12 weeks after completion of treatment (SVR12). Procedures during retreatment are detailed in the protocol (Section 3.2.2.11). HCV resistance assays will be obtained in both subjects with virologic failure during study drug treatment or in the post-treatment follow-up period.

5 SEQUENCE OF PLANNED ANALYSES

5.1 Interim Analyses

No formal interim analysis is planned as part of this trial. However, virologic failures will be monitored on a continuous basis and after each failure a decision will be made concerning whether this event triggers the early stopping rule, see section 6.1.

Interim safety reports will also be generated for the study's independent Data and Safety Monitoring Board (DSMB). The DSMB will be scheduled to review cumulative safety data biannually with the first meeting conducted in November 30, 2018.

5.2 Primary Analyses and Reporting

The Primary Analysis will be conducted on data and samples collected until all 12 patients in the MITT populations have passed their follow-up at week 30. Any data included in the Primary Analyses must be locked and quality controlled and will not be modified subsequent to the Primary Analysis unless approved by the investigators.

The primary analysis will include analysis of demographics and PK data, primary safety endpoints and efficacy endpoints. This analysis will include secondary endpoints, and exploratory outcomes.

Demographic characteristics (age, gender, race, and ethnicity) will be tabulated for all study participants as well as for the separate study populations (if different). Safety analyses will be based on the Safety Population data set. Efficacy analyses will be based on the MITT data and will be repeated using the Completer Population data. The re-execution of the analysis is to corroborate the results from the MITT analyses. Results of the analyses will be disclosed in oral presentations at scientific meetings and subsequent publications in scientific journals and regulatory reports.

5.3 Final Analyses and Reporting

The study Final Analysis will include the analysis of all primary, secondary and exploratory outcomes for which data are available. As described in the Primary Analysis, results of analysis of

the Safety and Efficacy datasets will be included in all reports of the Final Analyses. The CSR will be compiled following the Final Analysis.

6 SAMPLE SIZE CONSIDERATIONS

The sample size is 12 subjects. This sample size was chosen based on a consideration of the one-sided 95% confidence interval around the proportion reaching a given endpoint, see Table 6.1.

For example, if 0 of 12 patients develop a given SAE, the upper limit on the 1-sided 95% confidence interval is 0.221. In general, we are interested in *the upper limit of the interval for any adverse event*, and *the lower limit of the interval for any efficacy measure*. If 12 of 12 patients achieve SVR12, the lower limit of the 1-sided 95% confidence interval for the proportion of viral controls is 0.779.

Table 6.1. Upper and lower limits on the 90% confidence interval as a function of the number of responders/events.

Resp.	p	p_L	p_H	Width
0	0.000	-	0.221	0.221
1	0.083	0.004	0.339	0.334
2	0.167	0.030	0.438	0.408
3	0.250	0.072	0.527	0.455
4	0.333	0.123	0.609	0.486
5	0.417	0.181	0.685	0.504
6	0.500	0.245	0.755	0.509
7	0.583	0.315	0.819	0.504
8	0.666	0.391	0.877	0.486
9	0.750	0.472	0.928	0.456
10	0.833	0.562	0.969	0.408
11	0.916	0.661	0.996	0.335
12	1.000	0.779	-	0.221

Resp. : number of responders; p: sample proportion; p_L: lower limit of 90% CI; p_H: upper limit of 90% CI; Width: width of confidence interval

6.1 Early Stopping Rule

The trial will be stopped if 3 subjects (either during the treatment period or follow-up) are virologic (treatment) failures/relapse. In this situation, subjects receiving CDI-31244 will be discontinued from CDI-31244. Subjects receiving SOF/VEL will continue to receive SOF/VEL to complete a 12-week course of treatment. This stopping rule was agreed after FDA review. With availability of highly active HCV drugs in the market with cure rates of 90+ %, this stopping rule gives an 11% probability of early stopping if the combination tested here has an SVR12 probability of 90% or better. This is the risk of Type II errors (β), in other words, the power of the trial is 89%. An inferior combination with SVR12 equal to, say, 70%, will have a 74.7% probability of stopping the trial early, see Table 6.2.

