This is ACTG A5327 Cohort 1 SAP Version 1.0 with names of authors, names of publication writing team and analysis timeline redacted.

ACTG A5327

Cohort 1

STATISTICAL ANALYSIS PLAN

Sofosbuvir Plus Ribavirin Without Interferon For Treatment of Acute HCV in HIV-1 infected Individuals (SWIFT-C)

ClinicalTrials.gov Identifier: NCT02128217

Version 1.0:

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1 Introduction

This document describes the content proposed for the primary statistical analysis of ACTG A5327. The focus of this analysis will examine the primary objectives of safety and efficacy outcomes for Cohort 1 (12 weeks of treatment). Analysis of Cohort 2 will follow a similar plan but some details will depend on whether Cohort 2 receives treatment for 12 weeks or 8 weeks. A subset of these analyses will form the basis of reports provided to the Hepatitis TSG Study Monitoring Committee (SMC) while the study is ongoing. Also included is a summary of the analysis plans for the secondary objectives that will be analyzed either at the time of the primary analyses or at a later date as determined per the priorities of the A5327 study team. It is, however, recognized that this analysis plan may be modified by the study as new information becomes available outside of the study or to reflect recommendations made by SMC. In addition, some analyses, tables or figures may be omitted at interim analyses if there are insufficient data to warrant analysis or at the request of the SMC.

2 Study Overview

2.1 Study Schema

(Extracted from Protocol Version 1.0)

DESIGN

SWIFT-C is a Phase I, open-label, two-cohort clinical trial, in which between 44 and 50 acutely HCV-infected HIV-1 positive subjects will be enrolled and administered oral sofosbuvir (SOF) in combination with weight-based ribavirin (RBV).

The study will open the first cohort with treatment for 12 weeks with the potential to shorten therapy in a second cohort to 8 weeks if noninferiority of the 12-week regimen in the first cohort compared to a historical control is met. The first cohort will open with a planned accrual of at least 17 subjects. An interim efficacy analysis on the proportion of subjects with undetectable HCV RNA 4 weeks after the last dose of SOF/RBV (SVR4) will be conducted after 17 subjects complete the study treatment and are evaluated for SVR4. The second cohort will open with an 8-week treatment only if the SVR4 rate from the first 12-week treatment cohort is concluded to be noninferior to the study-defined historical sustained virologic response (SVR) rate of 60%. If at the interim analysis the first cohort does not meet noninferiority criteria, enrollment for cohort 2 will continue with a 12-week treatment duration to completion of the study. The second cohort will include at least 27 subjects. Each cohort will occur in two steps: on treatment (Step 1) and followup (Step 2). The cohorts will enroll sequentially.

DURATION

32-36 weeks (8-12 weeks on-treatment followed by 24 weeks of follow-up)

SAMPLE SIZE	A minimum of 44 subjects will be enrolled. If a subject is discontinued from study treatment for non-virologic reasons or is not evaluable for SVR12 while enrollment is ongoing to the same cohort, then an additional subject may be enrolled to that cohort to help ensure that an adequate number complete study treatment and are evaluable for SVR12, up to a maximum enrollment of 50 subjects.
POPULATION	HIV-1 coinfected individuals who have acute HCV infection or reinfection.
REGIMEN	SOF 400mg once daily and weight-based RBV (1000 or 1200 mg daily in two divided doses)

2.2 Hypothesis

An interferon sparing regimen of sofosbuvir (SOF) and ribavirin (RBV) can achieve sustained virologic response (SVR) 12 rates that are noninferior to the current standard of care assessed by historical control for the treatment of acute HCV in HIV-1/HCV co-infected individuals with an improved safety profile and a shorter length of treatment.

2.3 Primary Objectives

1. To evaluate HCV treatment response to SOF and weight-based RBV (1000 or 1200 mg daily in two divided doses) taken for 12 or 8 weeks as assessed by SVR12, defined as HCV RNA undetectable [<lower limit of quantification (LLOQ) target not detected (TND)] 12 weeks post-treatment in persons with existing HIV-1 infection who are acutely infected with any HCV genotype.

2. To evaluate the safety and tolerability of combination oral antiviral therapy with SOF and weight-based RBV taken for 12 or 8 weeks in persons with existing HIV-1 infection who are acutely infected with any HCV genotype.

