ACTG A5329

Primary Statistical Analysis Plan

Version 3.0

Interferon-Free Therapy for Chronic HepAtitiS C Virus GENotype 1 Infection in Participants with HIV-1 Coinfection Receiving Concurrent Antiretroviral Therapy (C_ASCENT) – Version 2.0 (06/08/16), LOA #4 (06/06/2018)

ClinicalTrials.gov Identifier: NCT02194998

April 29, 2019

Version History

Version	Changes Made	Date Finalized

3	• Protocol amendment reviews (LOAs #1-#4) – see dates below
	• Removed 'Other Outcome Measures' section as the outcomes are linked to exploratory objectives that will be addressed in the secondary analysis plan
	• Removed exploratory objectives pertaining to biomarkers and immune response based on decision from team conference call summary (02/05/2019)
	• Removed exploratory objectives pertaining to PK parameters based on decision from team conference call summary (01/08/2019)
	• Removed secondary outcomes and measures pertaining to HCV resistance mutation of participants who were HCV virologic failure based on decision of abandonment from team conference call summary (06/05/2018)
	• Updated study schema from protocol version 1.0 to version 2.0.
	• Updated A5329 Protocol History
	  ○ A5329 Letter of Amendment 1, Version 2.0 (11/07/2016)
	  ○ A5329 Letter of Amendment 2, Version 2.0 (07/07/2017)
	  ○ A5329 Letter of Amendment 3, Version 2.0 (08/04/2017)
	  ○ A5329 Letter of Amendment 4, Version 2.0 (06/06/2018)
	• Updated key analysis decisions
	• Updated schedule of evaluation windows to coincide with Version 2.0 of the protocol.
	• Included an overview of sample size considerations.
	• Included an overview of formal interim monitoring
	• Included a note on primary safety and tolerability outcome.
	• Updated report contents section to provide additional detail
	• Reformatted document to new template
	• Added appendices with writing team roster and analysis timeline
		4/24/2019

2	• Updated included population: remove references to HCV treatment naïve)
	• Updated ARV regimen
	  ○ Cohort A and B = integrase inhibitor (INI)-based (raltegravir [RAL] or dolutegravir [DTG]) ARVT regimen
	  ○ Cohort C and D = protease inhibitor (PI)-based (darunavir [DRV] or atazanavir [ATV] ART regimen
	  ○ Updated Abbvie's HCV drug names
	  ▪ ABT-450/r/ABT-267 = paritaprevir/ritonavir/ombitasvir (PTV/r/OBT)
	  ▪ ABT-333 = dasabuvir (DSV)
	  ○ HCV genotype 1a participants are receiving ribavirin (RBV), while HCV genotype 1b participants are not receiving RBV. References to DAA+RBV have been changes to DAA+/-RBV
	• Updated objectives to match Version 2.0 objectives
	  ○ Removed one objective from Version 1.0 and moved one secondary objective to exploratory objective.
		06/21/2016

	• Clarified calculations of analysis windows • Updated monitoring section to match Version 2.0 of the protocol • Clarified safety outcome • Update Secondary Outcome Measures Analyses to reflect the changes in objectives for Version 2.0 of the protocol	
1	Original Version	10/06/2015

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures and additional outcome measures of the A5329 study that will be included in the primary manuscript, and which address, at a minimum, the major primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary analysis report. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are included in the Analysis Implementation Plan (AIP).

Analyses for the Primary Analysis Report will be performed after the last participant has completed his/her last study visit at 24 weeks post-treatment, all queries have been resolved, and the study database closure/data lock has been completed.

Note: Primary Completion Date (PCD) is May 17, 2018. Results must be submitted to ClinicalTrials.Gov by one year after PCD.

1.2 Version History

See table above

2 Study Overview

2.1 Study Design

(Extracted from Protocol Version 2.0)

DESIGN Non-randomized, open-label, phase II study of interferon (IFN)-free hepatitis C virus (HCV) therapy for 24 or 12 weeks in sequentially enrolled cohorts of participants with HIV-1 coinfection who are taking protocol-defined antiretroviral treatment (ART).

DURATION Up to 48 weeks per participant

SAMPLE SIZE 100 participants, 25 participants per cohort

POPULATION HCV genotype 1a or 1b and HIV-1 coinfected participants (HCV treatment-naïve or HCV treatment-experienced) who are on a concurrent integrase inhibitor (INI)-based (raltegravir [RAL] or dolutegravir [DTG]) or protease inhibitor (PI)-based (darunavir [DRV] or atazanavir [ATV]) ART regimen.

