A5290 Statistical Analysis Plan

Version 3.0 (Primary Analysis)

A Randomized, Phase 2b Study of a Double-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifampin-Based Tuberculosis Treatment versus a Standard-Dose Lopinavir/Ritonavir-Based Antiretroviral Regimen with Rifabutin-Based Tuberculosis Treatment with or without Raltegravir in HIV-1-Infected Persons Requiring Treatment for Active TB and HIV

ClinicalTrials.gov Identifier: NCT01601626

14 July 2017

Filename: *U:\CTgov\documentation\A5290AnalysisPlanV3_*final.docx
Directory mapping: *\home\kendall*
Printed on: *December 19, 2017*

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1 Introduction

This statistical analysis plan has been developed to (1) provide a structured time-frame for database completion and preparation of the primary analysis report; (2) facilitate discussion of the key statistical analysis components among the study team; (3) provide agreement between the study team and statisticians regarding the statistical analyses to be performed; and (4) aid in setting priorities relating the data cleaning and development of statistical analysis programs.

The statistical analysis plan contains details of all statistical analyses that will be completed prior to the preparation of the primary analysis report.

2 Protocol Overview

A5290 is a prospective, randomized, open-label, Phase 2b study comparing three lopinavir/ritonavir (LPV/r)-based antiretroviral (ARV) regimens among participants in high tuberculosis (TB) endemic resource-constrained settings undergoing treatment for TB and HIV and requiring protease inhibitor (PI)-based antiretroviral therapy (ART). It was planned to have two accrual periods. Accrual period 1 aimed to randomize 60 participants in an effort to secure 54-60 evaluable participants for the PK interim analysis. It was planned that accrual would be suspended while the interim PK and safety evaluation is conducted. However, due to feasibility concerns, accrual period 2 will not open to randomize the additional 411 participants.

The study population is HIV-infected persons (male or female) at least 18 years of age with documented HIV infection, a clinical diagnosis of probable or confirmed active TB (including extrapulmonary TB) with susceptibility to rifampin (RIF), and who require a PI-based ARV regimen.

471 participants will be randomized in a 1:1:1 ratio to receive either:

- Arm A
  ART: LPV 400 mg/RTV 100 mg twice daily (BID) + two NRTIs.
  Anti-TB therapy: Isoniazid (INH), rifabutin (RBT), ethambutol (EMB), pyrazinamide (PZA), and pyridoxine.
  After completion of TB treatment through week 72: LPV 400mg/RTV 100mg BID + two NRTIs.
- Arm B
  ART: LPV 800 mg/RTV 200 mg BID + two NRTIs.
  Anti-TB therapy: INH, rifampin (RIF), EMB, PZA, and pyridoxine.
  After completion of TB treatment through week 72: LPV 400mg/RTV 100mg BID + two NRTIs.
- Arm C
  ART: LPV 400 mg/RTV 100 mg BID + two NRTIs + raltegravir (RAL) 400 mg BID.
  Anti-TB therapy: INH, RBT, EMB, PZA, and pyridoxine.
  After completion of TB treatment through week 72: LPV 400mg/RTV 100mg BID + two NRTIs + RAL.

LPV/r, RTV, RAL, and RBT are available through this study. RIF, INH, EMB, PZA, pyridoxine, and the NRTI background are not provided through the study and must be obtained by non-study prescription.

Each participant will be followed until week 72.

The study hypothesis is that, for HIV-1-infected participants with active tuberculosis (TB) who require protease inhibitor (PI)-based antiretroviral therapy (ART), a standard dose LPV/r regimen, with or without RAL, coupled with RBT-based TB treatment is superior to a double dose LPV/r regimen coupled with RIF-based TB treatment.

2.1 Protocol Objectives

2.1.1 Primary Objective

To compare rates of virologic suppression to <400 copies/mL at 48 weeks for the two standard dose LPV/r and RBT arms versus the double-dose LPV/r and RIF arm [Objective 1.2].