2.4 Secondary Objectives

1. To evaluate the antiviral efficacy of SOF and weight-based RBV as measured by the proportion of subjects with HCV RNA undetectable (<LLOQ TND) at weeks 1, 2, 4, 8, 12 and at 2 (SVR2), 4 (SVR4), 8 (SVR8), 12 (SVR12) and 24 (SVR24) weeks post-treatment.

2. To evaluate evidence of relapse, defined as HCV RNA undetectable (<LLOQ TND) at end-of-treatment but HCV RNA quantifiable (≥LLOQ) during followup.

3. To assess the emergence of viral resistance to SOF when administered with RBV for acute HCV infection.

4. To estimate RBV pharmacokinetics (PK) and evaluate covariates (including concomitant antiretroviral drugs) which may affect RBV PK.

5. To assess the relationship of viral clearance and RBV PK with baseline predictors including genetic polymorphisms (eg., IL28B and ITPA), expression of key host immune response genes and proteins.

6. To evaluate subjects' adherence by using several tools, including self-report, pill count, and RBV concentrations.

7. To evaluate the hypothesis that successful direct-acting antiviral (DAA)-based therapy alleviates type I (IFN)-induced immune dysfunction during acute HCV infection.

2.5 Visit and Evaluation Schedule

The Cohort 1 expected schedule for on-treatment clinic visits is shown in Table 1 and the expected schedule for post-treatment follow up clinic visits is shown in Table 2 below. Unless otherwise noted, analyses by A5327 study week will utilize these study week definitions (defined in days); the start time for calculation of study week will be the date of first dose of treatment.

Table 1: Weeks Since Starting Treatment

	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12
Days	0	4-10	11-17	21-42	49-70	77-98

Table 2: Weeks Since Starting Post-Treatment Follow up

	Week 0	Week 2	Week 4	Week 8	Week 12	Week 24
Days	Last day of treatment	9-22	23-50	51-78	79-112	161 onwards

2.6 A5327 Protocol History

Protocol Version 1.0 (finalized January 2, 2014)

A5327 Clarification Memo 1, Version 1.0 (03/13/2014) regarding clarification of eligibility criteria in Section 4 and the use of plasma HCV RNA in Section 6.

A5327 Letter of Amendment 1, Version 1.0 (05/21/2014) regarding changes to lipid panel as needed at entry and exemption from US FDA IND regulations.

2.7 Monitoring

2.7.1 Ongoing Monitoring

The A5327 team will monitor the following:

- Accrual and study status (monthly)
- Adverse events (AEs) (every two months)

- Toxicities which include signs and symptoms, laboratory abnormalities and diagnoses (every three months)
- HCV and HIV-1 failures (every 1 to 3 months, as needed)

Please refer to the most recent version of the Study Monitoring Plan (SMP) for more details.

2.7.2 SMC Reviews

The Hepatitis TSG SMC will review A5327 at least annually after the first subject is enrolled and as soon as possible after the SVR4 status is known for the first 17 subjects in the first cohort who complete study treatment (i.e. do not prematurely discontinue study treatment for non-virologic reasons) and are evaluable for SVR4. The SMC will monitor safety and efficacy of study treatment. In particular, the SMC will review outcome data to guide a decision about Cohort participants receiving 12 or 8 week duration of study treatment.

At the request of the SMC, an early interim analysis of the study accrual will occur 6 months after the study opens to enrollment. The SMC will examine accrual by site and by month.

Open Report: The following report will be distributed to the Core Team and the SMC. The report will include analyses from the following sections of this analysis plan by cohort.

- Study Status
- Baseline Characteristics
- Data Completeness
- Safety data

Closed Report: The following report will be distributed to the SMC members. The report will include analyses from the following sections of this analysis plan with summaries by cohort.

- Changes in HCV RNA
- SVR4, SVR8, SVR12, SVR24 rates based on the available data for HCV RNA as well as rates of virologic failure and relapse.