Table 6.2. Probability of early stopping as a function of SVR12 probability

SVR12 prob.	Prob. of early stop
0.7	0.747
0.8	0.442
0.9	0.111
0.93	0.048

6.2 Exploratory Analyses of Association between Two Continuous Variables

Potential associations between pharmacokinetic parameters and continuous efficacy or toxicity metrics such as laboratory values will be tested using Pearson's correlation coefficient, if necessary, after an appropriate transformation of the data. A sample size of 12 achieves 80% power (1-β) to detect a difference of -0.65 between the null hypothesis correlation of 0.00 and the alternative hypothesis correlation of 0.65476 using a one-sided hypothesis test with a significance level of α=0.05. If the transformation does not yield an approximate normal distribution of both parameters, we will use the non-parametric Spearman's rank correlation as an alternative.

7 GENERAL ISSUES FOR STATISTICAL ANALYSIS

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) and for continuous variables and frequency and percentages for categorical variables. Time to achieve HCV RNA levels (below LLOQ) and viral kinetics will also be summarized using descriptive statistics. Exploratory endpoints will be assessed using descriptive statistics.

Time-to-event analysis will be conducted using the Kaplan-Meier product-limit estimator to adjust for censored observations with 95% confidence intervals around the estimate calculated using Greenwood's formula.

7.1 Analysis Software

IBM® SPSS® Statistics for Windows, release 25.0.0.1 or later will be used for manipulation and analysis of study data.

7.2 Methods for Withdrawals, Missing Data, and Outliers

Treatment compliance will be evaluated by visits. This will include the date the study drug was dispensed, the number of capsules/tablets dispensed, and the number of tablets and capsules returned. Subjects who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal. Missing data will not be imputed for safety analyses. For efficacy analyses, some missing values may be imputed using the last observation carried forward method. However, viral load data will not be imputed. The site is instructed to use estimated start and stop dates for

concomitant medication use, which will be used in the analysis. Where relevant, time-to-event analysis with allowance for incomplete (censored) observations will be used as described above.

7.3 Data Transformations

Viral loads will be analyzed as the logarithm (base 10) of the measured value.

7.4 Multiple Comparisons and Multiplicity

Confidence intervals for incidence of adverse events will individually be 95% intervals and will not be adjusted to be simultaneous 95%.

7.5 Planned Subgroups and Covariates

7.5.1 Planned subgroup analyses

Subgroup analysis will be exploratory only in view of the limited overall sample size and the expected high response rate. In case of one or more virologic failures, we will consider the occurrence of these in relation to the following patient and disease characteristics:

1. HCV genotype (1a or 1b)
2. Baseline HCV RNA levels (IU/mL)
3. Baseline HCV Fibrosis Score (F0, F1, F2)
4. Those who have HCV RNA levels < or = 500 IU/mL by Day 3 (some studies used to call this, uRVR or ultrarapid virologic response) versus those who did not.
5. Those who have HCV RNA levels not detected at Week 6 (End of Treatment) versus those who did not.
6. Race (White, Black, Asian, Others)
7. Gender (M/F)
8. Presence or absence of NS5A RAVs (Resistance Associated Variants)
9. Presence or absence of NS5B RAVs
10. IL-28 polymorphisms (CC, CT, TT)

7.5.2 Covariates

No adjustment for covariates is planned in this limited-sample-size trial.

8 STUDY SUBJECTS

8.1 Disposition of Subjects and Withdrawals

The total number of enrolled subjects and all post-enrollment discontinuations will be tabulated and accompanied by the number of subjects completing each of the study follow-up visits. All tabulations will be both by study population (section 4.2) and in aggregate (total). A combination of tabulations and flow charts (www.consort-statement.org) will be used to present this information and describe all post-enrollment study withdrawals. Reasons for withdrawing from the study, as coded by the investigators, will be provided.

8.2 Protocol Deviations

All deviations from the study protocol, including the eligibility criteria, treatment administration/management, participant management and any other incidents potentially impacting study results, will be provided by study population. In addition, deviations will be summarized in aggregate, those related to eligibility/enrollment, treatment administration, protocol procedure/assessment, and follow-up visit schedule and cross-tabulated with reason for violation including participant illness, participant compliance/refusal, clinic error, laboratory error, investigator decision and pharmacy error.

8.3 Inclusion and Exclusion Criteria

8.3.1 Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

1. Age ≥ 18 years at screening.
2. Documented chronic HCV infection based on **any** of the following:
   - Anti-HCV antibody positivity for at least 6 months prior to study enrollment.
   - HCV genotype results for at least 6 months immediately prior to study enrollment.

- HCV RNA present in plasma by a sensitive and specific assay for at least 6 months prior to study enrollment.
- Histologic evidence of chronic HCV infection.

