



STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3b Randomized, Open-label, Controlled Study of the Efficacy, Safety and Tolerability of 12 Weeks of Ledipasvir/Sofosbuvir (LDV/SOF) Treatment for HIV/HCV Co-infected Subjects who Switch to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) or Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/R/TAF) prior to LDV/SOF HCV Treatment, the HIV/HCV Co-STARS study (Co-infection treatment with Single Tablet Antiviral Regimens)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT (SGPT)	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CLDQ-HCV	Chronic Liver Disease Questionnaire - HCV
CM	concomitant medication
CMH	Cochran-Mantel-Haenszel test
COBI	cobicistat, C
CRF	case report form
CSR	clinical study report
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, Genvoya [®]
EVG	elvitegravir, E
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eGFR _{CG}	estimated glomerular filtration rate using Cockcroft-Gault formula
ESDD	early study drug discontinuation
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine, F
F/R/TAF	emtricitabine/rilpivirine/tenofovir alafenamide
FTC/RPV/TAF	emtricitabine/rilpivirine/tenofovir alafenamide
GFR	glomerular filtration rate
GSI	Gilead Sciences, Inc.
GT	genotype
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV-1	human immunodeficiency virus (type 1)
HIV-TSQc	HIV Treatment Satisfaction Questionnaire – Change version
HIV-TSQs	HIV Treatment Satisfaction Questionnaire – Status version

HLGT	high-level group term
HLT	high-level term
HRQoL	health related quality of life
INR	international normalized ratio
ID	identification
KM	Kaplan-Meier
LDV/SOF	ledipasvir/sofosbuvir
LDL	low density lipoprotein
LTT	lower-level term
LLOQ	lower limit of quantitation
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside reverse transcriptase inhibitor
OL	open label
PK	pharmacokinetic(s)
PP	per protocol
PRO	patient reported outcome
PT	preferred term
PTH	parathyroid
Q1, Q3	first quartile, third quartile
RBP	retinol binding protein
RNA	ribonucleic acid
RPV	rilpivirine, R, Edurant [®]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SF-36	Short Form – 36 Version 2 Health Survey
SI (units)	international system of units
SOC	system organ class
SOF	sofosbuvir, Sovaldi [®]
SMQ	Standardised MedDRA Query
SVR	sustained virologic response
TAF	tenofovir alafenamide
TAM	thymidine analog associated mutations
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TG	triglycerides
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal

UPCR	urine protein to creatinine ratio
VAS	visual analogue scale
VR	virologic rebound
WHO	World Health Organization
WPAI:C	Work Productivity and Activity Impairment: Hepatitis C

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
CL_{ss}/F	apparent oral clearance after administration of the drug: at steady state: $CL_{ss}/F = \text{Dose}/AUC_{tau}$, where “Dose” is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

1. INTRODUCTION

GS-US-366-1992 is a Phase 3b, randomized, open-label, controlled study of the efficacy, safety and tolerability of 12 Weeks of ledipasvir (LDV)/sofosbuvir (SOF) (LDV/SOF) treatment for subjects who are coinfectd with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) who switch from their current antiretroviral (ARV) therapy to elvitegravir (EVG, E)/cobicistat (COBI, C)/emtricitabine (FTC, F)/tenofovir alafenamide (TAF) (E/C/F/TAF) or FTC/rilpivirine (RPV, R)/TAF (F/R/TAF) prior to LDV/SOF HCV treatment.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used in the summary and analysis of data collected during the study.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate efficacy of LDV/SOF as measured by the proportion of subjects achieving HCV RNA below the lower limit of quantification (LLOQ) 12 weeks after the last dose of LDV/SOF (sustained virologic response [SVR12])

The secondary objectives of this study are:

- To determine the proportion of subjects achieving HCV RNA < LLOQ 4 weeks after the last dose of LDV/SOF (SVR4)
- To evaluate maintenance of HIV type 1 (HIV-1) RNA suppression after switching to E/C/F/TAF or F/R/TAF 24 weeks from the start of the F/TAF-based regimen
- To evaluate the safety and tolerability of switching to E/C/F/TAF or F/R/TAF from the current ARV therapy in virologically suppressed, HIV-1/HCV coinfectd subjects
- To evaluate the safety and tolerability of 12 weeks of treatment for HCV with LDV/SOF in virologically suppressed, HIV-1 and HCV coinfectd subjects who switched to E/C/F/TAF or F/R/TAF.

1.2. Study Design

1.2.1. Design Configuration and Subject Population

This is a randomized, multicenter, open-label (OL), 2-part study in adult male and female subjects with HIV who are coinfectd with chronic genotype 1 HCV infection. Eligible subjects had maintained HIV-1 RNA < 50 copies/mL for at least 6 months on a stable ARV therapy met one of the following criteria:

- 1) No cirrhosis and no prior HCV treatment (treatment-naive);
- 2) No cirrhosis and have receive HCV treatment only with interferon (IFN) ± ribavirin (RBV) or IFN + RBV + an HCV protease inhibitor (PI) (ie, treatment experienced)
- 3) Compensated cirrhosis and no prior HCV treatment (treatment naive)

1.2.2. Randomization and Treatment Groups

Part 1: Approximately 120 subjects will be randomized 1:1 to switch from stable ARV therapy to 1 of the following treatments:

- **Treatment Group 1:** Switch from 2 nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) plus a third ARV agent to E/C/F/TAF fixed dose combination (FDC) (n = 60)
- **Treatment Group 2:** Switch from 2 NRTI plus a third ARV agent to F/R/TAF FDC (n = 60)

Randomization will be stratified by race (black vs non-black).

Part 2: After 8 weeks on the randomized F/TAF-based regimens, subjects maintaining HIV-1 RNA < 50 copies/mL and tolerating E/C/F/TAF or F/R/TAF through Part 1 will continue the F/TAF-based HIV therapy to which they were randomized and initiate LDV/SOF HCV treatment.

- LDV/SOF FDC tablet once daily for 12 weeks.

1.2.3. Key Eligibility Criteria

- Chronic genotype 1, HCV infected, male and nonpregnant/non-lactating female subjects. Subjects without cirrhosis who were HCV treatment naive or treatment experienced with IFN ± RBV ± HCV PI. Subjects with compensated cirrhosis must have been HCV treatment naive. Subjects with no prior treatment with an HCV nonstructural protein NS5A, and NS5B, or any HCV direct-acting antiviral (DAA), except boceprevir, telaprevir, or simeprevir in combination with IFN and RBV.
- Currently taking an ARV regimen (2 NRTI + a third agent) without change for 6 months prior to screening. Documented plasma HIV-1 RNA < 50 copies/mL (or undetectable HIV-1 RNA according to the local assay if the limit of detection is ≥ 50 copies/mL) for ≥ 6 months preceding the screening. After reaching HIV-1 RNA < 50 copies/mL, single values (“blips”) of HIV-1 RNA ≥ 50 copies/mL followed by resuppression will be allowed. For subjects with 3 or more prior ARV regimens, a regimen history should be provided for approval by the sponsor.
- Plasma HIV-1 RNA < 50 copies/mL at the screening visit.
- With no documented history of resistance to any of the HIV study agents, including but not limited to the reverse transcriptase resistance mutations K65R, K70E, K101E/P, E138A/G/K/R/Q, V179L, Y181C/I/V, M184V/I, Y188L, H221Y, F227C, M230I/L, the combination of K103N+L100I, or 3 or more thymidine analog associated mutations (TAMs) that include M41L or L210W (TAMs are M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). If a historical genotype prior to first ARV is not available or a subject had 3 or more prior ARV regimens, the subject will have proviral genotype analysis for archived resistance prior to Day 1.

1.2.4. Study Periods

Part 1: Subjects will be randomized to receive E/C/F/TAF or F/R/TAF for 8 weeks.

Part 2: Subjects will receive 12 weeks of LDV/SOF and continue their randomized F/TAF-based regimen for 12 weeks after completion of LDV/SOF (total approximately 24 weeks in Part 2).

After a subject has completed/terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating physician.

1.2.5. Schedule of Assessments

After obtaining informed consent, screening assessments will be completed within 42 days prior to the Day 1 visit, including physical examination, height, weight, vital signs, medical history, 12-lead electrocardiogram (ECG), screening procedure-related adverse events (AEs), concomitant medications (CMs), clinical laboratory tests (including hematology, coagulation, and chemistry, and), urinalysis, plasma concentrations of HIV-1 RNA and HCV RNA, serology (HIV, HCV, hepatitis B virus [HBV]), historical HIV resistance (if not available; HIV DNA archive genotype), HCV genotyping, IL28B genotyping, cirrhosis determination, serum β -hCG (females of child bearing potential only).

On treatment assessment will occur as follows:

- **Part 1:** Switch to F/TAF-based ARV regimen:
 - Day 1 and Weeks 4, 6 (HIV-1 RNA only), and 8
- **Part 2:** LDV/SOF treatment and follow-up
 - At first dose of LDV/SOF at Week 8, and at Weeks 12, 16, and 20 (ie, 4, 8, and 12 weeks after start of LDV/SOF) and follow up at 4 and 12 weeks post LDV/SOF treatment.

On treatment and post HCV treatment assessments will include HIV-1 RNA and HCV RNA plasma concentrations, CD4 cell count, adherence to study drug dosing (including pill count), physical examination, weight, vital signs, clinical laboratory tests, urine pregnancy tests (females of child bearing potential only), monitoring of AEs and CMs, and patient-reported quality-of-life (QoL) assessments.

Fasting lipid profile measurements and fasting glucose will be performed at Day 1, Weeks 8 and 20, and at Post HCV Treatment Week 12. Lipids will include total cholesterol (TC), high density lipoproteins (HDL), low density lipoproteins (LDL), non-HDL cholesterol, triglycerides (TGs) and cholesterol ratios.

Post HIV treatment assessments (30 days after the last dose of HIV study drug) will include HCV RNA, HIV RNA, CD4 count, physical examination (including vital signs and weight), 12-lead ECG, clinical laboratory tests (including hematology, chemistry, and urinalysis, urine pregnancy tests (females of childbearing potential only), and AEs and CMs.

Plasma samples for HCV RNA and HIV-1 RNA will be collected at Day 1 and every visit thereafter (no HCV RNA at Weeks 4 and 6).

Calculated creatinine clearance, hematology, serum chemistry, and urinalysis tests will be performed at all study visits and early study drug discontinuation (ESDD) visits as applicable.

Health Related Quality of Life (HRQoL) surveys will be conducted at Day 1, Weeks 8, 20, and Post HCV Treatment Week 12 and ESDD visits as applicable.

PPD



Blood samples for population pharmacokinetic (PK) evaluation will be collected at Weeks 4, 8, 12, 16, and 20.

1.2.6. Site and Stratum Enrollment Limits

Approximately 50 centers in North America will participate. There is no enrollment limit for individual sites.

1.3. Sample Size and Power

A sample size of 120 subjects will provide at least 85% power to detect an improvement of at least 8% in overall SVR12 rate from the performance goal of 88%, by using a 2-sided exact 1-sample binomial test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

2.1. Post HCV Treatment Week 4 Analysis

A post HCV treatment Week 4 analysis will be conducted for administrative purposes after all subjects have completed the post HCV treatment Week 4 visit or prematurely discontinued from the study. All safety and efficacy data through the post HCV treatment Week 4 visit will be included. There will be no changes to the study design, study conduct, or the sample size as a result of this administrative analysis.

2.2. Final Analysis (SVR12 Analysis)

The analysis for the primary endpoint SVR12 will occur after all subjects have either completed the study, including the 30-Day Follow-Up Visit, or prematurely discontinued from the study, outstanding data queries have been resolved, and the database has been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviate (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listing will be presented for all subjects in the All Randomized analysis set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The treatment group to which subjects were randomized will be used in the listings.

In general, age (in years) on the earliest date of the first dose of study drug, including E/C/F/TAF, F/R/TAF, and LDV/SOF, will be used for presentation in listings. For randomized but never dosed subjects, age on the date of randomization will be used. For screen failures, age on the date of the informed consent was signed will be used. If only birth year is collected on the eCRF, “01 January” will be used for the unknown birth day and month for the purpose of age calculation, similarly, if only birth year and month are collected on the eCRF, “01” will be used for the unknown birth day for the purpose of age calculation.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or planned completion of study drug.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all subjects who are randomized into the study. This is the primary analysis set for by-subject listings except for HCV efficacy endpoint listings, which are based on HCV Full Analysis Set defined in Section 3.1.2.2.

3.1.2. Efficacy Analysis Sets

For this HIV/HCV-coinfection study, the data will be analyzed to assess the treatment efficacy to both HIV and HCV. Therefore, efficacy analysis sets will be defined separately for the HIV drugs, E/C/F/TAF and F/R/TAF, and the HCV drug, LDV/SOF.