2.8 General Statistical Considerations

Key analysis decisions:

- Throughout, study entry is defined at the date of entry visit as recorded as the header date on the ADM0010 [*for interim*: if ADM0010 is not in database at the time of data retrieval, registration date will be used]

- The analyzed measurement will, in general, be the measurement closest to the scheduled evaluation time, and the acceptable windows will be based on time since first study treatment dose

- Unless otherwise specified, data summaries and analyses will be presented by cohort. Final analysis of data from Cohort 1 can occur while the second cohort proceeds. The analysis for Cohort 1 will occur after all subjects have completed follow-up (through 24 weeks post-treatment, as appropriate per protocol) and final data are available. Final analysis for Cohort 2 will depend on whether Cohort 2 receives 12 weeks of treatment or 8 weeks of treatment. If Cohort 2 receives 12 weeks of treatment, the analysis will combine Cohort 1 and Cohort 2. If Cohort 2 receives 8 weeks of treatment, the analysis will be separate. The analysis plan will be updated after the decision of treatment duration is made.

Notes for conventions used in the SMC and primary analysis reports:

- For the primary analysis report (*not SMC report*):
    - Lists will be sorted by variables in the order given with study participants identified using an alternate patient identifier (PubID, i.e. not ACTG patid).
    - Participant-specific dates will not be shown, but converted to time since study entry or start of study treatment.

- Each Table/Figure/Listing will be annotated with the name and location of the program used to create it

- Unless otherwise noted, tables/figures in Sections 4 through 10 will be included in the interim analysis reports for the SMC as well as the primary analysis report

- Validation:
    - Tables/figures requiring SDAC validation of the program used to generate the results will be flagged with "**[V]**"
    - Tables/figures requiring independent programming of results by the SDAC validator will be flagged with "**[IP]**"

3 Accrual

Purpose : To give a summary of accrual and the distribution of enrollment across sites.

a) Table: Number (%) enrolled overall and by month

   Note: Dates of first and last enrollments will be provided in a footnote to the table

b) Table Number (%) enrolled by enrolling site

4 Eligibility Violations and Exclusions

Purpose; To document why any participants who were enrolled were subsequently excluded from analysis and document any other exclusions.

a) List: violations of eligibility criteria by site and details of exclusions from analyses (if any)
b) List: participants who did not have treatment dispensed. These participants will be excluded from the analysis.

5 Baseline Characteristics

Purpose: To describe the study population

Baseline characteristics will be analyzed as continuous or as categories or both, as appropriate. Tables will provide # of subjects, # of missing data points, median, quartiles (Q1-Q3), minimum, maximum, mean and standard deviation for the continuous variables (with transformations as appropriate) and number (%) for the categorical variables. In calculation of percentages, subjects with missing data will not be included in the denominator.

a) Table summarizing demographic characteristics

i. Sex: number (%)
ii. Self-reported race/ethnicity: number (%)
iii. Age on the day of study entry (years): N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum; number (%) by age group (18-19, 20-29, 30-39, 40-49, 50-59; 60-69. 70+ years, rounded down).
iv. Intravenous drug use (IVD) history: number (%) by group (Never, current, previous user)
v. Weight (kg) (F0033):N, mean, standard deviation, median, 1st and 3rd quartile, 10th and 90th percentile; number (%) by weight group (< 75kg, ≥75kg)
vi. BMI (kg/m^2): N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum; number (%) by BMI group (Underweight[<18.5], normal [18.5-24.9], overweight [25-29.9], obese [>30])

b) Table summarizing health status information

i. Baseline HIV-1 RNA (copies/ml) and corresponding results for log10 copies/ml (F3109): N, median, 1st and 3rd quartile, minimum and maximum; number (%) by category (≤50, 50-400, 401 -1,000, 1,000-9,999, >10,000-99,999).
Note: Baseline is defined as the closest value to starting study treatment.
ii. Baseline CD4+ cell count ($/mm^3$) (LBW0054): N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum; number (%) by category (<50, 50-199, 200-349, 350-499, 500-649, 650-799, ≥800)
Note: Baseline is defined as the arithmetic mean of screening and entry values or, in the absence of one value, the one available.
iii. ARV treatment history (HXW0171): number (%) by category (Never used, off at entry but previously used, and currently on at entry), number (%) by ARV regimen
iv. Baseline HCV RNA (copies/ml) and corresponding results for log10 copies/ml (F3116): N, median, 1st and 3rd quartile, minimum and maximum
Note: Baseline is defined as the value at A5327 entry
v. IL28B genotype (GENOHUM): number (%) by category (CC, CT, TT)
vi. ITPA genotype (GENOHUM): number (%) by category (CC, CA, AA)
vii. HCV genotype (SRW0028): number (%) by category (1a, 1b, 2a, 2b, 3, 4, 5, 6)

