A5290 Statistical Analysis Plan

Version 2.0 (PK and Safety Interim 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

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1 Introduction

1.1 Purpose

This statistical analysis plan has been developed to (1) facilitate discussion of the key statistical analysis components amongst the study team; and (2) provide agreement between the study team and statisticians regarding the statistical analyses to be performed.

The plan contains details of all statistical analyses that will be completed prior to the preparation of the PK and Safety Interim Analysis report.

1.2 Closed Team Roster

The PK and Safety Interim Analysis report will be distributed to the team members who attend the SMC Review. This may include, but may not be limited to, the following team members: Protocol Co-Chairs, Protocol Vice-Chair, Protocol Pharmacologist, DAIDS Clinical Representative, Statisticians, and Clinical Trials Specialist.

1.3 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). A two accrual period design is being used, including a full pharmacokinetic (PK) and safety evaluation to be conducted when 54-60 participants enrolled during accrual period 1 have completed 28 days of ARV treatment and day 12 ± 2 (after initiation of study-provided ART and TB medications) drug levels are available. An early assessment by the team will also be completed when 10-12 participants per arm have completed 28 days of ARV treatment and day 12 ± 2 drug levels are available.

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.

Accrual will place in two accrual periods. Accrual period 1 will enroll 60 participants (20/arm) who will undergo an initial dose-finding period before continuing regular study follow-up. Accrual will then be suspended until the last SMC review of the interim PK and safety evaluation has been completed. Accrual period 2 will open and randomize the remaining participants to either three arms (n=411) or to the remaining two arms (n=TBD) and will be monitored by the DSMB.

Each participant will be followed until week 72.

The primary 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.

1.4 Study Monitoring History

Besides summarizing the monitoring history of A5290, a brief summary of the Early Assessment will be prepared specifically for this report. The Early Assessment occurred when 10-12/arm accrual period 1 participants completed 28 days of ART and day 12 ± 2 (after initiation of study-provided ART and TB medications) PK results were available. The report was sent to the SMC with the TDM's team decision on 14 January 2016.

1.5 PK and Safety Interim Objectives

1.5.1 PK Criteria

1) For LPV in Arm B, the primary PK parameter is the day 12 ± 2 (after initiation of study-provided ART and TB medications) C_{min} (C_{12}), and the acceptable lower limit value is ≥ 1 mg/L. LPV concentrations in Arm B will be judged acceptable if no more than three participants have a C_{min} < 1 mg/L.
2) For RBT (Arms A and C), equivalence analyses will compare day 12 ± 2 (after initiation of study-provided ART and TB medications) RBT 24-hour AUC and C_{max} with control data derived from prior PK studies, as determined by whether the 90% confidence intervals of the ratios of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r are fully contained within the pre-specified NEB of 67%-150%. RBT concentrations in Arms A and C will be judged acceptable if equivalence is declared according to these PK parameters.

1.5.2 Safety Criteria

1) No more than three participants in any treatment arm experience a Grade 3 or Grade 4 AE "related to study-provided drug(s)" (as deemed by the TDM Team: DAIDS Clinical Representative, Protocol Co-Chairs, Protocol Vice Chair, Protocol Pharmacologist, Statisticians, Data Manager, Laboratory Data Manager, and Clinical Trials Specialist) by 28 days after initiation of study-provided ART and TB medications.
2) No more than three participants in any treatment arm discontinue study-provided drug(s) for treatment-limiting toxicity or intolerance (such that PK assessments within the day 12 ± 2 [after initiation of study-provided ART and TB medications] window cannot be completed).

1.6 PK Study Objectives

Since Accrual Period 2 will not open to enroll participants, the PK objectives outlined in the protocol will also be analyzed at this time.

1) To evaluate LPV 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.
2) To evaluate the RBT PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arms A and C, accrual periods 1 and 2.
3) To evaluate RAL PK characteristics (AUC, C_{max}, C_{min}) in participants enrolled in Arm C, accrual period 2.