3. HCV genotype 1a or 1b infection by HCV genotyping performed at screening. (Note: No more than four subjects with HCV genotype 1b will be enrolled).
4. Serum HCV RNA >1,000 IU/mL during screening.
5. Must have a primary care provider(s) for medical management.
6. Absence of advanced fibrosis or cirrhosis by liver biopsy, fibroscan (<8 kPa) or FibroTest/FibroSure (F2 or lower) within 1 year of screening. If the preceding fibrosis tests are not available, FibroTest/FibroSure will be done at screening.
7. Females of childbearing potential must have a negative serum pregnancy test at screening and agree to use a medically reliable method of contraception until study completion.
8. Male subjects must be willing to abstain from heterosexual intercourse or use a condom with spermicide throughout the study period.
9. Be willing to have blood samples stored for future research.
10. Available for at least 30 weeks for study participation.
11. Written informed consent must be obtained before any study procedure is performed.

8.3.2 Exclusion Criteria

Patients meeting **any of** the following criteria will not be eligible to participate in the study:

1. Nursing or pregnant.
2. Active hepatitis B virus (HBV) infection, defined as positive hepatitis B surface antigen (HBsAg) at screening. If a subject is negative for both HBsAg and hepatitis B surface antibody (HBsAb), but hepatitis B core antibody (HBcAb)-positive, plasma HBV DNA levels will be tested and the subject excluded if HBV DNA detected.
3. Human immunodeficiency virus (HIV) infection.
4. History of use of any HCV direct-acting antiviral therapy.

5. Clinically significant illness other than HCV that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator.
6. Positive urine screen for amphetamines or cocaine.
7. Known current heroin, morphine, or methadone use. Current narcotic use other than methadone is acceptable if medically indicated (documented in medical records) and prescribed by a physician.
8. Substance abuse, including alcohol abuse, which in the opinion of the investigator is likely to interfere with medication adherence or study compliance.
9. Gastrointestinal disorder that could interfere with the absorption of the study drug (e.g., structural defect, digestive failure or enzyme deficiencies with the exception of lactose intolerance) and/or history of bariatric surgery.
10. Poor venous access interfering with required study blood collection.
11. Significant history of drug allergy (such as anaphylaxis or hepatotoxicity) to the study medications.
12. History of clinically significant chronic liver disease due to other etiology (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, α1-antitrypsindeficiency, alcoholic liver disease, known greater than moderate non-alcoholic steatohepatitis, and toxin exposures).
13. Use of herbal/natural remedies for potential benefit to the liver within 30 days before study entry.
14. Treatment with amiodarone within 180 days before study entry.
15. Treatment with digoxin within 30 days before study entry.
16. Treatment with rifabutin, rifampin, rifapentine, phenytoin, phenobarbital, St. John's wort, carbamazepine, oxcarbazepine, rosuvastatin, or atorvastatin within 10 days before study entry. However, switching to another statin is acceptable.
17. Chronic systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before study entry. Inhaled steroids are permitted per Investigator's discretion.
18. Screening or baseline electrocardiogram (ECG) with clinically significant findings.
19. QTcF (QT interval corrected using Fridericia's formula) > 450 msec at screening.

20. Clinically significant hematological and biochemical values at screening that may interfere with subject treatment, assessment, safety, or compliance with the protocol in the judgment of the investigator, including:
    - Absolute neutrophil count (ANC) <1,000 cells/mm^3.
    - Hemoglobin level < 10 g/dL.
    - Platelet count < 100,000 cells/mm^3.
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.
    - ALT or AST level ≥ 5 times upper limit of normal (ULN).
    - Direct bilirubin level ≥1.5 times ULN.
21. History of hepatocellular carcinoma (HCC).
22. History of malignant disease within previous 5 years (except for adequately treated basal cell carcinoma).
23. History of clinically significant myopathy.

9 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Abbreviated summaries of demographics and other baseline characteristics may be performed for presentation of the Primary Analysis. Full presentation of all demographics and baseline characteristics will be included in the study CSR.

9.1 Demographics

Demographic information including age, gender, race and ethnicity will be tabulated and presented.

9.2 Concomitant Medications

Concomitant medications ongoing at the time of first first dose or initiated during the study period will be presented with accompanying classification (e.g.: anti-coagulants, supplements, etc.).