2.1.2 Secondary Objectives

1. To evaluate TB treatment outcomes (as measured by week 8 mycobacterial culture conversion, treatment failure at or after week 24, TB relapse/recurrence by week 72) between RBT-containing arms and the RIF-containing arm, to include the association between RBT or RIF exposure as well as other factors potentially associated with outcomes of TB treatment [Objective 1.3.1].
2. To compare rates of virologic suppression to <50 copies/mL at 48 weeks for the two standard dose LPV/r and RBT arms versus the double-dose LPV/r and RIF arm [Objective 1.3.2].
3. To compare rates of virologic suppression to <50 copies/mL and <400 copies/mL at 48 weeks for standard dose LPV/r and RBT versus standard dose LPV/r, RBT, and RAL [Objective 1.3.3].
4. To compare safety and tolerability during TB treatment between the three treatment arms [Objective 1.3.4].
5. To compare the proportion of participants with virologic failure and time to virologic failure between the three treatment arms [Objective 1.3.5].
6. To compare the emergence of HIV-1 drug resistance mutations in gag, protease, reverse transcriptase (RT), and integrase in participants with virologic failure between the three treatment arms [Objective 1.3.6; to be addressed in a subsequent statistical analysis plan].
7. To compare the proportion of participants with TB drug resistance among cases of TB treatment failure and relapse/recurrence of TB between the three treatment arms [Objective 1.3.7].
8. To characterize TB immune reconstitution inflammatory syndrome (IRIS) events [Objective 1.3.8].
9. To compare changes in CD4+ T-cell count, and proportions of participants who experience new AIDS-defining illness, HIV disease progression (defined as new AIDS-defining illness or death), or death between the three treatment arms [Objective 1.3.9].
10. To evaluate LPV pharmacokinetic (PK) characteristics (area under the curve [AUC], maximum concentration [C_{max}], minimum concentration [C_{min}]) in participants enrolled in Arms A, B, and C, accrual periods 1 and 2 [Objective 1.3.10; addressed in the PK and Safety Interim Analysis Report].

11. To evaluate the RBT PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arms A and C, accrual periods 1 and 2 [Objective 1.3.11; addressed in the PK and Safety Interim Analysis Report].
12. To evaluate RAL PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arm C, accrual period [Objective 1.3.12; addressed in the PK and Safety Interim Analysis Report].
13. To evaluate the cost-benefit analysis of the addition of RAL [Objective 1.3.13; to be addressed in a subsequent statistical analysis plan].

2.1.3 Tertiary Objective

To submit sputum, serum, and urine specimens at specified time points for analysis of biomarkers associated with TB treatment response [Objective 1.4.1; this objective was not met since A5302 BioBank for Surrogate Marker Research for TB (B-SMART) did not open during accrual period 1].

2.2 Outcome Measures

2.2.1 Primary Outcome Measure

The primary HIV virologic suppression outcome is the occurrence of plasma HIV-1 RNA level <400 copies/mL at 48 weeks [Objectives 1.2 and 1.3.3].

2.2.2 Secondary Outcome Measures

1. The first secondary TB treatment outcome is mycobacterial culture conversion at week 8 [Objective 1.3.1].
2. The second secondary TB treatment outcome is occurrence of TB treatment failure at or after week 24, where TB treatment failure is defined as an MTB-positive mycobacterial culture after 16 weeks of TB treatment for a participant who was documented to be taking TB medications [Objective 1.3.1].
3. The third secondary TB treatment outcome is an occurrence of TB relapse/recurrence by week 72, where relapse/recurrence occurs when a participant has 2 consecutive MTB-negative mycobacterial cultures and who subsequently has clinical or radiographic deterioration consistent with active TB at or after week 24 and before the week 72 endpoint [Objective 1.3.1].
4. The secondary HIV virologic suppression outcome is the occurrence of plasma HIV-1 RNA level <50 copies/mL at 48 weeks [Objectives 1.3.2 and 1.3.3].
5. The secondary safety outcome is occurrence of a grade 3 or grade 4 adverse event or laboratory abnormality [Objective 1.3.4].
6. The secondary tolerance outcomes are occurrence of an interruption or discontinuation of at least one HIV drug due to toxicity and to at least one anti-TB drug due to toxicity [Objective 1.3.4].
7. The secondary HIV virologic failure outcomes are the occurrence of two consecutive plasma HIV-1 RNA levels ≥1000 copies/mL at or after 16 weeks and before 24 weeks of ART or ≥400 copies/mL at or after 24 weeks of treatment, regardless of ART status, and the time from randomization to the occurrence of HIV virologic failure [Objective 1.3.5].