Participants will be categorized according to evidence of cirrhosis (yes or no). For each 25-participant cohort, the number of participants enrolled with cirrhosis will be limited to 7.

REGIMENS Among participants taking an INI-based (RAL or DTG) ART regimen for HIV-1: 24 (Cohort A) or 12 (Cohort B) weeks of HCV treatment with HCV direct-acting antivirals (DAA) paritaprevir/ritonavir/ombitasvir (PTV/r/OBT) + dasabuvir (DSV) +/- ribavirin (RBV) therapy (DAA+/-RBV therapy):

Drug 1: PTV/r/OBT (150/100/25 mg; two 75/50/12.5 mg fixed -dose combination tablets) orally (PO) once a day (QD) plus

Drug 2: DSV (250 mg) PO twice per day (BID) plus

Drug 3: RBV (1000 or 1200 mg weight-based) dosed in two divided doses PO BID (participants with HCV genotype 1a only; participants with HCV genotype 1b will not receive RBV)

Among participants taking a HIV-1 PI-based (DRV or ATV) ART regimen for HIV-1: 24 (Cohort C) or 12 (Cohort D) weeks of HCV treatment with HCV DAA+/-RBV therapy:

Drug 1: PTV/r/OBT (150/100/25 mg; two 75/50/12.5 mg fixed-dose combination tablets) PO QD plus

Drug 2: DSV (250 mg) PO BID plus

Drug 3: RBV (1000 or 1200 mg weight-based) dosed in two divided doses PO BID (participants with HCV genotype 1a only; participants with HCV genotype 1b will not receive RBV)

Details for the qualifying ART concomitant regimens are in protocol section 5.4.1.

Each cohort will include two steps: on-HCV treatment (Step 1) and post-HCV treatment follow-up (Step 2).

2.2 Hypotheses (copied from protocol document v2.0 06/08/2016 and not revised in any subsequent LOA)

1.1.1 Combination therapy with the hepatitis C virus (HCV) direct-acting antiviral (DAA) treatment regimen of paritaprevir (PTV)/r (ritonavir)/ombitasvir (OBT) plus dasabuvir (DSV), with and without ribavirin (RBV) (DAA+/-RBV therapy) will be safe and well tolerated.

1.1.2 DAA+/-RBV therapy will result in sustained virologic response (SVR12) rates higher than 70% corresponding to the SVR12 rates observed with telaprevir (TVR) and boceprevir (BOC) plus pegylated interferon (PegIFN)/RBV.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

2.3.1 Primary Objectives

1. To evaluate the safety and tolerability of DAA+/-RBV therapy in participants coinfected with HIV-1.

2. To estimate the efficacy of DAA/-+RBV therapy in HCV/HIV-1 coinfected participants, as measured by the SVR at 12 weeks (SVR_{12}) after DAA+/-RBV therapy discontinuation, where SVR_{12} is defined as HCV RNA in the blood less than the assay lower limit of quantification (LLOQ).

Note: the LLOQ was not specified in the protocol in case a more sensitive assay was available at time of final analysis. The LLOQ and assay specifications will be documented in the final analysis report.

2.3.2 Secondary Objectives

Note: (only **bolded** objectives below addressed in this primary SAP)

1. **To evaluate HIV-1 virologic failure (VF),** defined in section 7.3 of protocol **and section 10.1 of this document) in HCV HIV-1 coinfected participants during coadministration of antiretroviral therapy (ART) and DAA+/-RBV therapy.**

2. **To evaluate acquisition of major HIV-1 resistance mutations in HCV/HIV-1 coinfected participants who experience HIV-1 VF during coadministration of ART and DAA+/-RBV therapy and during the initial four-week period following discontinuation of DAA+/-RBV therapy.**

3. To estimate the population plasma pharmacokinetic (PK) parameters of DAA+/-RBV therapy, during coadministration with antiretrovirals (ARVs) in HCV/HIV-1 coinfected participants, and to compare the participant-specific PK parameters obtained with those reported in prior studies for HIV-1 seronegative participants. [Note: this objective is being deferred to the secondary analysis.]