3.1.2.1. HIV Full Analysis Set

The **HIV Full Analysis Set (HIV FAS)** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of HIV study drug, E/C/F/TAF or F/R/TAF. Subjects will be grouped according to the treatment to which they were assigned at randomization. For the HIV FAS, all efficacy data, including data collected after the last dose of HIV study drug, will be included, unless specified otherwise. This is the primary analysis set for the efficacy analyses of HIV study drug.

3.1.2.2. HCV Full Analysis Set

The **HCV Full Analysis Set (HCV FAS)** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of HCV study drug, LDV/SOF. Subjects will be grouped according to the treatment to which they were assigned. For the HCV FAS, all efficacy data, including data collected after the last dose of HCV study drug, will be included, unless specified otherwise. This is the primary analysis set for the efficacy analyses of LDV/SOF.

3.1.3. Safety Analysis Sets

3.1.3.1. Safety Analysis Set

The **Safety Analysis Set (SAF)** will include all subjects who (1) are randomized into the study and (2) have received at least 1 dose of study drug (E/C/F/TAF, F/R/TAF, or LDV/SOF). All safety data collected up to 30 days after permanent discontinuation of all study drugs will be included in the safety summaries, unless specified otherwise. This is the primary analysis set for safety analyses of the whole study.

3.1.3.2. Part 2 Safety Analysis Set

The **Part 2 Safety Analysis Set (Part 2 SAF)** will include all subjects who entered Part 2 of the study and received at least one dose of study drug LDV/SOF. All safety data collected up to permanent discontinuation of all study drugs (E/C/F/TAF, F/R/TAF, and LDV/SOF) will be included in the safety summaries, unless specified otherwise. This is the analysis set for safety analyses of Part 2 of study.

3.1.4. Pharmacokinetic Analysis Set

The **PK analysis Set** will include all subjects who (1) are randomized into the study, (2) have received at least 1 dose of study drug, and (3) have at least 1 nonmissing PK concentration value for any analyte of interest reported by PK lab. The PK analysis set will be used for listing of PK concentrations.

3.2. Subject Grouping

For analyses based on the All Randomized Analysis Set, the HIV FAS, and the HCV FAS, subjects will be grouped by the HIV and HCV treatment combination to which they were randomized (E/C/F/TAF + LDV/SOF or F/R/TAF + LDV/SOF).

For other analyses, subjects will be grouped by actual treatments received:

- In analyses of data collected during Part 1 when LDV/SOF is not yet administered, subjects will be grouped by the actual HIV treatment received (E/C/F/TAF or F/R/TAF);
- In other analyses, subjects will be grouped by the combination of actual treatment received (E/C/F/TAF + LDV/SOF or F/R/TAF + LDV/SOF).

The actual treatment received will differ from the randomized treatment only when the actual treatment received differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Randomization was stratified by race (black or non-black) to provide balance across treatment groups.

3.4. Examination of Subject Subgroups

3.4.1. Subject Subgroups for Efficacy

The SVR endpoints SVR4 and SVR12 will be analyzed for the following subject subgroups:

- Age group (< 65 years, ≥ 65 years) at Part 2 Baseline as defined in Section 3.8.1
- Sex (male, female)
- Race (black, non-black)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- HCV RNA ($< 800,000$ IU/mL, $\geq 800,000$ IU/mL) at Part 2 Baseline
- Body mass index (BMI, < 30 kg/m², ≥ 30 kg/m²) at Part 2 Baseline
- Alanine aminotransferase (ALT, $\leq 1.5 \times$ ULN, $> 1.5 \times$ ULN) at Part 2 Baseline
- Adherence to SOF/LDV ($< 80\%$, $\geq 80\%$)
- Cirrhosis (presence, absence)
- Prior HCV treatment experience (treatment naive, treatment experienced)
- HCV study treatment status (completed, prematurely discontinued)

The proportion of subjects with HIV-1 RNA < 50 copies/mL 24 weeks after the start of HIV study drug determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015} will be analyzed for the following subject subgroups (see Section 6.2.2.2 for details):

- Age (< 50 years, ≥ 50 years) at Study Baseline as defined in Section 3.8.1.
- Sex (male, female)
- Race (black, non-black)
- HIV study drug adherence (< 95%, ≥ 95 %; based on adherence up to Post HCV Treatment Week 4 visit)

3.5. Multiple Comparisons

The study has defined a single primary endpoint of SVR12, which will only be analyzed at the Post HCV Week 12 analysis. Therefore, there is no multiple comparison issue.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window.

In general, values for missing data (including all safety data) will not be imputed, except for the imputation rules described (or referenced) below.

3.6.1.1. Missing Dates

For missing last dosing date of study drug, imputation rules are described in Section 3.8.1. The handling of missing or incomplete dates for AE onset is described in Section 7.2.5.2, and for prior (or disease-specific prior) and concomitant medications in Section 7.4.2.

3.6.1.2. Missing HCV RNA

For analyses of categorical HCV RNA data, missing posttreatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA data will be imputed up to the time of the last dose of LDV/SOF (for on-treatment displays). That is, if study days associated with the date of the last dose of LDV/SOF is greater than or equal to the lower bound of an HCV RNA analysis window, and the on-treatment value at the visit is missing, then the value will be

imputed. If the study days associated with the LDV/SOF last dose date is less than the lower bound of an HCV RNA analysis window then the on-treatment value at that visit will remain missing.

If imputation is needed following rules above, it will be proceed as below:

- If an HCV RNA data point is missing and is preceded and followed in time by values that are less than the lower limit of quantitation (LLOQ) target not detected (TND) (ie, “< LLOQ TND”), then the missing data point will be set to “< LLOQ TND”.
- If an HCV RNA data point is missing and preceded and followed by values that are “< LLOQ detected”, or preceded by “< LLOQ detected” and followed by “< LLOQ TND”, or preceded by “< LLOQ TND” and followed by “< LLOQ detected”, then the missing value will be set to “< LLOQ detected”.
- In above situations the data point will be termed a bracketed success; otherwise, the data point will be termed a bracketed failure (ie, \geq LLOQ detected).
- If a data point is missing and is not bracketed, the missing data point will also be termed a failure (ie, \geq LLOQ detected).

For analyses of continuous HCV RNA data, when and only when a missing HCV RNA value is imputed as < LLOQ TND or < LLOQ detected according to the imputation rule described above, the corresponding continuous value will be imputed to LLOQ – 1 IU/mL. No other imputation will be performed for continuous HCV RNA data.

3.6.1.3. Missing HIV-1 RNA

If an HIV-1 RNA data point is missing at a visit for categorical analyses, the following 2 methods will be used for imputing missing HIV-1 RNA values:

- Missing = Failure (M = F): In this approach, all missing data will be treated as HIV-1 RNA ≥ 50 copies/mL.
- Missing = Excluded (M = E): In this approach, all missing data will not be imputed and will be excluded from the analysis.

No imputation will be performed for HIV-1 RNA data for continuous analyses.

3.6.1.4. Missing CD4+ Cell Count

If a CD4+ cell count data point is missing at a visit, it will be imputed using the last observation carried forward (LOCF) method. The algorithm for LOCF is as follows:

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-treatment value (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug) observed before the analysis visit window that has the missing value.
- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no nonmissing postbaseline observation collected prior to that visit.

3.6.1.5. Missing Patient Reported Outcomes

For patient reported outcome (PRO) data, including the HIV Visual Analogue Scale (VAS), HIV Treatment Satisfaction questionnaire (HIV-TSQ) status form and change form, the Short Form Health Survey (SF-36), the Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and the Work Productivity and Activity Impairment: Hepatitis C (WPAI: Hep C) questionnaire, missing data at on-treatment visits, and posttreatment follow-up Week 12 (FU-12) visit will not be imputed, unless otherwise specified.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis processes. In general, all data will be included in the analyses. No sensitivity analyses to evaluate the impact of outliers on efficacy or safety outcomes are planned unless specified otherwise for specific measures.

3.7. Data Handling Conventions and Transformations

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows except for serum cystatin C and urine creatinine:

- A value that is 1 unit less than the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “< x” (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “> x” (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of “≤ x” or “≥ x” (where x is considered the LOQ).

For serum cystatin C, a value of “< 0.10” is handled as a missing value in summary and in the calculation of eGFR. For urine creatinine, a value of “< 1” is handled as a missing value in its summary and the calculation of related ratios.

The COBAS[®] Ampliprep/COBAS[®] TaqMan[®] HCV Quantitative Test v2.0 for use with the High Pure System was used to determine HCV RNA results in this study. The LLOQ of the assay is 15 IU/mL.

When the calculated IU/mL is within the linear range of the assay, then the result will be reported as the “<<numeric value>> IU/mL”. This result will be referred to in this document as the numeric result or as “≥ LLOQ detected” for categorical result.

When HCV RNA is not detected, the result is reported as “HCV RNA not detected” or “target not detected”. This result will be referred to in this document as “< LLOQ target not detected” or “< LLOQ TND”.

When the HCV RNA IU/mL is < LLOQ of the assay, the result is reported as “< 15 IU/mL HCV RNA detected”. This result will be referred to in this document as “< LLOQ detected”.

The overall category of HCV RNA < LLOQ includes “< LLOQ TND” and “< LLOQ detected.”

For numerical HCV RNA data, values below LLOQ will be set to the LLOQ – 1 IU/mL. HCV RNA values returned as “target not detected” will also be set to LLOQ – 1 IU/mL.

Logarithmic (base 10) transformations will be applied to HIV-1 RNA and HCV RNA for numerical analyses. HIV-1 RNA results of ‘No HIV-1 RNA detected’ and “< 20 cp/mL HIV-1 RNA Detected” will be imputed as 19 copies/mL for analysis purposes. HCV RNA results of “< 15 IU/mL HCV RNA detected” or “No HCV RNA detected” will be imputed as 14 IU/mL for analysis purposes.

Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as “BLQ” in the concentration data listing.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day 1, or the **first dose date of the randomized HIV study drug**, is defined as the day when the first dose of the randomized F/TAF-based regimen (ie, E/C/F/TAF or F/R/TAF) is taken, as recorded on the Study Drug Administration eCRF form.

Study Days will be calculated from Study Day 1 and derived as follows:

- For days on or after the Study Day 1 date: Assessment Date – Study Day 1 date + 1
- For days prior to the Study Day 1: Assessment date – Study Day 1 date.

Part 2 Day 1, or the **first dose date of LDV/SOF**, is defined as the day when the first dose of HCV study drug (ie, LDV/SOF) is taken, as recorded on the Study Drug Administration eCRF form.

Part 2 Days are calculated from Part 2 Day 1 and derived as follows:

- For days on or after the Part 2 Day 1 date: Assessment Date – Part 2 Day 1 date + 1
- For days prior to the Part 2 Day 1: Assessment date – Part 2 Day 1 date.

Last Dose Date of HIV Study Drug is the latest of the study drug end dates of E/C/F/TAF or F/R/TAF, recorded on the Study Drug Administration eCRF form with “Permanently Withdrawn” box checked for subjects who prematurely discontinued or completed the randomized HIV study drug according to the Study Drug Completion eCRF.

Last Dose Date of LDV/SOF is the latest of the LDV/SOF end dates recorded on the Study Drug Administration eCRF form with “Permanently Withdrawn” box checked for subjects who prematurely discontinued or completed LDV/SOF according to the Study Drug Completion eCRF.

If last dose date is missing (eg, only year of last dose date is known or completely missing due to lost to follow-up) for subjects who prematurely discontinued or completed study drug (E/C/F/TAF, F/R/TAF, LDV/SOF) by the data finalization date, the latest of the study drug start dates and end dates for that drug, the clinical visit dates and the laboratory visit dates (post HCV treatment visits and unscheduled visits will not be included for LDV/SOF, 30-day follow-up visit will not be included for any study drug), will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications for imputation rule details.

Last Study Date is the latest of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates including the 30-day follow-up visit date for subjects who prematurely discontinued study or who completed study according to Study Completion eCRF.

Study Baseline Value is defined as the last value obtained on or prior to Study Day 1 for all assessments.

Part 2 Baseline value is defined as the last value obtained on or prior to LDV/SOF Day 1 for all safety assessments in Part 2 and HCV RNA in Part 2.

In general, the baseline value will be the last nonmissing value on or prior to the first dose date of study drug.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to study analysis windows, starting from Study Day 1.

In addition, for Part 2 safety analyses and LDV/SOF efficacy analyses, Part 2 analysis window will be assigned to observations except HIV-1 RNA, CD4 cell count, and CD4%, starting from Part 2 Day 1.

No analysis window will be defined for ECG data, given 12-Lead ECG is only planned for Screening and ESDD visits.