9.3 Baseline and Screening Conditions

9.3.1 Baseline Medical History

The number of subjects with a positive medical history for the following body systems / areas will be tabulated:

Head, Ears, Eyes, Nose and Throat
Cardiovascular
Respiratory
Gastrointestinal
Genitourinary
Endocrine/Metabolic
Neurologic
Psychiatric
Dermatologic
Blood/Lymphatic
Musculoskeletal
Allergy
Cancer
Immunodeficiency
Autoimmune Disease
and any other significant medical problems in any body system/area

In addition, subject listings, including specification of the nature of the medical history, will be provided.

9.3.2 Baseline Physical Exam

Results of the baseline physical exam will be presented as the number of subjects presenting with an abnormality in the following body systems/areas:

General Appearance
Eyes
Otorhinolaryngology
Pulmonary/Chest
Cardiovascular/Heart
Gastrointestinal
Genitourinary
Skin
Lymphatic
Extremities
Musculoskeletal
Neurological

In addition, subject listings including specification of the abnormality will be provided.

10 SAFETY AND TOLERABILITY ANALYSES

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject.

10.1 Adverse Events

10.1.1 All Adverse Events

International Conference on Harmonisation (ICH) guideline E6 (R1) defines an adverse event (AE) as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews or by a participant presenting for medical care.

Each adverse event will be described by its duration (start date, time and duration), its severity, an assessment of its cause (coexisting disease, concomitant medication, the study medication, and others), its relationship to the study medication (not related, unlikely, possibly, probably, definitely), whether it influenced the course of the study medication, or whether it required specific therapy.

The investigator will make an assessment of intensity for each AE reported during the study. The assessment will be based on the investigator's clinical judgment. The Division of AIDS (DAIDS) Table for "Grading the Severity of Adult and Pediatric Adverse Events" version 2.1 (March 2017) will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the DAIDS criteria, the following guidelines should be used to grade severity:

- Mild (grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Moderate (grade 2): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicate.

- Severe (grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- Life-threatening (grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The term "severe" is a measure of intensity and a severe AE is not necessarily serious.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment. All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

Adverse events will be coded by MedDRA (Medical Dictionaries for Regulatory Activities) coded. Each AE may be associated with more than one MedDRA System Organ Class (SOC). However, for reporting purposes, an AE will be associated with the primary SOC only.

The relationship of an AE to the study drug should be based on the judgment of the investigator and assessed using the following the guidelines:

- **Definitely:** Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response patter n to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
- **Probably:** An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
- **Possibly:** An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.

- **Unrelated:** An event that can be determined with certainty to have no relationship to the study drug.

Summarization of AEs will be based both on the number of subjects experiencing the AE and the total number of AEs of a particular type. All AEs occurring while a subject is in the study will be reported. Incidence of events in each SOC and by MedDRA Preferred Term (PT) will be provided with accompanying 95% confidence intervals. Also, the proportion of subjects experiencing any adverse event, and any adverse event of moderate or greater severity, will be estimated and compared using 95% confidence intervals, Chi-squared tests or in the event of small counts, Fisher's Exact test.

10.1.2 Adverse Events Leading to Withdrawal

Adverse events leading to the withdrawal of the subject will be summarized and reported on separately. MedDRA coding and summarization by SOC will be presented in this listing. Timing of the withdrawal will also be included in the summary. The number of subjects experiencing adverse events leading to withdrawal will be compared between the two study groups using a Chi-squared test or Fisher Exact tests.

10.1.3 Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event[1],
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

[1] Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event, which, had it occurred in a more severe form, might have caused death.

- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  A summary of incidence rates (frequencies and percentages) of SAEs by participant group, SOC, and Preferred Term will be prepared for the study population. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF and accompanied by clinical narratives. No statistical tests will be performed.

10.1.4 Deaths

All deaths reported for the study will be provided in a listing and will be accompanied by a narrative describing the death and related clinical and laboratory parameters.

10.2 Clinical Laboratory Evaluations

Laboratory data will include evaluation of:

- Hematology: hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology, reticulocyte count.
- Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, uric acid, calcium, glucose, total protein, albumin, cholesterol, lipase, creatine kinase (CK).
- Coagulation: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR).
- Serum and urine beta hCG pregnancy test on females of childbearing potential.
- Urinalysis: specific gravity, pH, protein, glucose, blood, leukocyte esterase.