4. **To assess the relationship of markers of immune activation, including IP10 and sCD14, measured before, during and after administration of DAA+/-RBV therapy and DAA+/-RBV therapy outcome (SVR_{12})**

5. **To estimate the efficacy of DAA+/-RBV therapy in HCV/HIV-1 coinfected participants, as measured by the sustained virologic response at 24 weeks (SVR_{24}) after DAA+/-RBV therapy discontinuation where SVR_{24} is defined as HCV RNA in the blood less than the assay LLOQ.**

2.4 A5329 Protocol History

Protocol Version 1.0 (finalized May 19, 2014, IND# 122,987)

A5329 Clarification Memo 1, Version 1.0 (09/04/2015) regarding clarification on serum alfa-fetoprotein (AFP) entry criteria (Protocol Section 4.1.11). There was a typing error. The AFP value listed as ≤100 ng/dL should be ≤100 ng/mL.

A5329 Clarification Memo 2, Version 1.0 (09/25/2015) regarding clarification on referencing the Lab Processing Chart (LPC) for appropriate testing laboratories (protocol sections: Glossary; 4.1.9; 4.1.10; 6.4.10; 7.3.1).

A5329 Protocol Version 2.0 (finalized June 8, 2016, IND# 122,987)

A5329 Letter of Amendment #1, Version 2.0 (11/07/2016). Abbvie released an updated Investigator's Brochure (IB), which resulted in changes to the background and risk list. A specimen collection was added to the treatment discontinuation visit for participants in cohorts B and D. In addition, any partner of a participant would also need to comply with the same contraceptive approaches. ATV 300mg/Cobicistat 150 mg PO QD was added to the list of qualifying ART regimens for the PI regimen group. Enrollment of eligible participants into Cohorts A and C closed; enrollment of eligible participants B and D opened. HCV genotype 1a-infected participants with cirrhosis and prior interferon-based treatment-experience are not eligible to enroll into Cohorts B and D.

A5329 Letter of Amendment #2, Version 2.0 (07/07/2017). Participants must be screened for A5335S when screening for A5329. If he/she is not eligible to participate in A5335S, then he/she will not be able to continue in A5329. Participants must be classified as non-cirrhotic prior to study entry.

A5329 Letter of Amendment #3, Version 2.0 (08/04/2017). For participants on DRV, HIV-1 virologic suppression must have been attained while the participant was taking a dose of DRV/r 800/100 mg PO QD or DRV/c 800/150 mg PO QD.

A5329 Letter of Amendment #4, Version 2.0 (06/06/2018). These were updates to team membership, and updates to fulfill DAIDS requirements regarding informing participants that other US, local, and international regulatory entities may review study records. There were not updates to the study design, or analysis plan.

2.5 Overview of Sample Size Considerations

The goal of this study is to gather safety and efficacy data on the proposed regimens in HCV/HIV-1 co-infected participants on certain HIV-1 ART regimens; the primary study objective is framed as a one-sample evaluation testing whether or not a fixed point estimate can be excluded.

The planned sample size of 25 participants per cohort for the primary efficacy outcome analysis of SVR_{12}, a dichotomous (Bernoulli distributed) outcome, was based on assumptions for a one-sided significance level of 5% (compared similarly to a standard one-sided type I error of a 2.5%), and requiring at least 85% statistical power. If the data support a conclusion of the SVR_{12} rate higher than 70% (the excluded fixed point estimate), then the alternative hypothesis will be accepted. With 25 participants in each cohort, there is 86% power to conclude that SVR_{12} is greater than 70% when the true SVR_{12} rate is 92%.

Refer to section 9.4 of protocol version 2.0 for additional details on sample size considerations.

2.6 Overview of Formal Interim Monitoring

This study will be monitored at least annually by an ACTG-appointed Study Monitoring Committee (SMC). This initial review will occur when the first of either 25 participants enroll onto the study (irrespective of cohort) have a least 12 weeks of follow-up data available, or the 1-year anniversary of the first participant enrolling to the study (first participant enrolled September 16, 2015) occurs.

Any/all SMC reviews will include administrative/conduct data as well as safety data according to the safety-related outcomes, and any data (eg accrual, conduct, key specimen availability, and safety) from the substudies (A5334s/A5335s if/as available).

Note that since efficacy outcomes in the substudies are not being assessed in real-time, but being performed in retrospective, batch testing, that efficacy outcome data from substudies will likely not be available at the time of A5329 interim reviews, and therefore no efficacy outcome data will be presented, even if initial batch testing has commenced.