3.8.2.1. Study Analysis Windows

The study analysis windows for HIV-1 RNA, CD4+ cell count, CD4 % are provided in Table 3-1. Note that, in convenience of HIV efficacy analyses, the visit ID of study analysis windows are named as Weeks 24 and 32 instead of post HCV Treatment Weeks 4 and 12, and these study analysis windows are assigned relative to Study Day 1.

Table 3-1. Study Analysis Windows for HIV-1 RNA, CD4+ Cell Count, and CD4 %

Visit ID	Nominal Day	HIV-1 RNA	CD4+ Cell Count and CD4 %
Baseline		≤ 1	≤ 1
Week 4	28	[2, 35]	[2, 42]
Week 6 ^a	42	[36, 49]	N/A ^b
Week 8	56	[50, 70]	[43, 70]
Week 12	84	[71, 98]	[71, 98]
Week 16	112	[99, 126]	[99, 126]
Week 20	140	[127, 154]	[127, 154]
Week 24	168	[155, 196]	[155, 196]
Week 32	224	≥ 197	≥ 197

a Only HIV-1 RNA is planned for Week 6 assessment;

b N/A = not applicable;

The analysis windows for weight, vital signs, metabolic assessments, laboratory tests, and bone and renal biomarkers collected up to the last dose date of LDV/SOF + 3 days are provided in Table 3-2.

Table 3-2. Study Analysis Windows for HCV RNA^a, Weight, Vital Signs^b, Metabolic Assessments, and Laboratory Tests^c

Visit ID	Nominal Day	HCV RNA ^d	Laboratory Tests, Weight, and Vital Signs	Fasting Glucose and Lipid Panel ^d	Bone and Renal Biomarkers ^e
Baseline		≤ 1	≤ 1	≤ 1	≤ 1
Week 4	28	N/A	[2, 42]	N/A	[2, 42]
Week 8	56	≥ 2	[43, 70]	[2, 98]	[43, 70]
Week 12	84	N/A	[71, 98]	N/A	[71, 112]
Week 16	112		[99, 126]		N/A
Week 20	140		≥ 127	≥ 99	≥ 113

a For HCV RNA, this analysis window will be applied to data collected up to the first dose date of LDV/SOF only. Therefore, no Weeks 12-20 study analysis window is assigned to HCV RNA;

b Vital signs include resting blood pressure, pulse, respiratory rate and temperature;

- c Laboratory tests include chemistry, hematology, and coagulation profiles, estimated GFR, urinalysis and urine chemistry (except urine albumin), and urine pregnancy test. Note that visit schedule of urine protein to creatinine ratio (UPCR) is same as that of urine chemistry;
- d Lipid panel includes total cholesterol, HDL, direct LDL, triglycerides.
- e Bone and renal biomarkers include parathyroid (PTH) and serum OH-25 vitamin D; retinol binding protein, beta-2-microglobulin, and urine albumin. Note that visit schedule of urine albumin to creatinine ratio (UACR) is the same as that of urine albumin.

For assessments of HCV RNA, weight, vital signs, metabolic assessments, laboratory tests, and bone and renal biomarkers, data collected after the last dose date of LDV/SOF + 3 days are considered post LDV/SOF data. The study analysis window for post LDV/SOF data will be calculated from the last dose date of LDV/SOF (ie, FU Day = collection date – the last dose date of LDV/SOF) as shown in Table 3-3.

Table 3-3. Analysis Windows^a for Post LDV/SOF Data from HCV RNA, Weight, Vital Signs, Metabolic Assessments, and Laboratory Tests

Visit ID	Nominal FU Day	HCV RNA	Laboratory Tests, Weight, and Vital Signs	Fasting Glucose and Lipid Panel	Bone and Renal Biomarkers
FU-4 ^b	28	[21, 69]	[4, 69]	N/A	N/A
FU-12	84	[70, 146]	[70, 146]	[4, 147]	[4, 147]

a This analysis window will be applied to data collected after the last dose date of LDV/SOF + 3 days;

b FU-x visit = post-HCV Treatment Week x follow-up visit.

3.8.2.2. Part 2 Analysis Windows for HCV RNA and Part 2 Safety Data

For clarity of by-visit summary, the visit IDs of Part 2 analysis windows corresponding to the protocol planned visits Week 8, Week 12, Week 16, and Week 20 are renamed to Part 2 Baseline, Week 4, Week 8, and Week 12 respectively, as counted starting from Part 2 Day 1. Data of HCV RNA and safety assessments collected up to the last dose date of LDV/SOF + 3 days are considered to be **on-LDV/SOF data**. The Part 2 analysis windows for on-LDV/SOF HCV RNA, weight, vital signs, metabolic assessments, laboratory tests, and bone and renal biomarkers are provided in Table 3-4.

Table 3-4. Part 2 Analysis Windows^a for On LDV/SOF Data from HCV RNA, Weight, Vital Signs, Metabolic Assessments, and Laboratory Tests

Visit ID	Nominal LDV/SOF Day ^b	HCV RNA, Laboratory Tests, Weight, and Vital Signs	Fasting Glucose and Lipid Panel	Bone and Renal Biomarkers
Part 2 Baseline		≤ 1	≤ 1	≤ 1
Week 4	28	[2, 42]	N/A	[2, 56]
Week 8	56	[43, 70]		N/A
Week 12	84	≥ 71	≥ 2	≥ 57

a This analysis window will be applied to data collected up to the last dose date of LDV/SOF + 3 days;

b This analysis window will be calculated from Part 2 Days defined in Section 3.8.1.

The Part 2 analysis windows for post LDV/SOF data from HCV RNA, weight, vital signs, metabolic assessments, laboratory tests, and bone and renal biomarkers is the same as the study analysis windows specified in Table 3-3.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require one value per analysis window. When a single value is needed, the following rule(s) will be used:

If multiple nonmissing numeric observations exist in a window, records will be chosen as follows:

- For both Study and Part 2 baselines, the last available record on or prior to the dates of the first dose dates of HIV and HCV study drugs, respectively, will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic mean) will be used for the baseline value, except for HIV-1 RNA (see below).
- For postbaseline visits:
 - For CD4+ cell count, CD4%, and post LDV/SOF HCV RNA, the record(s) collected on the latest day in the window will be selected for analysis.
 - For other numeric observations (eg, except HIV-1 RNA, HCV RNA, CD4+ cell count, and CD4%), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.
 - For any numeric observations except HIV-1 RNA, If there is more than 1 record on the selected day, the average (arithmetic mean) will be taken.
- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both “HIV RNA Taqman 2.0” and “HIV RNA Repeat” (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the “HIV RNA Repeat” will be selected for analysis purposes; otherwise, if there are multiple “HIV RNA Taqman 2.0” records with the same collection time, the geometric mean will be taken for analysis purposes.

If multiple valid nonmissing categorical observations exist in an analysis window, records will be selected as follows:

- For baselines, the last available record on or prior to the first dose dates of study drugs will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal).
- For postbaseline visits, follow the same rules described above for postbaseline numeric observations, except that if there are multiple records with the same time or no time recorded on the same day, the value with the highest severity will be selected (eg, abnormal will be selected over normal).

PROs do not apply to above since no analysis window is assigned. For each nominal visit, if multiple observations exist, records will be set to missing.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects randomized at each country and by each investigator will be summarized by treatment group (E/C/F/TAF + LDV/SOF or F/R/TAF + LDV/SOF) and overall using the Safety Analysis Set. Similarly, the number and percentage of subjects enrolled in the randomization stratum of race (black, non-black) will also be summarized by treatment group and overall, using the Safety Analysis Set.

4.1.2. Disposition of Subjects

The summary of subject disposition will be provided by treatment group and overall. This summary will present the number and/or percentage of subjects screened, screen failure subjects who are not randomized, subjects who met all eligibility criteria and are not randomized, subjects randomized, subjects randomized but not treated, subjects in the Safety Analysis Set and Part 2 Safety Analysis Set, and subjects in the HIV FAS and HCV FAS.

In addition, the number and percentage of subjects meeting the following criteria will be summarized:

- Prematurely discontinued HIV study drug in Part 1 of the study (with summary of reasons for discontinuing treatment)
- Entered Part 2 of the study by starting LDV/SOF dosing while still on HIV study drug
- Prematurely discontinued LDV/SOF in Part 2 of the study (with summary of reasons for discontinuing treatment)
- Completed LDV/SOF treatment in Part 2 of the study
- Completed HIV study drug in Part 2 of the study
- Prematurely discontinuing HIV study drug in Part 2 of the study (with summary of reasons for discontinuing treatment)
- Completed study including the 12-week-follow-up period for HCV treatment
- Prematurely discontinued from the study including the 12-week-follow-up period for HCV treatment (with summary of reasons for discontinuing the study)

The denominator for the percentage of subjects in each category will be the number of subjects in the Safety Analysis Set.

No inferential statistics will be generated. A data listing of reasons for premature study drug (E/C/F/TAF, F/R/TAF, LDV/SOF) discontinuation will be provided. A figure of disposition of subjects will also be provided.

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to each study drug (E/C/F/TAF, F/R/TAF, LDV/SOF) will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to 1 decimal place, eg, 4.5 weeks). If subjects are still on study drug, the latest of the study drug start dates and end dates, the clinical visit dates, and laboratory visit dates, excluding the 30-day follow-up visit date (and the post HCV treatment Week 4 and 12 visit dates and unscheduled visit dates for LDV/SOF only), will be used to impute the last dose date for the calculation of the duration of study drug exposure.

Duration of exposure to study drugs will be summarized by treatment group for all study drugs and overall for LDV/SOF, using descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum). In addition, for E/C/F/TAF and F/R/TAF, the number and percentage of subjects in the following categories will be summarized: ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 16 weeks (112 days), ≥ 20 weeks (140 days), ≥ 24 weeks (168 days), and ≥ 32 weeks (224 days); for LDV/SOF, the number and percentage of subjects in the following categories will be summarized: ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), and ≥ 12 weeks (84 days).

Summaries will be provided for HIV study drug using the Safety Analysis Sets, and for LDV/SOF using Part 2 Safety Analysis Set. No inferential statistics will be provided.

Time to premature discontinuation of HIV study drugs will be analyzed using the Kaplan-Meier (KM) method by treatment group, based on the Safety Analysis Sets. The log rank test will be used to compare the difference in study drug exposure between the two treatment groups.

4.2.2. Adherence to Study Drug

Study drug regimen adherence will be computed based on pill counts. The numbers of pills of study drug (E/C/F/TAF, F/R/TAF, or LDV/SOF) dispensed and returned are captured on Study Drug Accountability eCRF.

4.2.2.1. Adherence to HIV Study Drug

Adherence (%) of HIV study drug (E/C/F/TAF and F/R/TAF) will be calculated as follows:

$$\begin{aligned}\text{Adherence (\%)} &= 100 \times \frac{\text{Total No. of pills taken}}{\text{Total No. of pills prescribed}} \\ &= 100 \times \frac{\sum \text{No. of pills taken at each dispensing period}^{[1]}}{\sum \text{No. of pills prescribed at each dispensing period}^{[2]}}\end{aligned}$$

- [1] Number of pills taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of pills prescribed for the study drug multiplied by **the duration of treatment** at the dispensing period of the same dispensing date, and (b) the number of pills taken for the study drug (number of pills dispensed minus the number of pills returned). Total number of pills taken is determined by summing the number of pills taken for each study drug contained in the study drug regimen from all evaluable dispensing periods.
- [2] Number of pills prescribed at a distinct dispensing period for a study drug is calculated as the daily number of pills prescribed for the study drug multiplied by the **duration of treatment** at the dispensing period of the same dispensing date. Total number of pills prescribed is determined by summing the number of pills prescribed for each study drug contained in the study drug regimen from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) **next pill dispensing date** of the study drug, minus dispensing date of the study drug.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with “Yes” answered for “Was the Bottle returned?” question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Descriptive statistics for overall and Week 24 adherence for HIV study drug (n, mean, SD, median, Q1, Q3, minimum and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by treatment group and overall for subjects who return at least 1 bottle of HIV study drug and have calculable adherence during the study in the Safety Analysis Set. Week 24 adherence will be calculated from HIV drug dispensing records up to Week 24 (exclusive).

4.2.2.2. Adherence to LDV/SOF

The presumed total number of LDV/SOF tablets administered to a subject will be determined by the data collected on the drug accountability eCRF using the following formula:

$$\begin{aligned}\text{Total Number of Doses Administered} &= \\ &= \left(\sum \text{No. of LDV/SOF Tablets Dispensed} \right) - \left(\sum \text{No. of LDV/SOF Tablets Not Administered} \right)\end{aligned}$$

The level of adherence to the study drug will be assessed based on the total amount of study drug administered relative to the total amount of study drug prescribed at LDV/SOF Day 1.