Descriptive statistics for clinical laboratory results including mean, median, range, and number of non-missing observations will be calculated for screening data and values measured during therapy or follow-up. Values of laboratory parameters will be plotted for the study group and be overlaid with boxplots showing the important distributional features of each parameter.

In addition, the number of subjects with clinical laboratory values of various grades at any point during follow-up will be calculated according to the DIAIDS AE Grading Table Version 2.1- March 2017:

HEMATOLOGY					
	Normal Range	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin Male Female	11.0-16.2 g/dL	10.0 –10.9 g/dL 9.5 – 10.4 g/dL	9.0-<10.0 g/dL 8.5- <9.5 g/dL	7.0 – <9.0 g/dL 6.5 - <8.5 g/dL	< 7.0 g/dL <6.5 g/dL
Platelets	125,000-310,000/mm^3	100,000 - 124,999/mm^3	50,000 - 99,999/mm^3	25,000 - 49,999/mm^3	<25,000/mm^3
WBCs	2,500-12,000/mm^3	2,000-2,499/mm^3	1,500-1,999/mm^3	1,000-1,499/mm^3	<1,000/mm^3
Absolute Neutrophil Count	1,001-8,000/mm^3	800-1,000/mm^3	600-799/mm^3	400-599/mm^3	<400/mm^3
CHEMISTRIES					
	Normal Range	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine, High	0.5-1.3 mg/dL	1.1-1.3 x ULN	1.31-1.8 x ULN	1.81-3.49 x ULN	≥ 3.5 x ULN
ALT, High	Males 0-44 IU/L Females 0-32 IU/L	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10.0 x ULN	≥10.0 x ULN
AST	<1.25 x ULN	1.25-2.5 x ULN	>2.5-5.0 x ULN	>5.0-10.0 x ULN	≥10.0 x ULN

10.3 Vital Signs

Vital signs, including temperature, pulse, respirations, and blood pressure measurements, will be presented graphically over time. Summary statistics including mean, median, range, and non-missing observations will also be calculated at each follow-up visit and for each study group.

In addition, the number of subjects with clinical laboratory values of various grades at any point during follow-up will be calculated according to the following toxicity table:

Vital Signs	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension (systolic) mm Hg	141-150	151-155	>155	Hospitalization for malignant hypertension
Hypotension (systolic) mm Hg	85-89	80-84	<80	Hospitalization for hypotensive shock

11 EFFICACY ANALYSES

HCV genetic material (RNA) testing uses polymerase chain reaction (PCR) to identify an active hepatitis C infection. HCV quantitative testing (also called viral load) is the standard measure used before and during treatment to assess the benefit of treatment (as well as to measure viral kinetics).

1. Means and 95% confidence intervals will be calculated at each time point for each study population (see 4.2) and presented both in tables and graphically.
2. Comparison of means between time points or groups of patients will be performed using a paired or standard, independent samples t-test. If the data, after an appropriate transformation, do not appear normally distributed, non-parametric tests will be applied as an alternative.

12 EXPLORATORY ANALYSES

Additional exploratory analyses will be conducted to determine if pharmacokinetic parameters are associated with any of the efficacy or toxicity related metrics.

13 REFERENCES

International Conference on Harmonisation (ICH) Guidelines: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995.

International Conference on Harmonization (ICH) Guidelines:
- Topic E3 Structure and Content of Clinical Study Reports
- Topic E8 General Considerations for Clinical Trials
- Topic E9 Statistical Principles for Clinical Trials

MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

IBM® SPSS® Statistics for Windows, release 25.0.0.1 or later (IBM Corp., Armonk, N.Y., USA).

14 PRESENTATION OF STUDY OUTCOMES

14.1 Planned Listing Descriptions

Listing numbering will follow ICH E3 and will be numbered according to the nomenclature used for the final clinical study report.

Table 14.1.1

Listing of Abnormal Clinical Laboratory Values, Safety Population

Safety Data

Subject ID	Study Day	Blood Draw Date	Hemoglobin (g/dL)	Platelets (10^3/µL)	WBC (10^3/µL)	Lymphocytes (10^3/µL)	Creatinine (mg/dL)	ALT (U/L)

Table 14.2.1
Adverse Events of Moderate or Greater Severity, Safety Population

Safety Data

Study Group	Subject ID	Adverse Event Description	Onset Date	Last Tx. Date	Last Tx. (Days Post)	Severity	Relationship to therapy	Outcome	Duration (days)	MedDRA® SOC	MedDRA® PT