Statistical Analysis Plan

A5279

Phase III Clinical Trial of Ultra-short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Individuals with Latent Tuberculosis Infection

ClinicalTrials.Gov Identifier: NCT01404312

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This is A5279 SAP Version 4.0 with names of authors, names of publication writing team members and analysis timeline redacted.

TABLE OF CONTENTS

Introduction

1.1   Purpose of the Statistical Analysis Plan (SAP)

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcome measures of ACTG A5279 that will be included in the primary manuscript addressing the major primary and secondary objectives of the study, as well as the primary and secondary outcome measures for which results will be posted on ClinicalTrials.gov. The Primary SAP also 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 amongst 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 statistical analysis report.

This SAP is modified from version 3.0 to comply with version 4.0 of the SDAC's updated SAP SOP (effective 11/1/2017). This document provides a general overview of analysis plans for primary and secondary outcome measures of A5279; a separate Analysis Implementation Plan (AIP) provides more specific coding details of the analysis (e.g. additional table/figure specifications, data sources, validation requirements).

1.2   Summary of Major Changes from V 3.0

- Exploratory objectives and outcome measures were removed.
- Removed DSMB report specifications.
- Added per-protocol assessment of primary outcome measure.
- Sensitivity analyses added to treat deaths differently than the primary analysis specifications.

2   Study Overview (Protocol Version 1.0; 2.0 changes in bold)

This study is a multicenter, randomized, open-label, phase III clinical trial comparing a 4-week rifapentine (RPT)/isoniazid (INH) regimen to a standard 9-month daily INH regimen for the prevention of tuberculosis (TB) in HIV-infected participants. The primary objective will be efficacy of TB prevention. The study will also assess safety and tolerability of the regimens, adherence to the treatments, and patterns of antibiotic resistance among Mycobacterium tuberculosis (MTB) isolates in participants who fail on these prophylactic regimens.

The study population is HIV-1 infected men and women ≥13 years old and ≥ 30 kg without evidence of active TB who: 1) Have tuberculin skin test (TST) reactivity ≥ 5 mm or a positive interferon gamma release assay (IGRA), OR 2) Live in high burden areas, defined as **areas** with **an estimated or reported** TB prevalence ≥ 60 cases/100,000 population/year. If a participant is taking antiretroviral therapy (ART) **at study entry**, only **approved** nucleoside reverse transcriptase inhibitors (NRTIs) **with EFV or NVP for at least 4 weeks are permitted**.

Participants will be stratified based on (1) CD4+ cell count at entry and (2) ART use at entry,

and randomized within strata in a 1:1 ratio to receive either:

- ARM A: 4-week daily regimen of weight-based RPT and INH, plus vitamin B6, or

- ARM B: 9-month (36-week) daily INH regimen, plus vitamin B6

Each participant will be followed for 3 years (156 weeks) after the last participant is enrolled.

The primary hypothesis is that ultra-short course (4-week) rifapentine (RPT)/isoniazid (INH) is not inferior to a standard 9-month (36-week) daily INH regimen for the prevention of tuberculosis (TB) in HIV-infected patients.

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.

2.1   Primary Objectives

To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to a standard 9-month (36 week) daily INH regimen for TB prevention in HIV-infected individuals

2.2   Secondary Objectives

- ➤ To compare safety and tolerability of the regimens
- ➤ To compare overall and non-TB mortality rates among participants receiving the two regimens

3   Outcome Measures

3.1   Primary Outcome

The primary study outcome measure is the time to active TB, death due to TB, or death from unknown cause.

Active TB is defined as Confirmed or Probable Pulmonary TB or Extra-pulmonary TB as defined by ACTG criteria for clinical and other events (Appendix 100) and judged to be such by at least one of two independent reviewers who are clinicians with expert knowledge in the diagnosis of TB, are not part of the study team, and are not involved in patient management of participants in the study. The reviewers are blinded to the participant ID, site, treatment arm, and treatment status. Deaths attributed to active TB confirmed by independent review will be considered to be a TB endpoint. For primary analyses, deaths with an unknown cause of death (COD) judged to be such by independent review will also be coded as TB outcomes as described in the protocol.

3.2   Secondary Outcomes

- ➤ Occurrence of one or more Serious Adverse Events (SAE) vs no SAE.

- ➤ Highest reported grade of each grade 3 or 4 laboratory value or sign/symptom that is at least one grade increase from baseline for the following targeted events: nausea

and vomiting; cutaneous, drug-associated fever; elevated AST (SGOT), ALT (SGPT), or bilirubin; peripheral neuropathy.

➢ Tolerability: Ordered categorical variable indicating most stringent level of study drug management due to toxicity that was required over the treatment period.

1) Premature permanent treatment discontinuation
2) Treatment hold for more than 7 consecutive days
3) None of the above

➢ Time from randomization to death from any cause.

➢ Time from randomization to death due to a non-TB event.

➢ EFV plasma concentrations at weeks 0, 2, and 4 for the first 90 eligible participants who are randomized to arm A under protocol version 1.0, and in the first 30 eligible participants randomized to arm A under protocol version 2.0.

➢ Under protocol version 2.0, EFV plasma concentrations at week 16 in the first 30 eligible participants who are randomized to arm A.

➢ Under protocol version 2.0, EFV plasma concentrations at weeks 0, 2, and 4 in the first 90 eligible participants randomized to arm B.

➢ NVP plasma concentrations at weeks 0, 2 and 4 in the first 90 eligible participants randomized to arm A

o Note: Due to shipping problems from one site, the full results for this outcome measure may not be available within one year of the primary completion date.