The level of adherence will be expressed in percentage using the following formula:

$$\text{Level of Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Prescribed at Baseline}} \right) \times 100$$

Note: If calculated adherence is greater than 100%, the result will be set to 100%.

In this study, the total amount of LDV/SOF FDC (90 mg/400 mg) prescribed for 12 weeks will require 84 tablets.

Subjects who prematurely discontinue study drug for lack of efficacy (ie, virologic failure) will have the total amount of study drug prescribed calculated up to the first date when virologic failure criteria were met. For virologic failure confirmed by 2 consecutive measurements the date of the first measurement will be used. If there are study drug bottles dispensed on or after the subject first met virologic failure criteria, these bottles will not be included in the calculation of adherence. If a bottle is dispensed and the bottle is returned empty, then the number of tablets returned will be entered as zero. If a bottle is dispensed but not returned (missing), the number of tablets taken from that bottle will be counted as zero.

Descriptive statistics for the level of LDV/SOF adherence (n, mean, SD, median, Q1, Q3, minimum and maximum) with the number and percentage of subjects belonging to adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90%) will be provided by treatment group and overall for the Part 2 Safety Analysis Set. No inferential statistics will be provided.

A separate by-subject listing of study drug administration and drug accountability will be provided by subject ID number and visit (in chronological order).

4.3. Protocol Deviations

A by-subject listing will be provided for those subjects who violate at least one inclusion or exclusion criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

Subjects who received the study drug other than their treatment assigned at randomization will be listed with the start and stop dates that they received incorrect study treatment.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic data (age, sex, race, and ethnicity) and baseline characteristics (body weight, height, BMI) will be summarized by treatment group and total at study baseline, using Safety Analysis Set; and by treatment group and total for each HCV genotype (1a, 1b, and other if applicable) and overall at Part 2 baseline, using Part 2 Safety Analysis Set. Continuous data will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and categorical data will be summarized by the number and percentage of subjects. Age is calculated as age in years. In addition, age categories (< 50 , $50 - < 65$, and ≥ 65 years) and BMI categories (< 30 and ≥ 30) will be summarized similarly.

In summary of demographic data at the study baseline, for continuous data, a 2-sided Wilcoxon rank sum test will be used to compare the two treatment groups; for categorical data, the Cochran-Mantel-Haenszel (CMH) test (general association statistic for nominal data and row means scores differ statistic for ordinal data) will be used to compare the two treatment groups.

5.2. Baseline Disease Characteristics

The following study baseline disease characteristics will be summarized for Safety Analysis Set by treatment group and overall, using data collected prior to or on **Study Day 1**:

- HIV-1 RNA categories (copies/mL): (a) < 50 , (b) ≥ 50
- CD4+ cell count (/ μ L)
- CD4+ cell count categories (/ μ L): (a) < 50 , (b) ≥ 50 to < 200 , (c) ≥ 200 to < 350 , (d) ≥ 350 to < 500 , and (e) ≥ 500
- CD4 percentage (%)
- HIV risk factors (mode of infection)
- HIV disease status
- eGFR_{CG} at Study Baseline (mL/min)
- Duration of prior ARV treatment (years)
- Log₁₀ HCV RNA at Study Baseline (log₁₀ IU/mL)
- HCV RNA Category at Study Baseline: (a) $< 800,000$ IU/mL; (b) $\geq 800,000$ IU/mL

In summary of disease characteristics at the study baseline, for categorical data, the Cochran-Mantel-Haenszel (CMH) test (general association statistic for nominal data, and row means scores differ statistic for ordinal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

The following Part 2 baseline disease characteristics will be summarized for Part 2 Safety Analysis Set by treatment group and total within each HCV genotype (1a, 1b, and other if applicable) and overall, using data collected prior to or on **Part 2 Day 1**:

- Log_{10} HCV RNA at Part 2 Day 1 (log_{10} IU/mL)
- HCV RNA Category at Part 2 Day 1: (a) $< 800,000$ IU/mL; (b) $\geq 800,000$ IU/mL
- IL28B
- Cirrhosis
- Cirrhosis determination method
- ALT at Part 2 Baseline
- ALT category at Part 2 Baseline: (a) $\leq 1.5 \times \text{ULN}$; (b) $> 1.5 \times \text{ULN}$
- Prior HCV treatment experience: (a) treatment-naïve; (b) treatment-experienced
- eGFR_{CG} at Part 2 Baseline (mL/min)

In summary of disease characteristics at Part 2 baseline, no between treatment p-value will be calculated.

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

A by-subject listing of disease-specific medical history will be provided by subject ID number (in ascending order) and medical history of abnormalities (in chronological order).

6. EFFICACY ANALYSES

The efficacy analyses include analyses of both HCV study drug (LDV/SOF) efficacy and HIV study drug (E/C/F/TAF and F/R/TAF) efficacy. The analysis of HCV efficacy endpoints will use HCV FAS, and the analysis of HIV efficacy endpoints will use HIV FAS.

In efficacy analysis, HCV efficacy data (HCV RNA) collected from the first dose date of LDV/SOF up to the last dose date of LDV/SOF + 3 days are considered **on-HCV-treatment** data; HIV efficacy data (HIV-1 RNA, CD4+ cell count, and CD4%) collected from the first dose date of HIV study drug up to the last dose date of HIV study drug + 1 day are considered **on-HIV-treatment** data.

6.1. Primary Efficacy Endpoint

6.1.1. Definition of Primary Efficacy Endpoint

The primary efficacy endpoint is SVR12 defined as HCV RNA < LLOQ 12 weeks after discontinuation of LDV/SOF in the HCV FAS. The COBAS[®] AmpliPrep/COBAS[®] TaqMan[®] HCV Quantitative Test, v2.0 will be used to measure HCV RNA. The LLOQ for this assay is 15 IU/mL.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

In the primary efficacy analysis, the SVR12 rate for each of the two treatment groups will be compared to the performance goal of 88% using a 2-sided exact 1-sample binomial test at the 0.025 significant level. The null (H_0) and alternative (H_1) hypotheses used to assess superiority of LDV/SOF relative to the performance goal of 88% are:

H_0 : SVR12 = 88%

H_1 : SVR12 \neq 88%

It is difficult to characterize a single historical control rate for the HIV/HCV coinfection population in this study. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary endpoint, a performance goal was defined as a benchmark against which the efficacy of LDV/SOF will be tested. The benchmark sets a higher comparator bar of 88%. The basis for this benchmark includes the overall trend toward increasing SVR rates in recent years; and the general appeal of using a fixed clinically relevant threshold as a measure of treatment benefit {Weins 2013} of LDV/SOF for the HIV/HCV coinfection population.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The 2-sided exact 1-sample binomial test will be used to test the statistical hypotheses described above. The 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method {Clopper 1934} will be provided for the SVR12 rate for each of the two treatment groups in HCV FAS.

6.1.4. Subgroup Analysis of the Primary Efficacy Endpoint

The point estimates and 95% exact CIs of the SVR12 rates for each treatment group will be displayed by HCV genotype (1a, 1b, and other if applicable) and total for each subgroup outlined in Section 3.4.1.

A Forest plot will graphically present the point estimates and the 2-sided 95% exact CIs of SVR12 rates for each subgroup by treatment group.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

Secondary HCV efficacy endpoint includes the following:

- The percentage of subjects with HCV RNA < LLOQ (ie, < 15 IU/mL) at 4 weeks after cessation of LDV/SOF (SVR 4);

Secondary HIV efficacy endpoints include the following:

- The percentage of subjects with HIV-1 RNA \geq 50 copies/mL 24 weeks after start of the HIV study drug as determined by the US FDA-defined snapshot algorithm {U. S. Department of Health and Human Services 2015}.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.2.1. Analysis of Secondary HCV Endpoint

SVR4 will be analyzed using exactly the same methods used for SVR12, including those used in subgroup analysis for SVR12.

6.2.2.2. Analysis of Secondary HIV Endpoints

The analysis of percentage of subjects with HIV-1 RNA \geq 50 copies/mL 24 weeks after start of the HIV study drug will be determined by US FDA-defined Snapshot algorithm.

US FDA-defined Snapshot Algorithm

The snapshot analysis window is defined as from Study Day 155 to Study Day 196, inclusive. All HIV-1 RNA data collected on-HIV-treatment (ie, data collected up to 1 day after permanent discontinuation of HIV study drug or all available data for subjects who were still on HIV study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL:** this includes subjects who have the last available on-HIV-treatment HIV-1 RNA < 50 copies/mL in the snapshot analysis window
- **HIV-1 RNA \geq 50 copies/mL:** this includes subjects
 - 1) Who have the last available on-HIV-treatment HIV-1 RNA \geq 50 copies/mL in the snapshot analysis window, or
 - 2) Who do not have on-HIV-treatment HIV-1 RNA data in the snapshot analysis window and
 - a) Who discontinue HIV study drug prior to or in the snapshot analysis window due to lack of efficacy, or
 - b) Who discontinue HIV study drug prior to or in the snapshot analysis window due to AE or death and have the last available on-HIV-treatment HIV-1 RNA \geq 50 copies/mL, or
 - c) Who discontinue HIV study drug prior to or in the snapshot analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA \geq 50 copies/mL.
- **No Virologic Data in the Snapshot Window:** this includes subjects who do not have on-treatment HIV-1 RNA data in the snapshot analysis window because of the following:
 - 1) Discontinuation of HIV study drug prior to or in the snapshot analysis window due to AE or death and the last available on-HIV-treatment HIV-1 RNA < 50 copies/mL, or
 - 2) Discontinuation of HIV study drug prior to or in the snapshot analysis window due to reasons other than AE, death, or lack of efficacy and the last available on-HIV-treatment HIV-1 RNA < 50 copies/mL or,
 - 3) Missing data during the window but on HIV study drug.

The flowchart of the US FDA-defined snapshot algorithm is provided in Appendix 2.

Summary and Inference of Virologic Outcomes

The virologic outcomes 24 weeks after start of the HIV study drug for the US FDA-defined snapshot algorithm will be listed.

Note: For treatment-experienced virologically suppressed study population, the US FDA-defined snapshot algorithm classifies subjects who discontinue study drug due to AE or death and have the last available on-HIV-treatment HIV-1 RNA value \geq 50 copies/mL in the “HIV-1 RNA \geq 50 copies/mL” category.

The differences in proportion of subjects with HIV-1 RNA ≥ 50 copies/mL and HIV-1 RNA < 50 copies/mL 24 weeks after start of the HIV study drug between the 2 treatment arms and the corresponding two-sided exact 95% CIs will be calculated based on an unconditional exact methods using 2 inverted 1-sided tests. P-value from the 2-sided Fisher's exact test will also be provided.

The analysis of virologic response (HIV-1 RNA < 50 copies/mL, US FDA-defined snapshot algorithm) 24 weeks after start of the HIV study drug will be performed within each subgroup specified in Section 3.4.1 based on the HIV FAS.

6.3.1. Definition of Tertiary Efficacy Endpoints

Responsibility	Percentage
Current government	85%
Previous government	15%

P
P
D

- PPD
- PPD
- PPD

6.3.2. Analysis of Tertiary Endpoints

PPD

6.3.2.1. Analysis of ALT Normalization

Tables for ALT normalization by visit will use similar methodology to the analyses of HCV RNA < LLOQ, but will use a missing – exclude analysis. Only those subjects with ALT > ULN range at baseline (defined as the last ALT value collected prior to first dose of study drug) will be included in the analysis of ALT normalization.

6.3.2.2. Analysis of HCV RNA < LLOQ while On HCV Treatment

For analyses of HCV RNA < LLOQ by visit while on HCV treatment and during the post LDV/SOF (SVR) follow-up period, subjects will be assigned a value at each visit based on the analysis window specified in Section 3.8.2.1. Missing values will be imputed based on the categorical imputation rules described in Section 3.6.1. The 2-sided 95% exact confidence interval based on the Clopper-Pearson method will be provided for the percentage of subjects with HCV RNA < LLOQ at each visit for each treatment group and overall by HCV genotype (1a and 1b). The overall category for “HCV RNA < LLOQ” will be split into the following 2 subcategories: “< LLOQ TND” for subjects with target not detected and “< LLOQ detected” for subjects with < LLOQ detected in tabular displays.

6.3.2.3. Analysis of HCV RNA (\log_{10} IU/mL)

Summary statistics will be presented for absolute values and change from baseline in HCV RNA (\log_{10} IU/mL) at each visit through EOT. Imputation rules described in Section 3.6.1 will be used to assign HCV RNA values for missing values at a visit that are bracketed by “< LLOQ TND” and/or “< LLOQ detected”. Otherwise, a missing = excluded analysis will be performed.