8. The secondary TB drug resistance outcome is the occurrence of TB drug resistance among cases of TB treatment failure or TB relapse/recurrence [Objective 1.3.7].
9. The secondary MTB IRIS outcome is the occurrence of MTB IRIS [Objective 1.3.8].
10. The secondary disease progression outcomes are CD4 cell counts, occurrence of new AIDS-defining illness, and death [Objective 1.3.9].

3 Statistical Methods

Accrual Period 2 did not open to enroll, leaving a sample size of 71 out of the required 471 participants. This provides fewer than 25 participants in each arm. Because of the limited sample size, formal statistical comparisons will not be made. Instead, the analysis will consist of summarizing the proportions and the 95% confidence intervals (CIs) calculated using Wilson's score method within each treatment arm. Time-to-event analyses will consist of Kaplan-Meier plots with 95% pointwise CIs. Other outcome measures will be summarized using numbers and proportions. Baseline data will be summarized using medians, quartiles, minimum, and maximums if continuous, and percentages if categorical.

All randomized participants will be included in this intent-to-treat analysis. Key study visit weeks were baseline (week 0) and weeks 8, 16, 24, 48, and 72. The visit window for baseline was -4.3 weeks to 0.4 weeks. The post-baseline visit windows were ±1 week.

4 Report Components

4.1 Study Accrual

- Summary of the number of participants enrolled by month and by site by treatment arm.

4.2 Baseline Characteristics

- Summary of age, sex, race, and ethnicity by treatment arm.
- Summary of Karnofsky performance score and body mass index (BMI) by treatment arm.
- Summary of CD4 count and HIV RNA (number below lower limit of quantification and $\log_{10}$ copy number for those above the lower limit of quantification).
- Summary of CD4 count and HIV RNA (number below lower limit of quantification and $\log_{10}$ copy number for those above the lower limit of quantification) by treatment arm.
- Summary of reason PI-based therapy was needed from eligibility checklist [Q0017-Q0018] (category and specific reason if category=other) by treatment arm.
- Summary of ANC, hemoglobin, platelet count, AST, ALT, and total bilirubin by treatment arm.
- Summary of the number of cumulative days of anti-TB treatment for the current TB episode prior to study entry by treatment arm.
- Summary of the number of years from completion of TB treatment for the last prior TB episode to study entry by treatment arm.
- Summary of chest x-ray findings by treatment arm.

- Summary of TST and IGRA results by treatment arm *[Note: These data were collected "if available;" none are available].*
- Summary of AFB smear and mycobacterial culture results by treatment arm (may include non-study data collected from the local TB program if the specimen was collected within 30 days prior to study entry).
- Summary of RIF and INH drug susceptibility testing (DST) results by treatment arm (may include non-study data collected from the local TB program if the specimen was collected within 30 days prior to study entry).
- Summary of level of certainty of the current TB episode as defined in Protocol Section 4.1.3 by treatment arm.

4.3 Study Retention

- Summary of weeks from randomization to last clinic visit by treatment arm.
- Summary of off-study reasons by treatment arm.

4.4 Study Treatment

- Summary of days from randomization to TB treatment initiation, days from randomization to study-provided ARV treatment initiation, and days from TB treatment initiation to ARV treatment initiation by treatment arm.