c) Table summarizing laboratory evaluations

For each laboratory evaluation the following will be presented unless otherwise specified: N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum;

i. Hematology characteristics (F2850): hematocrit, hemoglobin (g/dL), platelets (cells/mm3), red blood cell (RBC) count, white blood cell (RBC) count (cells/mm3), WBC differentials (lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocyte count) and mean corpuscular volume (MCV).
ii. Chemistry characteristics(F2841): alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin (g/dL), alkaline phosphatase, creatinine, total bilirubin, direct bilirubin, glucose (mg/dL), lipase, potassium (mEq/L), thyroid-stimulating hormone, sodium(mEq/L) and gamma-glutamyl transferase.
    a. ALT/SGPT and AST/SGOT: number (%) by category (≤ 5X ULN, >5X ULN)
    b. Total bilirubin: number (%) by category (≤2XULN, >2XULN)s
iii. Calculated creatinine clearance(LBW0060)
iv. Fasting Lipids (F2841): low density lipoprotein (LDL, mg/dL), high density lipoprotein (HDL, mg/dL), triglycerides (TG, mg/dL), total cholesterol (TC, mg/dL), and apolipoproteins B, E, and CII.
    Note: Fasting per protocol is defined as nothing to eat or drink except prescription medications and water for at least 8 hours prior to the procedure. Only fasting lipids will be included; lipid measurements collected non-fasting will be excluded and considered as missing.
v. Coagulation Markers (F2850): INR, prothrombin time (PT), activated partial thromboplastin (APTT)
vi. Urinalysis (F0869): appearance, blood, color, glucose, leukocyte erterase, PH, protein, urobilinogen

d) Table by ARV status at A5327 entry (yes vs no)
    i. Baseline HIV-1 RNA (copies/ml) and corresponding results for log10 copies/ml (F3109): N, median, 1st and 3rd quartile, minimum and maximum , number (%) by category (≤50, 50-400, 401 -1,000, 1,000-9,999, >10,000).

6 Study status and loss to follow up

Purpose: To summarize extend of follow-up on study.

a) CONSORT diagram: number of participants enrolled in each cohort, number who started treatment, completed treatment, and completed study *[ONLY included in primary analysis report]*
b) Table: On study treatment number (%) by category (F4003 and F1601)
    Categories included are:
    i. Completed planned treatment period and post treatment follow-up
    ii. Completed planned treatment period but off study early
    iii. Discontinued study treatment early and completed planned post treatment follow-up
    iv. Discontinued study treatment early and discontinued post treatment follow-up earl

c) List: Reasons off study treatment early (include both the category and text field from F4003)
d) List: Reasons off study early (include both the category and text field from F1601)

7 Study conduct

Purpose: To summarize how compliant participants are with study visits and completeness and timeliness of data entry and sample acquisition for key study outcomes [*ONLY included in interim analysis*]

a) Table: summarize missed visits reflected as the number(%) of expected and observed clinic visits in each table of data completeness (see below)
b) Table: data completeness of for key study outcomes (standard SDAC data availability report):
    i. HCV RNA (HCVRNALDMS)
    ii. HIV-1 RNA (RNALDMS)
    iii. CD4 cell count (LBW0054)
    iv. ALT(SGPT) and AST(SGOT) (F2841)
    v. Stored serum/plasma for HCV/HIV studies (L_ALIQ)
    vi. Stored plasma/PBMC (L_ALIQ)

8 Primary Endpoint Analyses

8.1 Efficacy Outcome (Final Analysis) [IP]

Primary Outcome Measure (from protocol section 9.2.1.1)

SVR12 is defined as HCV RNA undetectable (<LLOQ TND) of the assay at 12 weeks after date of last dose of study treatment.