6.3.2.4. Analysis of HCV Virologic Failure at Post HCV Treatment Weeks 4 and 12

For the SVR4 endpoint analysis, a summary table of the number and percentage of subjects with SVR4, virologic failure (VF), and Other will be created. This summary will be performed for each HCV genotype (1a, 1b, and other if applicable) and overall broken down by treatment group and total. All subjects who achieve SVR4 will be categorized as SVR4. Virologic failure will be descriptively summarized as “on-HCV-treatment virologic failure” and relapse (which will be broken down by study drug completed yes/no). Subjects who do not achieve SVR4 and do not meet criteria for virologic failure will be categorized as Other. The denominator for relapse will be the number of subjects who had HCV RNA < LLOQ on their last observed on-HCV-treatment HCV RNA measurement; otherwise, the denominator will be the number of subjects in the HCV FAS.

The same analysis method will be applied to SVR12 endpoint analysis.

In addition, a summary table of the number and percentage of subjects with HCV RNA < LLOQ and \geq LLOQ at the posttreatment follow-up visit (observed and imputed, with reasons for imputed) for each treatment group will be provided for each posttreatment follow-up visit by HCV genotype and overall. The 2-sided 95% Clopper-Pearson exact CIs will be presented for the overall proportion of subjects with HCV RNA < LLOQ.

6.3.2.5. Analysis of the Proportion of Subjects with HIV-1 RNA \geq 20 copies/mL as Determined by US FDA-defined Snapshot algorithm

The proportion of Subjects with HIV-1 RNA \geq 20 copies/mL as determined by US FDA-defined Snapshot algorithm 24 weeks after start of the HIV study drug will be analyzed using exactly the same method used for the secondary HIV efficacy endpoint with cutoff 50 copies/mL, as specified in Section 6.2.2.2, excluding the subgroup analysis.

6.3.2.6. Analysis of the Proportion of Subjects with HIV-1 RNA < 50 copies/mL (Missing = Excluded and Missing = Failure Approaches)

The proportion of subjects with HIV-1 RNA < 50 copies/mL will also be analyzed using the M = F and M = E for imputing missing HIV-1 RNA values, where the proportions will be expressed as percentages in all tables, listings, and figures.

For both M = F and M = E analyses, the number and percentage of subjects with HIV-1 RNA in the following categories will be summarized:

- < 50 copies/mL
- < 20 copies/mL
 - < 20 Not Detectable
 - < 20 Detectable
- 20 to < 50 copies/mL
 - \geq 50 copies/mL
 - Missing (only applicable for M = F analysis)

The proportion of subjects with HIV-1 RNA < 50 copies/mL as defined by the 2 different missing data imputation methods will be summarized by treatment group and overall. The differences in proportions of subjects with HIV-1 RNA < 50 copies/mL using M = E and M = F imputation methods between the 2 treatment groups and the corresponding two-sided exact 95% CIs will be calculated based on an unconditional exact methods using 2 inverted 1-sided tests. In addition, the 95% CI of the proportion of subjects with HIV-1 RNA < 50 copies/mL within each treatment at each visit will be provided using the Clopper-Pearson Exact method.

For both M = F and M = E analysis, results will be summarized by treatment group for all visits.

6.3.2.7. Analysis of CD4+ Cell Count and CD4 %

Both CD4 cell count and CD4 % will be summarized using observed, on-HIV-treatment data (ie, data collected up to 1 day after permanent discontinuation of HIV study drug or all available data for subjects who are still on HIV study drug) for subjects in the HIV FAS.

The change from baseline in CD4+ cell count will be summarized by visit for each treatment group and over all using descriptive statistics. The differences in changes from baseline 24 weeks after start of HIV study drug in CD4+ cell count between the 2 treatment groups and the associated 95% CI will be constructed using ANOVA models, including treatment group and race as fixed effects.

In addition, the change from baseline in CD4+ cell counts with missing values imputed using the last observation carried forward (LOCF) method will be summarized at each visit based on the FAS. The algorithm for LOCF as follows:

- If a value is missing in an analysis visit window, the missing value will be replaced with the last on-HIV-treatment value (ie, data collected up to 1 day after the last dose date of HIV study drug) observed before the analysis visit window that has the missing value.
- Baseline values will be carried forward to impute the postbaseline value at a specific visit, if there is no nonmissing postbaseline observation collected prior to that visit.

CD4% will be analyzed the same as CD4+ cell count, except that the by-visit summary using LOCF method is not planned for CD4%.

7. SAFETY ANALYSES

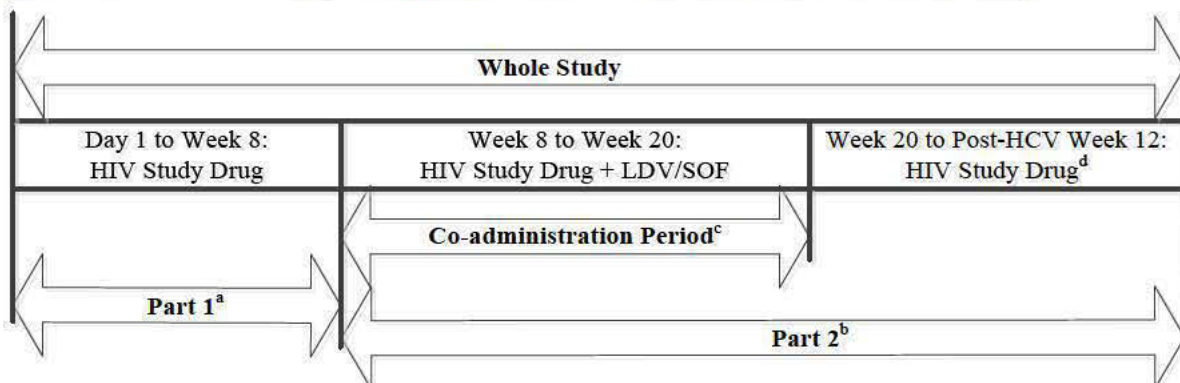
7.1. General Consideration for Safety Analysis

In general, safety data will be summarized for the subjects in the safety analysis set. Safety data collected up to 30 days after permanent discontinuation of all study drugs (including HIV study drug and LDV/SOF) and available data for subject who are still on study drug will be summarized by treatment group and overall, unless specified otherwise. All safety data will be included in listings.

7.1.1. Administration Periods for Safety Analysis

In the 2-part coinfection study, subjects receive different treatments at different periods of the study (Figure 7-1). Four administration periods, Part 1, Part 2, Co-administration, and Whole Study, are defined accordingly in Table 7-1 with start, end, and safety cutoff dates provided.

Figure 7-1. Study Treatments Received in Different Periods of Study



- a In Part 1 of the study, subject receive HIV study drug only.
- b Part 2 is applicable only if subjects took at least one dose of LDV/SOF.
- c Subjects who entered Part 2 receive both LDV/SOF and HIV study drug for at most 12 weeks and this is defined as the co-administration period. The co-administration period is terminated by permanent discontinuation of LDV/SOF or HIV study drug, which ever happens earlier;
- d By the end of co-administration period, if subject permanently discontinued LDV/SOF while still receiving HIV drug, HIV study drug will continue to be administered until the end of Part 2 as planned in protocol. If subject prematurely discontinued HIV study drug while still receiving LDV/SOF, LDV/SOF will continue to be administered until 12 weeks of HCV treatment is completed. If subject permanently discontinued both LDV/SOF and HIV study drug at the same date, no study drug will be administered after the co-administration period until the end of Part 2.

Table 7-1. Start, End, and Safety Cutoff Dates of All Administration Periods

Administration Period	Start Date	End Date	Safety Cutoff Date
Part 1	HIV study drug first dose date	Minimum of HIV study drug last dose date and Part 2 Day 1	End date if subject is ever dosed with LDV/SOF; or end date + 30 days if subject is never dosed with LDV/SOF
Part 2	HCV study drug first dose date if applicable	Maximum of HIV and HCV study drug last dose dates if applicable	30 days after Part 2 period end date
Co-administration	HCV study drug first dose date if applicable	Minimum of HIV and HCV study drug last dose dates if applicable	30 days after Co-administration period end date
Whole Study	HIV study drug first dose date	Maximum of HIV and HCV study drug last dose dates	30 days after Whole Study period end date

Summary of safety data is planned by administration periods as below:

- Adverse events and laboratory abnormalities will be summarized for Part 1, Co-administration, and Whole Study periods respectively.
- By-visit laboratory assessment and vital signs will be summarized for Whole Study and Part 2 periods respectively.
- Concomitant medication will be summarized for Whole Study period only.

7.2. Adverse Events and Deaths

7.2.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset.

7.2.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.2.3. Relationship of Adverse Events to Study Drugs

Related AEs are those for which the investigator answers “Related” to the question “Related to Study Treatment?” in the CRF. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.2.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health (DSPH) Department before data finalization.

7.2.5. Treatment-Emergent Adverse Events

In this study, Treatment-emergent adverse events (TEAEs) are defined for the study treatment subject received during Part 1, Co-Administration, and Whole Study periods separately.

7.2.5.1. Definition of Treatment-Emergent Adverse Events

TEAEs for a given administration period are defined as 1 or both of the following:

- Any AEs with an onset date on or after the start date and no later than the data cutoff date of the administration period as defined in Table 7-1.
- Any AEs leading to study drug premature discontinuation during that administration period (ie, the study drug premature discontinuation date is on or after the start date of the period and no later than the period end date as defined in Table 7-1).

7.2.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the start date of an administration period, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent during that period. The event is considered treatment emergent during an administration period if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the start date of the period, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the data cutoff date of the period

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date on or after the start date of an administration period, will be considered to be treatment emergent of the period. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the start date of an administration period will be considered treatment emergent of the period.

7.2.6. Summaries of Adverse Events and Deaths

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized, using Safety Analysis Sets, by PT and treatment group and overall for each of Part 1, Co-administration, and Whole Study periods respectively. For other AEs described below, summaries will be provided the same as TEAE:

- Any Grade 3 or 4 treatment-emergent AEs
- Any Grade 2, 3, or 4 treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from HIV study drug
- All treatment-emergent AEs that caused premature discontinuation from LDV/SOF (for co-administration and whole study periods only)

A brief, high-level summary of AEs described above will be provided for Safety Analysis Sets, by treatment group and overall, and by the number and percentage of subjects who experienced the above AEs during each of Part 1, Co-administration, and Whole Study periods respectively. Treatment-emergent deaths observed in the study will be also included in this summary.

Treatment-emergent death at an administration period refers to deaths that occurred between the start date of the period and the data cutoff date of the period.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed by PT in descending order of total frequency during Co-administration period. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during each analysis period.

In addition, data listings will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Deaths report
- AEs leading to premature discontinuation of study drug

7.2.7. Additional Analysis of Adverse Events

7.2.7.1. AIDS-Indicator Conditions

On an ongoing basis, AEs will be reviewed for events that might meet the definition of AIDS-indication conditions that are indicative of an AIDS-Defining Diagnoses (see Protocol Appendix 6). The Gilead medical monitor will review the possible AIDS-indication conditions and approve the events that meet the definition. Events that meet the definition of an AIDS-indication condition will be listed.

7.3. Laboratory Evaluations

Summaries of laboratory data will be provided by-visit for both Whole Study and Part 2 periods using Safety Analysis Sets, unless specified otherwise. Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, urinalysis, and urine chemistry separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No inferential statistics will be generated.

7.3.1. Summaries of Numeric Laboratory Results

In summary of numeric laboratory results for Whole Study and Part 2 periods, descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided for each laboratory test specified in the study protocol by treatment group and overall as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

For Whole Study period, the baseline refers to Study Baseline. The postbaseline visits are counted from Study Day 1. For the Part 2 period, the baseline refers to Part 2 Baseline as defined in Section 3.8.1. And the postbaseline visits in Part 2 of the study (Weeks 12, 16, 20) are re-counted from Week 8 visit and presented as Weeks 4, 8, 12 in by-visit summaries of laboratory data.

The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for estimated GFR, ALT, and AST will be plotted using a line plot by treatment group and visit.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Metabolic Assessments

For metabolite assessments, including fasting glucose and the lipid panel (ie, total cholesterol, triglycerides, LDL, HDL, total cholesterol to HDL ratio), only those measurements under fasting status will be summarized by treatment group and overall.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized. The following formula will be used when both serum calcium and albumin results for a given blood draw are available and serum albumin value is < 4.0 g/dL.

- $\text{Calcium corrected for albumin (mg/dL)} = \text{serum calcium (mg/dL)} + 0.8 \times (4.0 - \text{albumin (g/dL)})$

Toxicity grading for calcium will be applied based on the corrected values.

7.3.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (eg, grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be grade 0, except for lipid tests.