4.4.1 HIV Treatment

- Summary of the numbers and proportions of participants who interrupted or permanently discontinued at least one HIV drug due to toxicity, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.4].
- Listing of participants who interrupted or permanently discontinued at least one HIV drug due to toxicity, with all PK parameters for all drugs and metabolites.
- Summary of weeks from study-provided ART initiation to the first interruption, to permanent discontinuation, and to the first interruption or permanent discontinuation of an HIV drug due to toxicity by treatment arm.
- Summary of the reasons for interruptions of HIV drugs due to toxicity by treatment arm.
- Summary of the reasons for interruptions of HIV drugs due to other reasons by treatment arm.
- Summary of the reasons for permanent discontinuations of HIV drugs due to toxicity by treatment arm.
- Summary of the reasons for permanent discontinuations of HIV drugs due to other reasons by treatment arm.

4.4.2 TB Treatment

- Summary of the numbers and proportions of participants who interrupted or permanently discontinued at least one TB drug due to toxicity, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.4].

- Listing of participants who interrupted or permanently discontinued at least one TB drug due to toxicity, with all PK parameters for all drugs and metabolites.
- Summary of weeks from study-provided TB medications initiation to the first interruption, to permanent discontinuation, and to the first interruption or permanent discontinuation of a TB drug by treatment arm.
- Summary of the reasons for interruptions of TB drugs due to toxicity by treatment arm.
- Summary of the reasons for interruptions of TB drugs due to other reasons by treatment arm.
- Summary of the reasons for permanent discontinuations of TB drugs due to toxicity by treatment arm.
- Summary of the reasons for permanent discontinuations of TB drugs due to other reasons by treatment arm.

4.5 Adverse Events

Note: TB signs/symptoms grade 2 or higher were reportable; otherwise, grade 3 or higher signs/symptoms and laboratory toxicities were reportable.

- Summary of all new, post-baseline grade 2 or higher signs/symptoms and laboratory toxicities by type and by treatment arm [Objective 1.3.4].
- Listing of participants who developed Grade 3 or 4 AEs, with all PK parameters for all drugs and metabolites.
- Summary of numbers and proportions of participants who died, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.9].
- Summary of the primary and contributing causes of death with weeks from study-provided ART and TB medications initiation and attribution to study drug by treatment arm.

4.6 Diagnoses

- Summary of all new, post-baseline diagnoses by treatment arm.
- Summary of all new, post-baseline primary diagnoses of grade 3 or 4 and primary diagnoses that had grade 3 or 4 associated signs, symptoms, and laboratory abnormalities with associated signs/symptoms and laboratory abnormalities by treatment arm.
- Listing of all uveitis cases with all PK parameters for RBT and des-RBT.
- Summary of MTB-IRIS diagnoses with weeks from TB treatment initiation, grade, associated signs/symptoms and laboratory abnormalities, and weeks to resolution, if available, by treatment arm [Objective 1.3.8].

4.7 Predictors of HIV Disease Progression

4.7.1 CD4

- Summary of CD4 counts at weeks 8, 24, 48, and 72 by treatment arm.
- Summary of change in CD4 count from baseline to week 8, baseline to week 24, baseline to week 48, and baseline to week 72 by treatment arm [Objective 1.3.9].

4.7.2 New AIDS-Defining Illnesses

- Summary of numbers and proportions of participants diagnosed with a new AIDS-defining illness, with 95% confidence intervals (CIs) based on Wilson's score method, by treatment arm [Objective 1.3.9].
- Summary of numbers and proportions of participants diagnosed with a new AIDS-defining illness or died, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.9].

4.8 Efficacy

4.8.1 HIV Virologic Suppression

Note: Participants who were lost-to-follow-up or dead by week 48 will be coded as not suppressed as per Protocol Section 9.6.2.

- Summary of HIV RNA at weeks 8, 16, 24, 48, and 72 by treatment arm.
- Summary of the evaluability of all participants with respect to HIV RNA at week 48 by treatment arm.
- Summary of numbers and proportions of participants with HIV RNA <400 copies/mL at week 48, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.2 & Objective 1.3.3].
- Summary of numbers and proportions of participants with HIV RNA <400 copies/mL at week 48, with 95% CIs based on Wilson's score method, by pooled Arms A/C and Arm B [Objective 1.2 & Objective 1.3.3].
- Summary of numbers and proportions of participants with HIV RNA <50 copies/mL at week 48, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.2 & Objective 1.3.3].
- Summary of numbers and proportions of participants with HIV RNA <50 copies/mL at week 48, with 95% CIs based on Wilson's score method, by pooled Arms A/C and Arm B [Objective 1.3.2 & Objective 1.3.3].