The 12 week measurement will be the measurement obtained closest to 84 days (i.e. 12*7 days), within the window 79 to 112 days inclusive after study treatment discontinuation. This analysis will be intent to treat (ITT) analysis.

If a subject has no HCV RNA measurement within this window, then the subject will be considered as having detectable HCV RNA at 12 weeks unless the preceding and subsequent HCV RNA measurements are both undetectable (<LLOQ TND).

Planned Analysis

a) Table: summarize proportion and two-sided 90% confidence interval around the observed SVR12 proportion using the Blyth-Still-Casella(BSC) method for binomial outcomes (HCVRNALDMS)
b) Table: summarize proportion and two-sided 90% confidence interval around the observed SVR12 proportion of subjects who are evaluable for SVR12 but exclude subjects who prematurely discontinue study treatment for nonvirologic reasons (Completer Analysis) using the Blyth-Still-Casella(BSC) method for binomial outcomes (HCVRNALDMS)

8.2 Efficacy Outcome (Interim Analysis) [V]

Primary Outcome Measure (from protocol section 9.5)

The ACTG Hepatitis SMC will review this study as soon as possible after the SVR4 status is known for at least 17 subjects in Cohort 1. SVR4 is defined as HCV RNA undetectable (<LLOQ TND) of the assay 4 weeks after day of last dose of study treatment.

The 4 week measurement will be the measurement obtained closest to 28 days (i.e. 4*7 days), within the window 23 to 50 days inclusive after study treatment discontinuation. This analysis will be ITT analysis.

Planned Analysis

a) Table: summarize proportion and two-sided 90% confidence interval around the observed SVR4 proportion using the Blyth-Still-Casella(BSC) method for binomial outcomes (HCVRNALDMS).
b) Table: summarize proportion and two-sided 90% confidence interval around the observed SVR4 proportion of subjects who are evaluable for SVR4 but exclude subjects who prematurely discontinue study treatment for nonvirologic reasons (Completer Analysis) using the Blyth-Still-Casella(BSC) method for binomial outcomes (HCVRNALDMS)

   NOTE: If the SVR4 rate from Cohort 1 (12 weeks of treatment) is concluded to be noninferior to the study-defined historical SVR rate of 60% (i.e. the lower confidence bound is above 60%), then Cohort 2 will be opened to 8 weeks of treatment. Otherwise, Cohort 2 will receive 12 weeks of treatment. Other secondary efficacy information (detailed below) may be considered by the SMC to make the recommendation of treatment duration for Cohort 2.

8.3 Safety Outcome [IP]

Primary Outcome Measure (from protocol section 9.2.1.2)

Occurrence of a Grade ≥ 2 AE (diagnosis, sign, symptom, or laboratory abnormality), SAE according to ICH criteria, or treatment-limiting AE (i.e., an AE reported as the reason for permanent discontinuation of study treatment).

Any event occurring after initiation of study treatment through to 28 days after date of last dose of study treatment will be included (except for an event that is ongoing at the same grade from before start of study treatment will be excluded).

Planned Analysis

a) Table: summarize proportion and two-sided 90% confidence interval around the proportion of subjects who have one of the defined AEs (EVW0206, EVW0207)
b) Table: summarize primary safety outcome (i.e. type of AE, grade, whether or not an SAE, whether or not it was a treatment limiting AE)

9 Secondary Outcome Measures Analyses

9.1 HCV RNA while on study treatment

Secondary Outcome Measure (from protocol section 9.2.2.1)

HCV RNA undetectable (<LLOQ TND) at 1, 2, 4, 8 and, for the 12-week regimen, 12 weeks after starting study treatment. Measurements will be assigned to these times within windows of 4 to 10, 11 to 17, 21 to 42, 49 to 70, and 77 to 98 days, inclusive, respectively. If there is more than one measurement within a window, then the measurement closest to the targeted time will be used. If there is no measurement within a window, then the subject will be considered as having detectable HCV RNA at the targeted time, unless both the preceding and succeeding measurements are undetectable (<LLOQ TND).