2 Study Conduct

- Table summarizing the number of participants enrolled by month and by site, by treatment arm.
- Table of study status categories (i.e., completed, death, etc.) by treatment arm.
- Table summarizing weeks from randomization to last clinic visit by treatment arm.

3 Baseline Characteristics

- Table of age, sex, race, and ethnicity by treatment arm.
- Table of Karnofsky performance score and body mass index (BMI) by treatment arm.
- Table of CD4 count and HIV RNA (log_{10} copy number and number below lower limit of quantification).
- Table of reason PI-based therapy was needed from eligibility checklist [Q0017-Q0018] (category and specific reason if category=other) by treatment arm.
- Table of AFB smear and mycobacterial culture results by treatment arm.
- Table of RIF and INH drug susceptibility testing (DST) results by treatment arm.
- Table summarizing 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 Safety

4.1 Grade 3 or Higher Adverse Events

- Table summarizing all grade 3 or higher adverse events within 28 days after study-provided ART and TB treatment initiation that the TDM Team deemed "related to study-provided drug(s)" or "probably related to study-provided drug(s)" or "possibly related to study-provided drug(s)" by treatment arm *[Safety Criterion #1; see section 1.5.2].*
- Table summarizing all new, post-baseline grade 2 or higher signs/symptoms and laboratory toxicities within 28 days after ART initiation from EVW0206 and EVW0207 forms, by type and by treatment arm.
- Table summarizing all grade 3 or higher adverse events beyond 28 days after study-provided ART and TB treatment initiation that the TDM Team deemed "related to study-provided drug(s)" or "probably related to study-provided drug(s)" or "possibly related to study-provided drug(s)" by treatment arm
- Table summarizing all new, post-baseline grade 2 or higher signs/symptoms and laboratory toxicities beyond 28 days after ART initiation from EVW0206 and EVW0207 forms, by type and by treatment arm.

4.2 Study Treatment Tolerability

- Table summarizing discontinuations of study-provided drugs within 28 days after study-provided ART and TB treatment initiation by treatment arm *[Safety Criterion #2; see section 1.5.2].*
- Table summarizing discontinuations of study-provided drugs beyond 28 days after study-provided ART and TB treatment initiation by treatment arm.

4.3 Diagnoses

- Table summarizing all new, post-baseline diagnoses by treatment arm.
- Table summarizing of all new, post-baseline primary diagnoses of grade 3+ and primary diagnoses that had grade 3+ associated signs, symptoms, and laboratory abnormalities from EVW0206 and EVW0207 forms, by type, with associated signs/symptoms and laboratory abnormalities by treatment arm.

4.4 MTB-IRIS

- Table summarizing MTB-IRIS diagnoses with time from TB treatment initiation, grade, and time to resolution, if available, by treatment arm.
- Table summarizing the MTB-IRIS diagnoses, with associated signs/symptoms and laboratory abnormalities by treatment arm.

4.5 Deaths

- Table summarizing the primary and contributing causes of death with time from study-provided ART and TB medications initiation and attribution to study drug, by treatment arm.