For triglycerides, LDL, and cholesterol, the protocol-specified toxicity grading scale is for fasting test values, so nonfasting lipid results (or lipid results without a known fasting status) will not be graded or summarized by toxicity grades.

7.3.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities will be presented for each of Part 1, Co-administration, and Whole Study periods respectively. Treatment-emergent laboratory abnormalities within each administration period will be summarized by treatment group and overall using Safety Analysis Set.

Treatment-emergent laboratory abnormalities in an administration period are defined as values that increase at least one toxicity grade from baseline (Study Baseline for Part 1 and Whole Study periods, Part 2 Baseline for Co-administration period) at any time postbaseline, up to and including the safety cutoff date of the administration period. If the relevant baseline laboratory data are missing, then any abnormality of at least Grade 1 up to the safety cutoff date will be considered treatment emergent in the administration period.

For serum glucose, fasting glucose and nonfasting glucose are graded based on different grading criteria as specified in the protocol. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Since nonfasting glucose was not assessed at Study Baseline, the maximum postbaseline grade instead of treatment-emergent laboratory abnormalities will be summarized for Part 1 and Whole Study period. For consistency, the maximum post Part 2 baseline grade instead of treatment-emergent laboratory abnormalities will be summarized for Co-administration period.

7.3.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities during Part 1, Co-administration, and Whole Study periods will be provided by treatment group and overall for each lab test; subjects will be categorized according to the most severe postbaseline abnormality grade within the administration period for a given lab test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities in an administration period, the denominator is the number of subjects with nonmissing postbaseline values up to safety cutoff date of the period.

A by-subject listing of treatment-emergent Grade 3 or above laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.3.2.3. Postbaseline Liver-Related Laboratory Abnormalities

Liver-related abnormalities that are post Study Baseline within Part 1 and Whole Study periods, and that are post Part 2 Baseline within Co-administration period will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values:

- Aspartate aminotransferase (AST): (a) $> 3 \times \text{ULN}$, (b) $> 5 \times \text{ULN}$, (c) $> 10 \times \text{ULN}$, (d) $> 20 \times \text{ULN}$
- ALT: (a) $> 3 \times \text{ULN}$, (b) $> 5 \times \text{ULN}$, (c) $> 10 \times \text{ULN}$, (d) $> 20 \times \text{ULN}$
- AST or ALT: (a) $> 3 \times \text{ULN}$, (b) $> 5 \times \text{ULN}$, (c) $> 10 \times \text{ULN}$, (d) $> 20 \times \text{ULN}$

- Total bilirubin: (a) $> 1 \times \text{ULN}$, (b) $> 2 \times \text{ULN}$
- Alkaline phosphatase (ALP) $> 1.5 \times \text{ULN}$
- AST or ALT $> 3 \times \text{ULN}$ and total bilirubin: (a) $> 1.5 \times \text{ULN}$, (b) $> 2 \times \text{ULN}$
- AST or ALT $> 3 \times \text{ULN}$, total bilirubin $> 2 \times \text{ULN}$, and ALP $< 2 \times \text{ULN}$

The summary for an administration period will include all postbaseline data up to the safety cutoff date of the period. For individual laboratory test, subjects will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the safety analysis set with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date.

Subjects with AST or ALT $> 3 \times \text{ULN}$, total bilirubin $> 1 \times \text{ULN}$, or ALP $> 1.5 \times \text{ULN}$ will be listed with HCV RNA (\log_{10}).

7.3.3. Renal-Related Laboratory Evaluations

All renal safety data will be analyzed using Safety Analysis Sets, unless otherwise specified.

7.3.3.1. Serum Creatinine and eGFR_{CG}

Baseline, postbaseline and change from baseline in serum creatinine and eGFR_{CG} at each visit will be summarized by treatment group and overall using descriptive statistics for safety periods Part 2 and Whole Study periods, respectively. The following formulae will be used to calculate eGFR :

- Cockcroft-Gault

$$\text{eGFR}_{\text{CG}} (\text{mL/min}) = [(140 - \text{age (years)}) \times \text{weight (kg)} \times (0.85 \text{ if female})] / (\text{SCr (mg/dL)} \times 72),$$

where weight is total body mass in kilograms, and SCr is serum creatinine.

Median (Q1, Q3) of change from baseline in serum creatinine and eGFR_{CG} over time will be plotted by treatment group and overall.

7.3.3.2. Proteinuria by Urinalysis (Dipstick)

The proteinuria by urinalysis (dipstick) toxicity grade (Grade 0 to Grade 3) at each postbaseline visit will be summarized by baseline proteinuria toxicity grade for both treatment groups and overall.

7.3.3.3. Proteinuria by Quantitative Assessment

The baseline, postbaseline, changes from baseline, and percentage change from baseline in urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) will be summarized by visit, treatment group and overall using descriptive statistics.

The number and percentage of subjects with $UPCR \leq 200$ mg/g versus > 200 mg/g {KDIGO Guideline Development Staff 2013} will be summarized by baseline category at each visit.

The number and percentage of subjects with $UACR < 30$ mg/g versus ≥ 30 mg/g {KDIGO Guideline Development Staff 2013} will be summarized by baseline category at each visit.

7.3.3.4. Renal Safety Tests: Urine Retinol Binding Protein (RBP) to Creatinine Ratio and Beta-2-microglobulin to Creatinine Ratio

Baseline, postbaseline, change from baseline and percentage change from baseline in renal safety tests, including urine retinol binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio, will be summarized for both treatment groups and overall, by visit using descriptive statistics.

7.3.3.5. Other Renal Safety Data

Baseline, postbaseline, change from baseline in urine creatinine will be summarized by treatment group and visit using descriptive statistics, for both Whole Study and Part 2 periods.

7.3.4. Bone Laboratory Evaluations

Baseline, postbaseline, and change from baseline in bone biomarkers PTH and serum OH-25 vitamin D will be summarized by treatment group and visit using descriptive statistics, for both Whole Study and Part 2 periods.

7.3.5. Body Weight, Height and Vital Signs

Vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min]) at each visit, and change from baseline at each visit will be summarized for both Whole Study and Part 2 periods using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and overall. The baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug (HIV drug when summarizing for Whole Study period, LDV/SOF when summarizing for Part 2). Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No inferential statistics will be generated.

A by-subject listing of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [°C]) will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI will be provided separately.

7.4. Prior and Concomitant Medications

7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications used prior to, during, or after the study (if collected) will be coded using the GSI-modified World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. All nonstudy drug ARV medications will be listed. No inferential statistics will be provided.

7.4.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications (ie, medications other than study drug that are taken while receiving either LDV/SOF or HIV study drug) will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Use of concomitant medications from Study Day 1 up to the maximum of HIV study drug last dose dates and LDV/SOF last dose date will be summarized (number and percentage of subjects) by treatment group and overall, WHO drug class and preferred name. Multiple drug use (by preferred name) will be counted only once per subject. The summary will be sorted alphabetically by drug class and then by decreasing total frequency within a class.

If the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start (or year of start if month is not recorded) of the medication is after both LDV/SOF last dose date and HIV study drug last dose date
- The month and year of stop (or year of stop if month is not recorded) of the medication is before both LDV/SOF first dose date and HIV study drug first dose date

If the start and stop date of non-ARV medications are complete, the start date is not after both last dose dates of the study drugs and the stop date is not before both first dose date, or the non-ARV medications are marked as ongoing and start date is on or before both last dose date, the non-ARV medications are concomitant.

Summaries of non-ARV concomitant medications will be provided by treatment group and overall, for Whole Study period only. Subjects with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

A listing of safety ECG results will be provided including treatment, assessment date and time, and ECG results.

7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study.

7.7. Changes From Protocol-Specified Safety Analyses

No change from the protocol-specified safety analysis is planned.

8. PHARMACOKINETIC ANALYSES

The following listings will be provided for predose and postdose PK analysis for subjects in the PK analysis set:

- Listing of PK sampling details
- Listing of study drug administration record for PK dosing.

9. PATIENT REPORTED OUTCOMES

The patient reported outcome (PRO) questionnaires include:

- Visual Analog Scale (VAS) adherence questionnaire for HIV study treatment;
- HIV Treatment Satisfaction Questionnaire (HIV-TSQ) (status form assessed at Study Day 1, and change form at other visits)
- Short Form-36 (SF-36) Version 2 Health Survey.
- FACIT-F
- CLDQ-HCV
- WPAI: Hepatitis C

PRO data will be summarized for the subjects in the safety analysis set. All PRO data collected up to 30 days after subjects who permanently discontinued all study drug will be summarized by treatment group.

Unless otherwise stated, multiple responses and out of range responses will be set to missing and missing responses will not be imputed. The PRO data will be listed.

9.1. Analysis of VAS

The VAS (%) absolute value and its change from baseline at Study Baseline, Week 8, Week 20, Week 32 (ie, post HCV treatment Week 4), and End of HIV Treatment (EOT-HIV) will be summarized using descriptive statistics.

Number of days with missed doses in the past 30 days and past 4 days will be summarized categorically (eg, < 2 , 2 to < 4 , 4 to < 6 , ≥ 6 for the past 30 days; 0 and > 0 for the past 4 days) at the same set of visits.

9.2. Analysis of HIV-TSQ

A treatment satisfaction scale total will be calculated as the sum of the responses to the 10 question items on the Status form, ranging from 0 to 60, and on the Change form, ranging from -30 to 30 . If the number of missing responses is ≥ 2 then the treatment satisfaction scale total will be set to missing; otherwise, the missing item scores will be imputed by the average of the non-missing item responses from the same subject at the same visit, and treatment satisfaction scale total will be calculated.

Descriptive summary of the number and percent of subjects with responses to each question and the treatment satisfaction scale total at Study Baseline, Weeks 8, 20, and 32, and EOT-HIV will be provided.

9.3. Analysis of SF-36, FACIT-F, CLDQ-HCV, and WPAI: Hepatitis C

The transformed scale scores (0 to 100 scale) at Study Baseline, Part 2 Baseline (Week 8), Week 20, End of HCV Treatment (EOT-HCV), FU-12, and EOT-HIV will be presented for each of the 8 domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and for the physical component summary and mental component summary. Following changes will also be presented in similar manner:

- Change from Study Baseline at each visit (if applicable),
- change from Part 2 Baseline at Week 20, EOT-HCV, and FU-12,
- change from EOT-HCV at FU-12.

Scoring of the SF-36 scales will be performed as described in Chapter 6 of the SF-36 Health Survey: Manual and Interpretation Guide, Version 2. A Wilcoxon signed rank test will be used to explore within treatment group changes described above.

The same analyses will be carried out for CLDQ-HCV (overall score), FACIT-F (trial outcome index and total score), and WPAI: Hep C (% overall work impairment due to HCV for subjects who worked in the past week and % activity impairment due to hepatitis C for all subjects), except that, EOT-HIV and change from Study Baseline as EOT-HIV will not be presented.

The calculation algorithms for CLDQ-HCV, FACIT-F, and WPAI:Hep C are described in Appendix 3.

For imputation of missing data in the QOL data, please refer to Section 3.6.1.5.

10. REFERENCES

- Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Dec. Biometrika* 1934;26 (4):pp. 404-13.
- KDIGO Guideline Development Staff. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney international. Supplement* 2013;3 (1):v-150.
- U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. *Guidance for Industry*. Silver Spring, MD. November, 2015.
- Weins BL, Lystig TC, Berry SM. Recent Statistical Contributions to Medical Device Development. *Therapeutic Innovation & Regulatory Science* 2013:1-8.