4   Statistical Methods

4.1   Primary Objective

For each participant, the time to TB is defined as the time from randomization to the first diagnosis of active TB at any level of certainty, or time from randomization to death if there was no prior active TB diagnosis and the death is to be included as an endpoint. The diagnosis date of 'confirmed TB' will be the date the specimen was collected that was positive for *Mycobacterium tuberculosis*. The diagnosis date of 'probable TB' is that listed on the CRF by the site.

For the primary analysis of the time to TB, participants' time at risk will be censored at the last visit with a TB assessment prior to loss to follow-up, including events unrelated to treatment or outcome such as incarceration, moving, and site closure; at death where the Cause of Death is

known to be not related to TB; or at the last visit with a TB assessment prior to close of follow-up otherwise.

This will be a modified intent-to-treat (mITT) analysis, with all eligible participants that initiated treatment analyzed according to randomized study arm. The reason for the exclusion of those that did not initiate treatment is that some left the study immediately, some were followed on study per the SOE, and some remained on study with little or no follow-up until declared lost follow-up.

The primary objective will be evaluated by calculating a confidence interval (CI) around the difference between the observed TB incidence rates in the RPT and INH arms, with the confidence level adjusted for interim monitoring. For DSMB analyses specified by the group sequential design (see the Study Monitoring Plan and protocol) and the final analysis, the IRD between treatment arms will be presented as a stratified Mantel-Haenszel estimate with the confidence interval (CI) computed using the method of Greenland and Robins (Biometrics 1985;41:55-68) that adjusts the variance estimate for rare events. The CI will be appropriately adjusted for sequential monitoring with a Haybittle-Peto use function boundary (alpha-value) at both interim and final analyses, where interim analyses will use a 99.9% CI and the final will use a (95.0 + 0.1*k)% CI where k is the number of DSMB meetings that review formal interim analyses of the IRD. There was 1 interim analysis, conducted for the 2016 DSMB, so the final analysis will use a 95.1% CI. This is slightly more conservative than the Haybittle-Peto bound, but used to ensure no inflation of the type I error. SAS PROC STDRATE will be employed. Randomization was stratified by: (1) the most recent CD4+ cell count obtained within 180 days prior to entry (<100, 100-250, and >250 cells/mm^3) and (2) ART use at entry (Yes/No). However, slightly less than 2.5% had screening CD4 <100; to avoid over-stratification, the lower two categories of screening CD4 counts will be combined for stratified analyses. Non-inferiority of ultra-short-course RPT/INH regimen will be demonstrated if the upper bound of the confidence interval for the IRD is less than 1.25/100PY.

Data from prior studies are consistent with a constant TB rate over time, but this will be confirmed in these data. If this assumption does not hold, a piecewise constant hazards model will be used to estimate the incidence rate difference. The intervals over which hazards are constant will be chosen upon visually inspecting plots of the empirical hazard functions. As noted above, deaths attributed to TB will be considered to be TB endpoints. Deaths attributed to known causes other than TB will be censored. Deaths from unknown causes are expected to be minimal. For the primary analysis, deaths from unknown causes will be coded as TB events.

Sensitivity analyses

1) A per-protocol analysis that will exclude any participants who had permanently prematurely discontinued treatment
2) Including all non-traumatic deaths as a primary outcome event
3) Censoring all deaths from unknown causes
4) Competing risk analysis that treats deaths from unknown cause as a competing risk

5) Competing risk analysis that treats all deaths not due to TB or of unknown cause as a competing risk

6) Competing risk analysis that treats all deaths as a competing risk

For competing risk analyses above, hazard ratios and 95% CI will be presented for the treatment effect.

As required by NIH, interactions of sex and race/ethnicity with treatment will be formally tested and presented. This will be done by treating sex and race/ethnicity, and the combination of the two, as stratification factors and presenting the incidence rate difference estimates and 95% CIs within each level of the strata. As noted above, we will also evaluate the non-inferiority of short-course RPT/INH within the CD4+ cell count and ART strata as differences could be important to inform the field. There will be no adjustment to the alpha level for multiple comparisons, and results will be presented cautiously.

4.2   Secondary Objectives

The safety population will be the same as the primary efficacy population.

➤ Proportion of participants with one or more SAEs will be compared between arms using Fisher's exact test.

➤ Proportion of participants with a targeted event (described in section 3.2) of grade 3 or 4 and one grade increase from baseline will be compared between arms using Fisher's exact test. Rates of targeted events of grade 3 or 4 and one grade increase from baseline will be compared between arms using a Poisson regression model. If overdispersion is present, a negative binomial or quasi-Poisson model will be used instead.

➤ Tolerability will be compared between arms using a proportional odds model, with the ordered categories as described in section 3.2. If the proportional odds assumption appears to be violated, a baseline category logit model will be used instead.

➤ Time from randomization to death from any cause will be compared between arms using a log-rank test.

➤ Time from randomization to death due to TB or unknown cause will be compared between arms using the Fine-Gray model for competing risks, with death not due to TB treated as a competing risk.

➤ Time from randomization to death due to a non-TB event of known cause will be compared between arms using the Fine-Gray model for competing risks, with death due to TB or unknown cause treated as a competing risk.

➢ EFV plasma concentrations will be summarized in arm A and arm B at weeks 0, 2, and 4, and in arm A at week 16

➢ NVP plasma concentrations will be summarized in arm A at weeks 0, 2, and 4