Planned Analysis

a) Table: summarize the proportion of HCV undetectable (<LLOQ TND) of the assay at 1, 2, 4, 8, and, for the 12-week regimen, 12 weeks after starting study treatment. A 90% two-sided confidence interval will be provided around the observed proportions (HCVRNALDMS)
b) Figure: summarize the proportion of HCV undetectable, with the upper and lower limit of the confidence interval at 1, 2, 4, 8, and for the 12-week regimen, 12 weeks after starting study treatment (HCVRNALDMS).

9.2 HCV RNA during follow-up

Secondary Outcome Measure (from protocol section 9.2.2.2)

HCV RNA undetectable (<LLOQ TND) at 2 (SVR2), 4 (SVR4), 8 (SVR8), and 24 (SVR24) weeks after last dose of study treatment. The windows for these measurements will be 9 to 22, 23 to 50, 51 to 78, and 161 days onwards. If there is more than one measurement within a window, then the measurement closest to the targeted time will be used. If there is no measurement within a window, then the subject will be considered as having detectable HCV RNA at the targeted time, unless (for weeks 4 and 8) the preceding and subsequent HCV RNA measurements are both <LLOQ TND.

Planned Analysis

a) Table: summarize the proportion of HCV undetectable (<LLOQ TND) of the assay at 2 (SVR2), 4 (SVR4), 8 (SVR8) and 24 (SVR24) weeks after last dose of study treatment. A 90% two-sided confidence interval will be provided around the observed proportions (HCVRNALDMS)
b) Figure: summarize the proportion of HCV undetectable, with the upper and lower limit of the confidence interval at 2 (SVR2), 4 (SVR4), 8 (SVR8) and 24 (SVR24) weeks after last dose of study treatment (HCVRNALDMS).

9.3 HCV RNA Relapse

Secondary Outcome Measure (from protocol section 9.2.2.3)

To evaluate virologic evidence of relapse, defined as HCV RNA undetectable (<LLOQ TND) at end-of-treatment but HCV RNA quantifiable (≥LLOQ) during followup, will require confirmation and should be performed as soon as possible but within 2 weeks after determination of initial observation.

For analysis purposes, confirmatory values obtained after 2 weeks will be included.

Planned Analysis

a) List: Subjects who have virologic evidence of relapse. The listing will include week of HCV RNA undetectable (<LLOQ TND), HCV RNA undetectable at end of study treatment, post treatment week of HCV RNA detectable (≥LLOQ) and confirmation of HCV RNA detectability (HCVRNALDMS)

9.4 SOF-associated resistance mutations

Secondary Outcome Measure (from protocol section 9.2.2.4)

Development of SOF-associated resistance mutations. The set of mutations to be considered will be defined at the time of analysis based on information from other studies available at that time.

The analysis plan will be updated when additional information is available.

Planned Analysis

a) List: Subjects with SOF-associated resistance mutations. The listing will include sample week of resistance testing, whether the subject was off study treatment at that time, SOF-associated resistance mutation, and HCV RNA at the time of the resistance testing (Table TBD)

9.5 AEs by type of event

Secondary Outcome Measure (from protocol section 9.2.2.5)

Occurrence of the AEs detailed in section 9.2.1.2 of the protocol (Section 9.1 in this document) by type of event. Type of events include: diagnosis, sign, symptom, laboratory abnormality, SAE according to ICH criteria, or treatment-limiting AE.

Planned Analysis

a) Table: summarize grades of events and the number (%) of persons experience each type/grade (EVW0206, EVW0207).

9.6 Changes in Hemoglobin

Change in hemoglobin from last measurement prior to start of study treatment to each subsequent scheduled hemoglobin measurement time. Windows for measurements to be included and the algorithm for selecting measurements within each window will be as described for HCV RNA measurements above.

Planned Analysis

a) Table: summarize hemoglobin measurements at each time point (F2850: N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum)
b) Table: summarize hemoglobin changes from the last measurement prior to study treatment to each subsequent CD4+ cell count measurement (F2850: N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum)
c) Figure: summarize hemoglobin median and IQR (Q1, Q3)
d) Figure: summarize hemoglobin change median and IQR (Q1, Q3)

9.7 Change in HIV-1 RNA

Secondary Outcome Measure (from protocol section 9.2.2.6)

Change in HIV-1 RNA from last measurement prior to start of study treatment to each subsequent scheduled HIV-1 RNA measurement time: for subjects on ART at study entry, these will be categorized as changes from <50 copies/mL to ≥50 copies/mL, or vice versa; for subjects not on ART at study entry, quantitative change in $\log_{10}$ HIV-1 RNA will be considered. Windows for measurements to be included and the algorithm for selecting measurements within each window will be as described for HCV RNA measurements above.