For the main study (A5329), there are no plans for formal interim monitoring of the efficacy outcome of SVR_{12} or related earlier HCV RNA outcomes. However, HCV RNA descriptive summaries will be provided to the SMC. While HIV-1 VF has been removed as a safety event of interest in Version 2.0, HIV-1 RNA descriptive summaries will be provided to the SMC.

The interim analysis report will be distributed to the Core Team (as identified in the Study Monitoring Plan, and is a subset of the named protocol team on the protocol), and the SMC. The report will include analyses for the following by cohort (and by cirrhosis status, if needed):

- Accrual and Study Status
- Baseline Characteristics
- Data Completeness
- Safety information
- HCV RNA and HIV-1 RNA summaries

3 Statistical Principles

3.1 General Considerations

3.1.1 Key Analysis Decisions:

- Throughout, study entry is defined at the date of first dose of study medications. For interim analyses, if the date of first dose of study medications 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. For the protocol and analysis windows of each study visit, refer to the study's AIP. For SVR, see SVR outcome definitions below.
- Because persons who never start study treatment are taken off study following entry of baseline visit CRF (per protocol section 6.3.6), persons who never start study treatment will be excluded from all analyses. For interim and final analyses, the CONSORT diagram will explain the difference between number of participants enrolled and number in the analysis sample (and thus number and reasons for exclusion due to never starting treatment), but then all subsequent analyses (accrual, baseline and post baseline follow-up), will exclude these persons and thus be limited to those who started (or for interim analyses who intend to start—to allow for data entry delay for start of RX date) study treatment.
- In SMC reports:
    - Lists will be sorted by variables in the order given with study participants identified using an alternate participant identifier (PubID, i.e. not ACTG patid).
    - Participant-specific dates will not be shown, but converted to time since start of study treatment or time since discontinuing study treatment, when applicable.
- Data will be summarized by individual Cohort (A, B, C, and D, as defined above) for analyses and analysis subgroups (i.e. cirrhosis classification), but will not be analyzed separately by protocol version, as noted above. [Note: this is an update from earlier protocol versions which made reference to analysis groups, which combined data across cohorts. With updates to the protocol, all groupings used for analysis and report will be the cohorts A-D, irrespective of version (with information provided to show how protocol version may have resulted in ARV or HCV treatment variation within cohort).

4 Outcome Measures

Note: Italicized texts in section 4 of this document are formatted in the results style of ClinicalTrials.gov

4.1 Primary Outcome Measures

4.1.1 Primary Efficacy Outcome

Measure Title: *Sustained Virologic Response at 12 Weeks after HCV Treatment discontinuation*

Measure Description: *SVR_{12} evaluated at least 12 weeks post HCV treatment discontinuation. Responders will be those whose HCV RNA is less than the assay LLOQ. For those whose HCV early responses prior to SVR_{12} evaluation meet the guidelines for HCV VF, their SVR_{12} outcome*

will be defined as non-response. Two-sided 90% confidence interval using exact binomial distribution according to the method of Clopper-Pearson will be calculated.

Time Frame: *At least 12 weeks after date of last dose of study treatment. The duration for study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Percentage of Participants*

Summary statistics: *Point wise estimate and associated 90% two-sided confidence interval.*

Statistical analysis: *A one-sided exact test for a single binomial population will use the null hypothesis response rate of 70%.*

Analysis Approaches: The unit of outcome, SVR_{12}, is binary/dichotomous (responder or non-responder). SVR12 will be evaluated at least 12 weeks post HCV treatment discontinuation. Responders will be those whose HCV RNA is less than the assay of LLOQ.

For those whose HCV early responses prior to SVR12 evaluation meet the guidelines for HCV virologic failure, their SVR12 outcome will be defined as non-response. Those missing a HCV RNA result from the week 12 post HCV therapy discontinuation visit, which can occur as early as 10 weeks post treatment discontinuation, (and missing all subsequent evaluations) will be considered non-responders. However, if HCV RNA evaluations subsequent to week 12 post treatment are non-missing, then the first HCV RNA subsequent to week 12 post treatment will instead be used to define the primary outcome.

[Note: 2-sided, 90% exact interval corresponds to 2, one-sided exact bounds each at 5% significance level.]

For participants who are non-responders, reasons for not achieving SVR_{12} will be enumerated and summarized.

The analysis will be performed within each cohort and estimation (but not testing) will also be repeated within the subgroups defined by the following baseline characteristics: sex, HCV genotype, HCV treatment experience, cirrhosis status.