5 Pharmacokinetics (PK)

- ***Notes:***
  - *These analysis programs will require validation (successful execution). Verification that the programs correctly determined the PK evaluable participants will be done by comparing lists with the pharmacology lab.*
  - *For analysis, the LDMS analcd for each drug was as follows: LPV=131, RBT=116, desRBT=216, RAL=770, and RTV=114.*
  - *Study participants will be included in the analyses of the PK interim and the PK study objectives based on the following criteria:*
    - *There were no missed doses of any TB or HIV medication on the day prior to the PK study; and*
    - *The pharmacology lab did not determine the participant unevaluable based on the participant's PK profile.*
    - *For the PK interim objectives, the following additional criteria were required:*
      - *The LPV C_{12} was not BLQ; and*
      - *The RBT pre-dose concentration was not BLQ.*
  - *<u>From the Protocol Pharmacologist</u>: In the comparison of the RBT PK parameters with the Naiker paper, a comment about C_{last} vs. C_{min}. These PK parameters are subject to some imprecision in use. C_{last} is the last measured concentration. For RBT in A5290, that is at 24 hours post dose. C_{min} by definition is the minimum concentration observed. While that usually occurs right before the next dose is given, it doesn't always. There are drugs, for example, where a lag phase is seen after the dose is taken and concentrations can actually go down for a short time after dose intake until absorption starts. So, C_{min} is not necessarily the same as C_{last} and we saw this in A5290. There were some PIDs (e.g., 1211756) where the 2 hour post dose concentration was lower than the pre-dose concentration. Thus, that 2 hour value would be the C_{min}, and the C_{last} value would be that obtained at 24 hours, which for the PID I mentioned, is higher than the 2 hour concentration. In the RBT PK file that I transferred, I included values for both Clast and C_{min}. In the Naiker paper, Table 1, they provide C_{min} but define it as at 24h or 48 hours, thus, they are really defining their C_{min} as a C_{last}. In my summary table that I sent where I provided historical comparisons, you will see then that I showed the Naiker C_{min} values as being compared with our C_{last}, because their Cmin is really a C_{last}.*
- Table summarizing the reasons why PK samples were not collected strictly within the time frame specified in the protocol by treatment arm.

5.1 PK Interim Objectives

5.1.1 Lopinavir (LPV)

- ***Note:*** *The LPV PK interim analysis will be analyzed in Arm B only.*

- Table summarizing the number of participants excluded from the LPV interim PK analysis with reasons.
- Table summarizing the number of participants in Arm B whose C_{min} is <1 mg/L. LPV concentrations in Arm B will be judged acceptable if no more than three participants have a C_{min} <1 mg/L. *[PK Criterion #1; see section 1.5.1].*
- Table summarizing the number of participants in Arm B whose C_{min} is <1 mg/L, including those participants the pharmacologist deemed PK-evaluable (based on the participants' plasma LPV concentrations). LPV concentrations in Arm B will be judged acceptable if no more than three participants have a C_{min} <1 mg/L. *[PK Criterion #1; see section 1.5.1].*
- Table of C_{min} and C_{max} values for participants meeting the LPV PK criterion of C_{min} <1 mg/mL.

5.1.2 Rifabutin (RBT)

- ***Note:*** *Only Arms A and C will be included.*
- Table summarizing the number of participants excluded from the RBT PK interim analysis with reasons by treatment arm.
- Table summarizing the comparison of the RBT AUC and C_{max} to historical controls (Sekar) with ratios and 90% confidence intervals around the ratios by treatment arm. RBT concentrations in Arms A and C will be judged acceptable if the 90% confidence intervals of the ratios of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r are fully contained within the pre-specified NEB of 67%-150%. *[PK Criterion #2; see section 1.5.1]*.
- Table summarizing the comparison of the RBT AUC and C_{max} pooled over Arms A and C to historical controls (Sekar) with ratios and 90% confidence intervals around the ratios. RBT concentrations in this analysis will be judged acceptable if the 90% confidence interval of the ratio of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r is fully contained within the pre-specified NEB of 67%-150%. *[PK Criterion #2; see section 1.5.1]*.
- Table summarizing the comparison of the RBT AUC and C_{max} pooled over Arms A and C and including those participants the pharmacologist deemed PK-evaluable (based on the participants' plasma RBT concentrations) to historical controls (Sekar) with ratios and 90% confidence intervals around the ratios. RBT concentrations in this analysis will be judged acceptable if the 90% confidence interval of the ratio of the RBT concentrations (when co-administered with LPV/r) relative to daily RBT concentrations in the absence of LPV/r is fully contained within the pre-specified NEB of 67%-150%. *[PK Criterion #2; see section 1.5.1]*.