11. SOFTWARE

SAS[®] Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 7.0. Statistical Solutions, Cork, Ireland.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

13. APPENDICES

- Appendix 1. Study Procedure Table
- Appendix 2. Flowchart of US FDA-Defined Snapshot Algorithm (for Switch Study Trial)
- Appendix 3. QOL Score Calculation Algorithms
- Appendix 4. Programming Specification

Appendix 1. Study Procedure Table

	Screening ^a	Day 1 ^b	End of Week ^c Part 1 On Treatment		End of Week ^c – Part 2						30-Day Follow-Up ^d	ESDD ^e
			On Treatment				Post-HCV Treatment					
			4	6	8	12	16	20	4	12		
Written Informed Consent	X											
Medical History	X											
Liver Cirrhosis Determination	X											
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X
Complete Physical Examination	X	X								X		X
Symptom-Directed Physical Examination ^f			X		X	X	X	X	X		X	
Vital Signs & Weight	X	X	X		X	X	X	X	X	X	X	X
Height	X											
12-Lead ECG (performed supine)	X											X
Urinalysis & Urine Chemistry	X	X	X		X	X	X	X	X	X	X	X
Urine Storage Sample		X	X		X	X	X	X	X	X		X
Urine Pregnancy Test ^g		X	X		X	X	X	X	X	X	X	X
Serum Pregnancy Test ^g	X											
Chemistry Profile ^h	X	X	X		X	X	X	X	X	X	X	X
Hematology Profile ⁱ	X	X	X		X	X	X	X	X	X	X	X
Coagulation Assessments ^j	X	X	X		X	X	X	X	X	X		
Metabolic Assessments ^k		X			X			X		X		
CD4+ Cell Count	X	X	X		X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Proviral Genotype ^l	X											
HIV-1 Genotype/Phenotype ^m												X

	Screening ^a	Day 1 ^b	End of Week ^c Part 1 On Treatment		End of Week ^c – Part 2						30-Day Follow-Up ^d	ESDD ^e
			4	6	On Treatment				Post-HCV Treatment			
					8	12	16	20	4	12		
Plasma HCV RNA	X	X			X	X	X	X	X	X	X	X
HCV Genotype & Subtype	X											
HCV IL28B Genotype	X											
HIV, HBV & HCV Serologies ⁿ	X											
Evaluations of Bone & Renal Safety, Inflammation and Platelet and Coagulation Function ^o		X	X		X	X		X		X		X
Plasma Storage Sample ^p		X	X	X	X	X	X	X	X	X		X
Serum Storage Sample ^p		X	X		X	X	X	X	X	X		X
<div></div> PPD		X	X		X			X		X		X
Estimated GFR _{CG} ^r	X	X	X		X	X	X	X	X	X		X
Population PK ^s			X		X	X	X	X				
Health Related Questionnaires ^t		X			X			X		X		X
Randomization		X										
Study Drug Dispensation and Accountability ^u		X	X		X	X	X	X	X	X		X ^v

a Evaluations to be completed within 42 days prior to the Day 1 visit

b Subjects will be dispensed HIV study drugs only at the Day 1 visit; initiation of HIV treatment with the study drugs must take place within 24 hours after the Day 1 visit.

c All study visits are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol specified date through Post-HCV Treatment Week 4 visit, and ± 4 days of the protocol specified date at Post-HCV Treatment Week 12.

d For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used

e Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Refer to Section 6.5.1 of the protocol for management of early study drug discontinuation of Parts 1 and 2.

f Symptom-directed physical examination as needed

g For females of childbearing potential only as defined by Appendix 5 of the protocol. Positive urine pregnancy tests will be confirmed with a serum test.

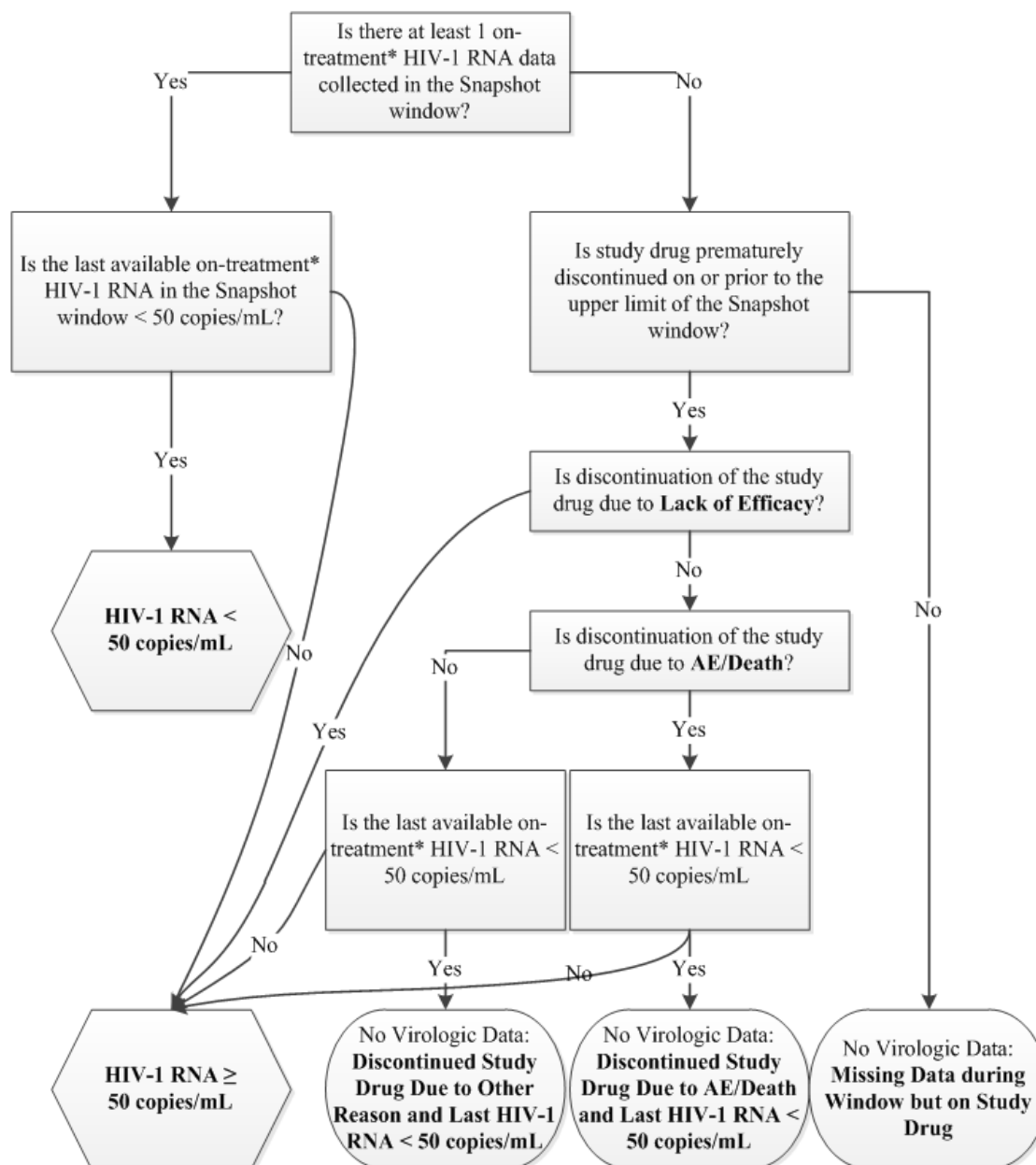
h Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, and uric acid. At visits in which metabolic assessments are to be performed, analyses of glucose will be done as part of the fasting metabolic assessments and not as part of the chemistry profile

i CBC with differential and platelet count

- j Coagulation assessments: International Normalized Ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT)
- k Metabolic assessments (collected fasted, no food or drink, except water, at least 8 hours prior to blood collection): glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides)
- l If a historical genotype report prior to first ARV is not available, or subject has 3 or more prior ARV regimens, whole blood sample for proviral genotype analysis of archived resistance
- m HIV-1 genotype/phenotype resistance testing for subjects with unconfirmed virologic rebound with HIV-1 RNA value ≥ 400 copies/mL
- n Serology testing includes HIV and HCV antibody, and HBV core antibody (HBcAb), surface antibody (HBsAb), surface antigen (HBsAg), e-antibody (HBeAg), e-antibody (HBeAb), and HBV DNA.
- o Blood for bone safety, parathyroid (PTH) and serum OH-25 vitamin D; Inflammation may include cystatin-C, IL-6, hs-CRP, sCD14, sCD163, sTNF-1R, and Lp-PLA2; Platelet and coagulation function may include soluble glycoprotein VI (sGPVI), P-selectin, soluble CD40 ligand, and D-dimer will be collected. Urine for renal safety, including retinol binding protein, beta-2-microglobulin, urine albumin, and urine protein will be collected. Samples will be collected fasted. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state.
- p Plasma storage samples for safety, virology, and/or PK testing. Serum storage samples for possible additional clinical testing.
- q **PPD**
- r Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance (see Section 4.2 of the protocol for details)
- s Two (2) blood samples will be collected: 1) the predose sample should be drawn prior to observed study drug dosing; 2) the postdose sample should be drawn between 15 mins and 4 hours postdose
- t Health related questionnaires: adherence for HIV (VAS), HIV-TSQs – Status version (at Day 1 only), HIV-TSQc – Change version (at all other visits), SF-36, FACIT-F, CLDQ-HCV, and WPAI: Hepatitis C.
- u Part 1: HIV study drugs are dispensed after all Day 1 assessments are completed and randomization occurred, and through the duration of the study.
Part 2: After determination of HIV suppression (< 50 copies/mL) based on the Week 6 HIV-1 RNA value and tolerability of HIV study drugs, LDV/SOF will be dispensed at Weeks 8, 12, and 16 only.
Post-HCV Treatment Week 12: drug accountability only; study drug will not be dispensed at this visit.
- v If subjects discontinue during Part 1, only drug accountability will be performed; study drug will not be dispensed at this visit. In Part 2, if subject discontinues LDV/SOF but still continues with HIV study drug, HIV study drug will be dispensed until the last study visit. If subject discontinues HIV study drug but still continues with LDV/SOF, LDV/SOF will be dispensed. If subject discontinues both HIV and HCV study drugs, only drug accountability will be performed; no dispensation will occur at this visit.

Appendix 2. Flowchart of US FDA-Defined Snapshot Algorithm (for Switch Study Trial)

The following flowchart for US FDA-defined snapshot algorithm is based on the US FDA Guidance on Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for treatment {U. S. Department of Health and Human Services 2015}



* On-Treatment HIV-1 RNA data include all HIV-1 RNA data for subjects who are on-going and HIV-1 RNA data up to 1 day after the last dose date of study drug for subjects who prematurely discontinue or complete study drug.

Appendix 3. QOL Score Calculation Algorithms

CLDQ – HCV

CLDQ-HCV scores are calculated using subject responses to 29 questions in the questionnaire. If R_i is the score for the patient's response to the item i , for $i=1, 2, \dots, 29$ then the 4 domain scores are calculated as follows:

- Activity/Energy (AE) = Mean of $\{R_1, R_3, R_4, R_5, R_7, R_{18}\}$
- Emotion (EM) = Mean of $\{R_6, R_8, R_9, R_{11}, R_{16}, R_{23}, R_{24}, R_{27}, R_{28}\}$
- Worry (WO) = Mean of $\{R_{14}, R_{15}, R_{17}, R_{19}, R_{20}, R_{21}, R_{22}, R_{29}\}$
- Systemic (SY) = Mean of $\{R_2, R_{10}, R_{12}, R_{13}, R_{25}, R_{26}\}$

Here “Mean” is the average of nonmissing items (SAS mean function). Each score is calculated only if at least half of corresponding items are not missing. Otherwise, the score will be missing.

Over all CLDQ-HCV score is calculated by taking the mean of 4 domain scores $\{AE, EM, WO, SY\}$.

FACIT-F

Patient responses to 40 questions in FACIT-F questionnaire are rated in 0-4 score.

If less than 50% of responses in the corresponding domain are missing, the subscales for five domains are calculated as follows:

- Physical Well-Being (PWB) = $7 \times \text{Mean of } \{GP1-GP7\}$
 - Social/Family Well-Being (SWB) = $7 \times \text{Mean of } \{GS1-GS7\}$
 - Emotional Well-Being (EWB) = $6 \times \text{Mean of } \{GE1-GE6\}$
 - Functional Well-Being (FWB) = $7 \times \text{Mean of } \{GF1-GF7\}$
 - Fatigue Subscale (FS) = $13 \times \text{Mean of } \{HI7, HI12, An1-An5, An7, An8, An12, An14-An16\}$
- and

- FACIT-F Trial Outcome Index (TOI) = $PWB+FWB+FS$

If less than 20% of all 40 questions are not missing,

- TACIT-F Total Score = $PWB+SWB+EWB+FWB+FS$

WAPI: Hepatitis C

The response to Question 1 of this questionnaire provides the binary endpoint whether or not the subject had been in a paid employment during the week prior to assessment.

If the subject had been in a paid employment (Response to Q1 is “Yes”) at the visit when questionnaire was given, then following three scores are derived:

- Percent work time missed due to hepatitis C = $100 \times Q2 / (Q2 + Q4)$
- Percent impairment while working due to hepatitis C = $100 \times Q5 / 10$
- Percent overall work impairment due to hepatitis C =

$$100 \times \left[\frac{Q2}{(Q2 + Q4)} + \left(1 - \frac{Q2}{Q2 + Q4} \right) \times \frac{Q5}{10} \right]$$

Question 6 is applicable to all subjects:

- Percent activity impairment due to hepatitis C = $100 \times Q6 / 10$.

Appendix 4. Programming Specification

1) AGE calculated as follows:

- a) AGE (years) at each baseline for HIV and HCV study drug is calculated from the number of days between the date of birth (DOB) and first dose date of HIV or HCV study drug,
- b) Use the SAS INTCK function to determine the number of “1st-of-month days” (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),
- c) Divide the result in (b) by 12,
- d) AGE = the integer of the result in (c),
- e) If the DOB and the first dose date have the month in common and the birthday is later in the month than the date of first dose, subtract one from the AGE result above.