4.1.2 Primary Safety and Tolerability Outcomes

Safety and tolerability outcomes will be summarized within each cohort. The method of Kaplan-Meier can be used to estimate the cumulative probability of these outcomes (eg, time to first SAE, or time to first qualifying sign/symptom), at various follow-up times, but no comparisons to internal or external (ie, historical controls) groups is planned. Note that these analyses will be as-treated, where “as-treated” is defined as participants being evaluated for these outcomes only during receipt of HCV therapy and for 30 days following HCV therapy discontinuation (including premature discontinuation). For grading diagnoses, signs and symptoms, and laboratory results,

sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

Note: Only primary events can count towards a safety outcome. If a participant experienced multiple events of the same type, the most serious grade will be counted for summarizing outcome severity grading. If a participant's entry information meets the safety outcome definition (eg. Entry lab abnormality is grade 3), then post-treatment initiation safety information must be one grade worse than baseline to meet the safety outcome definition.

4.1.2.1 SAEs as Defined by ICH Criteria

Measure Title: *Participants with an Occurrence of SAEs as Defined by ICH Criteria*

Measure Description: *Participants experiencing any Serious Adverse Events (SAEs) as defined by ICH occurring after initiation of study treatment through 30 days after the date of last dose of study treatment.*

Time Frame: *From treatment initiation until 30 days post HCV study treatment discontinuation (whether planned or premature discontinuation). The duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with at least one observed SAEs*

Statistical analysis*: None*

Analysis Approaches: Refer to Section 4.1.2 of this document.

4.1.2.2 Premature HCV Study Treatment Discontinuation Due to Any Reason Other than HCV VF

Measure Title: *Participants who Prematurely Discontinued HCV Study Treatment for Any Reason Other than HCV Virologic Failure.*

Measure Description: *Participants who discontinue HCV study treatment prematurely due to any reason other than HCV virologic failure.*

Time Frame: *From treatment initiation until either 24 or 12 weeks later. The duration for HCV study treatment for Cohorts A and C and Cohorts B and D were 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with premature HCV study treatment discontinuation*

Statistical analysis*: None*

Analysis Approaches: Refer to Section 4.1.2 of this document.

4.1.2.3 Occurrence of Signs/Symptoms Grade 3 or Higher

Measure Title: *Participants with an Occurrence of Signs/Symptoms Grade 3 or Higher*

Measure Description: *Signs/symptoms of Grade 3 or higher after initiation of study treatment through 30 days after the date of last dose of study treatment. Participants with grade 3 sign/symptom prior to initiation of study treatment must have one grade higher than pre-treatment.*

Time Frame: *From treatment initiation until 30 days post HCV study treatment discontinuation (whether planned or premature discontinuation). The duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and started first dose of study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with premature HCV study treatment discontinuation*

Statistical analysis*: None*

Analysis Approaches: Refer to Section 4.1.2 of this document.

4.1.2.4 Diagnoses Leading to HCV Study Treatment or HIV-1 ARV Discontinuation

Measure Title: *Participants with an Occurrence of Diagnosis Leading to premature HCV Study Treatment or HIV-1 ARV Discontinuation*

Measure Description: *Participants who had diagnoses leading to premature HCV study treatment or HIV-1 ARV discontinuation.*

Time Frame: *From treatment initiation until end of study follow-up at 48 weeks.The planned duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with diagnoses leading to HCV study treatment or HIV-1 ARV discontinuation*

Statistical analysis*: None*

Analysis Approaches: Refer to Section 4.1.2 of this document.

4.1.2.5 Occurrence of Laboratory Abnormalities Grade 3 or Higher

Measure Title: *Participants with an Occurrence of Laboratory Abnormalities Grade 3 or Higher*

Measure Description: *Participants with an observed laboratory abnormalities Grade 3 or higher. If entry (pre-treatment) lab result was grade 3, then a grade 4 result would be required to meet this outcome.*

Time Frame: *From treatment initiation until 30 days post HCV study treatment discontinuation (whether planned or premature discontinuation). The duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with an occurrence of laboratory abnormality of Grade 3 or higher.*

Statistical analysis*: None*

Analysis Approaches: Refer to Section 4.1.2 of this document.