4.8.2 HIV Virologic Failure

Note: HIV virologic failure is defined as two consecutive HIV RNA levels ≥1000 copies/mL at or after 16 weeks and before 24 weeks of ART or ≥400 copies/mL at or after 24 weeks of treatment (and up to 72 weeks), regardless of whether or not randomized ART is being taken at the time of failure.

Note: Participants without the data needed to determine virologic failure will be coded as failures.

- Summary of numbers and proportions of participants within each category of virologic failure by treatment arm.
- Summary of numbers and proportions of participants with virologic failure, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.5].
- Kaplan-Meier plot of time to virologic failure with 95% pointwise CIs, by treatment arm [Objective 1.3.5].

4.8.3 TB Treatment Outcomes

Note: According to Protocol Section 6.3.7: "For participants who enroll with probable TB and do not have a positive mycobacterial culture from any site available to meet these outcome definitions, but who have specimens with a positive AFB smear, the AFB smear result will be submitted for the mycobacterial culture result in assessing TB outcomes. If there are no positive AFB smear results, then the assessment of TB outcomes will be based on the best clinical judgment and further reviewed by the team and an independent endpoint reviewer.

- Summary of numbers and proportions of participants for each TB treatment status and outcome determination by treatment arm.

4.8.3.1 Week 8 Mycobacterial Culture Conversion

- Summary of participants who met the mycobacterial culture conversion outcome at week 8. Details will be provided in the table to show why participants did not meet the definition of mycobacterial culture conversion at week 8 outcome measure.
- Summary of numbers and proportions of participants with mycobacterial culture conversion at week 8, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.1].
- Summary of numbers and proportions of participants with mycobacterial culture conversion at week 8, with 95% CIs based on Wilson's score method, by pooled Arms A/C and Arm B [Objective 1.3.1].
- Kaplan-Meier plot of time to mycobacterial culture conversion, with 95% pointwise CIs, by treatment arm [Objective 1.3.1].
- Kaplan-Meier plot of time to mycobacterial culture conversion, with 95% pointwise CIs, by pooled Arms A/C and Arm B [Objective 1.3.1].

4.8.3.2 TB Treatment Failure

- Summary of numbers and proportions of participants with TB treatment failure at or after week 24, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.1].
- Summary of numbers and proportions of participants with TB treatment failure at or after week 24, with 95% CIs based on Wilson's score method, by pooled Arms A/C and Arm B [Objective 1.3.1].
- Summary of cases of TB treatment failure with TB diagnostics on the baseline sputum, TB outcome at time of TB treatment discontinuation, weeks from TB treatment discontinuation to TB treatment failure, and results from TB diagnostics on the sputum collected at time of TB treatment failure (i.e., AFB smear, culture, and DST) by treatment arm.

4.8.3.3 TB Relapse/Recurrence

- Summary of numbers and proportions of participants with TB relapse/recurrence by week 72, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.1].
- Summary of numbers and proportions of participants with TB relapse/recurrence by week 72, with 95% CIs based on Wilson's score method, by pooled Arms A/C and Arm B [Objective 1.3.1].

4.8.3.4 TB Drug Resistance

- Summary of numbers and proportions of participants with TB drug resistance among cases of TB treatment failure or TB relapse/recurrence by week 72, with 95% CIs based on Wilson's score method, by treatment arm [Objective 1.3.7].
- Summary of drug-resistant TB among cases of TB treatment failure or TB relapse/recurrence noted, with TB diagnostics on the baseline sputum, TB outcome at time of TB treatment discontinuation, weeks from TB treatment discontinuation to TB treatment failure or TB relapse/recurrence, and results from TB diagnostics on the sputum collected at time of TB treatment failure or suspected TB relapse/recurrence (i.e., AFB smear, culture, and DST) by treatment arm.