Planned Analysis

Each analysis will be done by ARV use at study entry (yes vs no) (RNALDMS, HXW0171)

a) Table: summarize HIV-1 RNA measurements at each time point
b) Table: summarize HIV-1 RNA changes from last measurement prior to study treatment to each subsequent HIV-1 RNA measurement
c) Figure: summarize HIV-1 RNA measurements at each time point
   i. For subjects on ARVs at study entry: the figure will summarize the proportion of subjects who had HIV-1 RNA < 50 copies/mL with 95% confidence interval around the proportion
   ii. For subjects not on ARVs at study entry: the figure will summarize the HIV-1 RNA median and IQR (Q1, Q3)
d) Figure: summarize HIV-1 RNA changes at each time point
   i. For subjects on ARVs at study entry: the figure will summarize the proportion of subjects who had HIV-1 RNA < 50 copies/mL with 95% confidence interval around the proportion
   ii. For subjects not on ARVs at study entry: the figure will summarize the HIV-1 RNA median and IQR (Q1, Q3)

9.8 Change in CD4+ cell count

Secondary Outcome Measure (from protocol section 9.2.2.7)

Change in CD4+ cell count from last measurement prior to start of study treatment to each subsequent scheduled CD4+ cell count measurement time. Windows for measurements to be included and the algorithm for selecting measurements within each window will be as described for HCV RNA measurements above.

Planned Analysis

a) Table: summarize CD4+ cell count measurements at each time point (LBW0054: N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum)
b) Table: summarize CD4+ cell count changes from the last measurement prior to study treatment to each subsequent CD4+ cell count measurement (LBW0054: N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum)
c) Figure: summarize CD4+ cell count median and IQR (Q1, Q3)
d) Figure: summarize CD4+ cell count change median and IQR (Q1, Q3)

9.9 Adherence

Secondary Outcome Measure (from protocol section 9.2.2.8)

Measures of adherence: for each of SOF and RBV at each visit: (a) self-reported adherence as measured by whether or not a subject reports having taken all doses; and (b) proportion of doses taken since the previous visit as determined by pill count.

Planned Analysis

a) Table: summarize proportion of subjects taking all doses of medication within the 3 days prior to the evaluation (QL0757)
b) Table: summarize the number (%) of doses taken since the previous visit, along with descriptive statistics (N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum) (EVW0320)
c) Adherence analysis based on RBV concentrations are TBD.

9.10 Immune Parameters

Secondary Outcome Measure (from protocol section 9.2.2.9)

Immune parameters: changes in magnitude of induction of ISGs by Nanostring, changes in IP-10 levels, and changes in T cell function (CD4+ proliferative and CD8 CTL assays) at end of treatment and end of followup compared to study entry. Analysis will be performed as a function of IL28B genotype. [*ONLY included in the final analysis*]

Planned Analysis

The analysis plan may be updated with additional analysis for this secondary outcome. Immune parameter tables are TBD.

a) Table: summarize ISGs at each time point and change in ISG from baseline
b) Table: summarize IP-10 levels at each time point and change in IP-10 from baseline
c) Table: summarize T cell function at each time point and change in T cell function from baseline

9.11 Pharmacology Analysis

A separate Statistical Analysis Plan will be developed for the Pharmacology objectives.

10 Analysis datasets

Preliminary list of analysis datasets **[V]**

baseline – key baseline variables used in multiple summaries

studystatus – study status information, e.g. on study, off study, reason off study

hivrna – longitudinal HIV-1 RNA with calculated study weeks

cd4 – longitudinal CD4 cell count with calculated study weeks

psafety[IP] – primary safety events with calculated weeks on treatment

hcvrna[IP] – primary efficacy analysis with longitudinal HCV RNA with calculated study weeks

NOTE: Other datasets that are created will be added in a later version of this document.