4.2 Secondary Outcome Measures

4.2.1 HIV-1 Virologic Failure

Measure Title: *Participants who experienced HIV-1 Virologic Failure*

Measure Description: *HIV-1 virologic failure defined as two consecutive HIV-1 RNA results ≥ 200 copies/mL*

Time Frame: *From treatment initiation until 4 weeks after permanent discontinuation of HCV study treatment. The duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and started first dose of study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit of measure: *Number of Participants*

Summary statistics: *Number participants who experience HIV-1 virologic failure.*

Statistical analysis: *None.*

Analysis Approaches: Detailed presentation listing of HIV-1 VF case(s) that includes: pre-treatment/history information, ARV and HCV treatment information, longitudinal safety information, other conduct information, longitudinal plasma HIV-1 RNA during the study, HCV RNA (only as adherence surrogate for HCV medications), HIV-1 resistance information, and narrative of HIV-1 failure.

4.2.2 HIV-1 Resistance Mutations

Measure Title: *Selected HIV-1 Resistance Mutations among participants who experience HIV-1 Virologic Failure*

Measure Description: *Presence of genotypic mutations conferring major resistance to any HIV-1 protease inhibitor drug, from plasma sample drawn following confirmed HIV-1 virologic failure outcome.*

Time Frame: *From treatment initiation until confirmation of HIV-1 virologic failure. The duration for HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who experienced HIV-1 virologic failure outcome.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Number of Participants*

Summary statistics: *Number of participants with one or more genotype mutations in protease conferring major resistance to any Protease Inhibitors antiretroviral drug.*

Statistical analysis: *None*.

Analysis Approaches: Listing to include: week of first HIV RNA ≥ 200 IU/mL, week of confirmed HIV RNA ≥ 200 IU/mL, assigned cohort and list of all significant (ie. associated with ARV PI resistance), mutations, and the resistance interpretation at the ARV level. Listing will note whether observed mutations are associated with ARV drugs currently being received.

4.2.3 Biomarkers of Immune Activation

4.2.3.1 Measurement of Soluble CD14 (sCD14) Levels

Measure Title: *Changes in Monocyte Activation from entry as measured by biomarker soluble CD14*

Measure Description: *Absolute change from entry in sCD14 levels in plasma*

Time Frame: *End of HCV treatment (EOT), and 12 weeks post (EOT). The end of HCV study treatment for Cohorts A and C and Cohorts B and D was 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit (of measure): *ng/mL*

Summary statistics: *Median (Inter-Quartile Range), N with observed results*

Secondary analysis: *None*

Analysis Approaches: sCD14 levels will be summarized at entry, end of HCV treatment, and post-treatment week 12; changes of sCD14 levels from baseline will also be summarized.

4.2.3.2 Measurement of Interferon Gamma-Induced Protein 10 Levels

Measure Title: *Changes in inflammation from entry as measured by biomarker CXCL10 Levels*

Measure Description: *Absolute change from entry in CXCL10 (also known as Interferon gamma-induced protein 10 (IP-10) levels in plasma.*

Time Frame:*. End of HCV treatment (EOT), and 12 weeks post (EOT). The end of HCV study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit (of measure): *pg/mL*

Summary statistics: *Median (Inter-Quartile Range), N with observed results*

Statistical analysis: *None.*

Analysis Approaches: Details are parallel to section 4.2.3.1.

4.2.4 Measurement of SVR_{24}

Measure Title: *Sustained Virologic Response 24 weeks after discontinuation of HCV Treatment*

Measure Description: *Responders will be those whose HCV RNA is less than the assay LLOQ. For those whose HCV early responses prior to SVR_{24} evaluation meet the guidelines for HCV VF, their SVR_{24} outcome will be defined as non-response.*

Time Frame: *At least 24 weeks after date of last dose of HCV study treatment. The duration for study treatment for Cohorts A and C and Cohorts B and D are 24 and 12 weeks, respectively.*

Population Description: *Participants who enrolled and initiated study treatment.*

Reporting Groups: *Cohorts A, B, C, and D.*

Unit: *Percentage of participants*

Summary statistics: *Point wise estimate and associated 2-sided 90%, exact (Clopper-Pearson) confidence interval*

Statistical analysis: *None*

Analysis Approaches: The SVR_{24} outcome will be summarized and described using parallel methods to the primary SVR_{12} outcome as described in Section 9.6.1 of the protocol and Section 4.1.1 of this document.

The visit window for SVR_{24} will start at the week 24 post-treatment (which can occur as early as 20 weeks post discontinuation), and use imputation parallel to that for SVR_{12} to account for missing data, if relevant.

5 Report Contents

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