5.2 PK Study Objectives

5.2.1 Lopinavir (LPV)

- ***Note:*** *The historical controls are Umeh, Schöller-Gyüre, Ngoc Lan, Naiker, and Matteelli.*

- Table summarizing the number of participants excluded from the LPV PK analysis with reasons by treatment arm.
- Table summarizing the LPV PK parameters (all available) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles by treatment arm, with Wilcoxon p-values.
- Table summarizing the LPV PK parameters (AUC, C_{max}, C_{min}, C_{last}) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles by Arm B versus pooled Arms A and C, with Wilcoxon p-values *[PK Study Objective #1; see section 1.6]*.
- Figure of A5290 and historical control LPV PK parameters (AUC, C_{max}, C_{min}, C_{last}). A5290 data will be pooled over all arms and each historical control will be plotted separately *[PK Study Objective #1; see section 1.6]*.
- Table summarizing the comparison of LPV PK parameters (AUC, C_{max}, C_{min}, C_{last}) to historical controls, with Wilcoxon p-values. A5290 data will be pooled over all arms and each historical control will be tested separately *[PK Study Objective #1; see section 1.6]*.

5.2.2 Rifabutin (RBT)

- ***Note:*** *The historical controls are Sekar, Ngoc Lan, and Naiker. Only Arms A and C will be included.*
- Table summarizing the number of participants excluded from the RBT PK interim analysis with reasons by treatment arm.
- Table summarizing the RBT PK parameters (all available) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles by treatment arm, with Wilcoxon test p-values *[PK Study Objective #2; see section 1.6]*.
- Figure of A5290 and historical control RBT PK parameters (AUC, C_{max}, C_{last}). A5290 data will be pooled over both arms and each historical control will be plotted separately *[PK Study Objective #2; see section 1.6]*.
- Table summarizing the comparison of RBT PK parameters (AUC, C_{max}, C_{last}) to historical controls, with Wilcoxon p-values. A5290 data will be pooled over both arms and each historical control will be tested separately *[PK Study Objective #2; see section 1.6]*.
- Table summarizing the desacetyl RBT PK parameters (all available) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles by treatment arm, with Wilcoxon test p-values *[PK Study Objective #2; see section 1.6]*.
- Figure of A5290 and historical control desRBT PK parameters (AUC, C_{max}, C_{last}). A5290 data will be pooled over both arms and each historical control will be plotted separately *[PK Study Objective #2; see section 1.6]*.
- Table summarizing the comparison of desRBT PK parameters (AUC, C_{max}, C_{last}) to historical controls, with Wilcoxon p-values. A5290 data will be pooled over both arms and each historical control will be tested separately *[PK Study Objective #2; see section 1.6]*.

5.2.3 Raltegravir (RAL)

- ***Note:*** *The historical controls are Rizk and Brainard*. *Only Arm C will be included.*
- Table summarizing the number of participants excluded from the RAL analysis with reasons.
- Table summarizing the RAL PK parameters (all available) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles.
- Figure of A5290 and historical control RAL PK parameters (AUC, C_{max}, C_{last}). Each historical control will be plotted separately *[PK Study Objective #3; see section 1.6]*.
- Table summarizing the comparison of RAL PK parameters (AUC, C_{max}, C_{last}) to historical controls, with Wilcoxon p-values. Each historical control will be tested separately *[PK Study Objective #3; see section 1.6]*.

5.2.4 Ritonavir (RTV)

- ***Note:*** *The historical controls are Umeh, Schöller-Gyüre, and Ngoc Lan.*
- Table summarizing the number of participants excluded from the RBT analysis with reasons by treatment arm.
- Table summarizing the RTV PK parameters (all available) with sample size, mean, standard deviation, coefficient of variation, median, and quartiles by treatment arm, with Wilcoxon p-values.
- Figure of A5290 and historical control RTV PK parameters (AUC, C_{max}, C_{min}, C_{last}). A5290 data will be pooled over all arms and each historical control will be plotted separately.
- Table summarizing the comparison of RTV PK parameters (AUC, C_{max}, C_{min}, C_{last}) to historical controls, with Wilcoxon p-values. A5290 data will be pooled over all arms and each historical control will be tested separately.

5.3 Adherence for PK Evaluable Participants

- Table summarizing adherence by treatment arm.

6 Summary

The summary will include whether the PK and safety interim criteria were judged to be acceptable (see section 1.5). It will also discuss the PK study objectives and other safety analyses/summaries.