For subjects randomized and never dosed with any study drug, age at baseline for HIV drug will be calculated from the date of randomization and age at baseline for HCV drug will be set to missing.

- 2) All screened subjects refer to all subjects who are screened (ie, with nonmissing screening date) and have a screening number. For summaries, the same subject is counted only once. DOB and other demographic information such as sex, race, ethnicity, country, and initials will be used to identify unique screened subjects.
- 3) Screen failure subjects are the subjects who answered “No” for any inclusion criteria or “Yes” for any exclusion criteria regardless of which version of protocol the subject was consent to.
- 4) Subjects in All Randomized analysis set are defined as subjects randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with nonmissing RGMNDTN in the IXRSRAND dataset) and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN = “Yes” in ENROLL dataset).
- 5) In disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.
- 6) Body mass index (BMI)

Calculated from height in meters (eg, height in cm/100) and weight in kilograms as:

$$\text{BMI} = (\text{weight [kg]}) / (\text{height [meters]}^2)$$

Baseline height and weight will be used for this calculation.

7) SAS codes for treatment comparison for demographics and baseline characteristics tables.

- a) CMH test for nominal variable (Y), p-value from general association test should be used for nominal variable:

```
proc freq order=adsl;  
  tables trtgrp * Y /cmh /*general association test*/  
run;
```

- b) CMH test for ordinal variable (Y), p-value from row mean score test should be used for ordinal variable:

```
proc freq order=adsl;  
  tables trtgrp * Y / cmh2 ; /*row mean score test*/  
run;
```

- c) Wilcoxon rank sum test for continuous variable (Y), p-value from normal approximation two-sided test should be used for continuous variable:

```
proc npar1way wilcoxon data=adsl;  
  class trtgrp;  
  var Y;  
run;
```

- 8) Please note, “Not Permitted” or missing categories will be excluded for p value generation for categorical data analysis (eg, CMH test or Fisher exact test). Except for Mode of infection (HIV Risk Factors), where “Unknown” will be included for percentage calculation, since a subject may fit more than 1 HIV risk factors, therefore percentage may add to more than 100% and no p-value will be generated.

Subject with Race or Ethnicity = “Not Permitted” will also be excluded to define Race subgroup (ie, black vs. nonblack) or Ethnicity subgroup (ie, Hispanic or nonhispanic) for efficacy subgroup analysis.

9) SAS codes for treatment comparison using Fisher’s exact test.

```
proc freq order=adsl;  
  tables trtgrp * Y /fisher riskdiff;  
run;
```

10) HIV Taqman Calculations

If a HIV-1 RNA test value is reported as “< 20 cp/mL HIV-1 RNA Detected” or “No HIV-1 RNA detected”, a numeric value of 19 will be used for summary purpose. “No HIV-1 RNA detected” will be treated as < 20 cp/mL.

11) For table: Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL by Visit (Missing=Failure):

The denominator for percentages is based on the number of subjects in the full analysis set, excluding ongoing subjects who have missing HIV-1 RNA at a visit and have not reached the upper limit of the analysis window for the corresponding visit.

“Ongoing subjects” refers to subjects who did not discontinued from the study, use the lab data transfer date as the cutoff date.

“Have not reached the upper limit of the analysis window for the corresponding visit” refers to: Cutoff date –first dose date+1< upper limit of the analysis window for a visit.

12) Toxicity Grades:

- a) With regards to Triglycerides, LDL, and Hypercholesterolemia, if the fasting status is not ‘Y’, in other words it is blank, ‘N’, or ‘U’ (for unknown), the lab result value would not be graded since nonfasting values are not interpretable.
- b) For toxicity grade summary, we will include all postbaseline graded results up to 30 days after last dose of study drug, not just those at summarized visits.
- c) For hematuria grading, if the laboratory reports urine blood using the plus system (+1, +2, etc) and also provides quantitative results on reflex (ie, urine RBC), summarize only the grade of the urine RBC results, but list both grades of urine blood and urine RBC if applicable.

13) Efficacy analyses:

- a) Exact method for difference in primary endpoint or other efficacy endpoints with proportion of HIV-1 RNA < 50 c/mL between treatment group: the code below provides exact CIs (on an unconditional exact method using 2 inverted 1-sided tests) in SAS v9.3 or above:

```
data example;
input  grp trt01a  outcome count ;

datalines;
1      Treat-A      2-Fail      1
1      Treat-A      1-Succ     189
1      Treat-B      2-Fail      4
1      Treat-B      1-Succ     88
run;

data example;
input  grp trt01a $  outcome $ count ;

datalines;
1      Treat-A      2-Fail      1
1      Treat-A      1-Succ     189
1      Treat-B      2-Fail      4
1      Treat-B      1-Succ     88
run;
```

```
proc freq data = example;
table trt01a*outcome /riskdiff(CL=(exact)) alpha=0.04999;
weight count; exact RISKDIFF(METHOD=SCORE);
output out=ciexact(keep=_RDIF1_ XL_RDIF1 XU_RDIF1) riskdiff;
run;

data final(keep=A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate ="Percentage Difference"
LowerCL = "95% Lower Confidence Limit"
UpperCL = "95% Upper Confidence Limit"
A1 = "Percentage of Success in Treat-A"
B1 = "Percentage of Success in Treat-B";
Estimate=100*_RDIF1_;
LowerCL = 100*XL_RDIF1;
UpperCL = 100*XU_RDIF1;
A1 = 100*_RSK11_;
B1 = 100*_RSK21_;
ocharc1 = right(compress(put(Estimate,8.1)) || '%' ( ' ||
compress(put(LowerCL,8.1)) || '% to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

- b) Fisher's exact test for categorical efficacy response (eg, HIV-1 RNA < 50 copies/mL in US FDA-defined snapshot algorithm), where *trtgrp* is the treatment, and *response* is the categorical efficacy response. P-value from 2-sided Fisher's exact test should be used to test superiority.

```
proc freq data=adeff;
tables trtgrp*response/fisher; /*p value from Fisher's exact test*/
run;
```

- c) ANOVA model for continuous efficacy variable (eg, CD4):

The differences in changes from baseline in CD4 cell count between treatment groups and the associated 95% CI will be constructed using ANOVA, including the prior treatment regimen as fixed effects in the model.

SAS code is as follows:

```
proc glm data=adeffi;
class trtgrp;
model CD4 = trtgrp;
lsmeans trtgrp /alpha=0.05 cl pdiff;
run;
```

Similar code will be used for the analysis of CD4 %.

- d) Subgroup analyses

For the subgroups of age, race, sex, region and study drug adherence, p-value from 2-sided Exact method should be used to test superiority. The proportion difference between two treatment groups and 95% CIs are calculated based on an unconditional exact method using 2 inverted 1-sided tests, similarly to that for the primary efficacy endpoint.

14) Treatment-emergent AE (TEAE)

Events with Missing Onset Day and/or Month

The event is treatment emergent in a safety period, if the following 3 criteria are met:

- a) The month and year (or year) of onset date is the same as or after the month and year (or year) of the start date of the safety period, and
- b) The month and year (or year) of the onset date is the same as or before the month and year (or year) of safety cutoff date of the safety period, and
- c) AE end date is as follows:
 - i) The (complete) AE end date is on or after the safety period start date, or
 - ii) The month and year (or year) of end date is the same or after the month and year (or year) of the safety period start date, or
 - iii) AE end date is completely missing.

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE for a safety period if AE end date meets any of the criteria specified in 3) above.

15) Renal related laboratory evaluation

Urine Protein Correction

- a) The calibrator material used in the quantitative assay for the measurement of urine protein (UP) was changed globally in Covance on May 27, 2016. All samples reported prior to May 27, 2016 (ie, *RPTDTM* < 'May 27, 2016') were tested by the calibrator material manufactured by Roche Diagnostics, while the samples reported on or after May 27, 2016 were tested by the calibrator material manufactured by Quantimetrix. Covance had 3 regional lab centers to run the samples. Each regional lab center conducted its own alternate (quantitative) method comparison, all of these comparison demonstrate that calibrator materials manufactured by the Roche and Quantimetrix yield comparable results as noted in the table below:

Regional Lab Center	Accession Numbers ^a	Regular Regression for UP Correction ^b	Correlation Coef.	Bias
Indianapolis Auto Chemistry	Start with 65	$Y = 1.028 X - 3.70$	0.9982	-2.34 (-4.91%)
Geneva Auto Chemistry	Start with 62 or 63	$Y = 0.981 X - 1.44$	0.9993	-2.42 (-4.74%)
Singapore Auto Chemistry	Start with 64 or 66	$Y = 0.980 X - 1.62$	0.9996	-2.73 (-5.08%)
BML in China	Start with 67 or 68	NA	NA	NA

a Accession numbers specified which regional lab center tested the sample . For example, samples with accession number started with 65 were tested in Indianapolis Auto Chemistry Center.

b X and Y are the UP results using calibrator materials manufactured by Roche Diagnostics and Quantimetrix, respectively.

- b) In order to combine UP results from 2 different assay methods for summary/comparison purpose, we will convert the UP results analyzed using the calibrator from Roche (ie, results reported prior to May 27, 2016) to Quantimetrix results by using the regression equation listed in above table.

Original UP based on Reported Date	Original UP Categories	Accession Number	AVALC of Corrected UP ('UP' stands for Original UP)
UP reported on/after May 27, 2016	_ALL_	_ALL_	AVALC of UP
UP reported before May 27, 2016	UP < 4.0	_ALL_	'< 4.0'
	UP ≥ 4.0	Start with 65	$1.028 \times \text{UP} - 3.70$; if $1.028 \times \text{UP} - 3.70 \geq 4.0$ '< 4.0'; if $1.028 \times \text{UP} - 3.70 < 4.0$
		Start with 62 or 63	$0.981 \times \text{UP} - 1.44$; if $0.981 \times \text{UP} - 1.44 \geq 4.0$ '< 4.0'; if $0.981 \times \text{UP} - 1.44 < 4.0$
		Start with 64 or 66	$0.980 \times \text{UP} - 1.62$; if $0.980 \times \text{UP} - 1.62 \geq 4.0$ '< 4.0'; if $0.980 \times \text{UP} - 1.62 < 4.0$

- c) The corrected UP results will be used for the following analysis and referred as "UP" in following text. If AVALC of the corrected UP is "< 4.0", the AVAL of the corrected UP will be imputed as 3.9 mg/dL.

Unit conversion for renal safety tests derived from related tests with conventional units

- a) Urine RBP (ug/L) to creatinine (mg/dL) ratio: $1 \text{ (ug/L)} / \text{(mg/dL)} = 100 \times \text{ug/g}$
- b) Urine Beta-2-microglobulin (mg/L) to creatinine (mg/dL) ratio: $1 \text{ (mg/L)} / \text{(mg/dL)} = 10^5 \text{ ug/g}$
- c) Urine Protein (mg/dL) to creatinine (mg/dL) ratio: $1 \text{ (mg/dL)} / \text{(mg/dL)} = 1000 \times \text{mg/g}$
- d) Urine Albumin (mg/dL) to creatinine (mg/dL) ratio: $1 \text{ (mg/dL)} / \text{(mg/dL)} = 1000 \times \text{mg/g}$

Calculation of ratios:

To calculate laboratory ratios (eg, urine RBP to creatinine ratio), the lab value of each test in the ratio needs to be from the same accession number; if any test value used for the ratio calculation from the same accession number is missing, then the ratio is not calculable (ie, missing). For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios. For urine protein, a value of "< 4.0" is handled as a missing value in the calculation of UPCR.

Combined category of UP and UPCR

- a) First merge UP and UPCR based on the subject identifier and accession number.
 - b) At each visit, based on UP to select which pair of records should be used for the analysis. That is, once a UP record is selected for that visit, the UPCR with the same accession number (if calculated) will be selected. Please note, UPCR is missing when UP < 4.0 mg/dL.
 - c) Subject will be classified as “UPCR \leq 200 mg/g” if UP < 4.0 mg/dL or UPCR \leq 200 mg/g; Subject will be classified as “UPCR > 200 mg/g” if UPCR > 200 mg/g; Otherwise, subject will be classified as “Missing”.
- 16) Concomitant nonstudy-drug ARV medications (ie, ARV medications other than study drug that are taken while receiving study drug) will be flagged in “Nonstudy-Drug Antiviral Medication” listing. The logic to define concomitant nonstudy-drug ARV is similar to concomitant non-ARV Medications (see details in Section 7.4.2).
- 17) Age for laboratory test reference range will be based on the age at the sample collection date.