This is IMPAACT P1101 SAP Version 1.0 with names of authors, names of publication, writing team members, and analysis timeline redacted.

Pharmacokinetic Statistical Analysis Plan

Version 1.0

IMPAACT P1101

Phase I/II dose-finding, Safety, Tolerance and Pharmacokinetics Study of a Raltegravir-Containing Antiretroviral Therapy (ART) Regimen in HIV-infected and TB Co-infected Infants and Children

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1. Introduction

This Pharmacokinetic Statistical Analysis Plan (PK SAP) is complementary to the IMPAACT P1101 Primary SAP (version 2.0) and the IMPAACT P1101 PK Data Management Plan (version 2.0). This document describes the non-compartmental pharmacokinetic (PK) analysis to be performed by the IMPAACT P1101 protocol pharmacologist at the end of study on the completed study dataset and included in study abstracts and manuscripts.

2. PK-Related Study Background

IMPAACT P1101 is a Phase I/II dose-finding, safety, tolerance and pharmacokinetics study of a raltegravir (RAL)-containing antiretroviral therapy (ART) regimen in HIV-infected and TB co-infected infants and children. There is an urgent need for better tolerated, potent, simple agents (i.e. simple dosing, administration and storage) to be included in first line ART regimens to widen the treatment options for children and infants co-infected with TB and HIV. Based on data from prior studies of drug interactions of RIF and RAL in adults, doubling the dose of RAL to 12 mg/kg/dose (maximum 800 mg/dose) is an appropriate starting point for this study. The UGT1A1 metabolic pathway is fully mature after the first 3 months of life; therefore, co-administration of RAL and RIF is expected to lead to significant reductions in RAL concentrations in children. As pediatric RAL dosing regimens have been shown to achieve PK parameters comparable to those in adults, doubling the RAL dose for children when given with RIF will likely yield similar improvements in PK parameters. Participants will be enrolled into the study into the following cohorts:

- Cohort I: ≥ 2 to < 6 years of age on TB treatment (n = 12 minimum)
- Cohort II: ≥ 6 to < 12 years of age on TB treatment (n = 12 minimum)
- Cohort III: ≥ 4 weeks to < 2 years of age on TB treatment (n = 12 minimum)

Cohorts I, II, III will enroll simultaneously. Each age cohort will start with a mini-cohort of six participants, followed by six additional participants to make up a full cohort.

3. Dose-Finding Approach

HIV-infected and TB co-infected children ≥ 4 weeks to < 12 years of age taking RIF-based TB therapy and who are eligible for antiretroviral (ARV) treatment as defined by local or WHO guidelines. An initial dose of RAL will be given at 12 mg/kg (up to a maximum of 800 mg) twice daily for chewable formulation, with two NRTIs. Following the intensive PK study for RAL (5 to 8 days after the start of RAL therapy), a fourth ARV drug will be added to the regimen. The four-drug ARV regimen will be continued until TB treatment is completed. Each child will be followed up to assess safety, clinical, immunological and virological parameters, from the time that RAL is started on a TB containing regimen until 3 months after stopping RAL while standard of care treatment continues.

Each age cohort will start with a mini-cohort of six participants to assure that preliminary PK and safety criteria are met at that dose. Data from each age cohort will be reviewed independently and, if the mini-cohort data meets established metrics an additional 6 participants per age cohort will be enrolled (full cohort), and evaluated for safety and PK. If the mini-cohort (n = 6) at a RAL dose of 12 mg/kg achieves 1) a geometric mean RAL AUC0-12hr of approximately 14 to 45 µMxhr and 2) an approximate GM C12h ≥ 75nM, and meets safety criteria, then 6 additional participants will be enrolled at this dose. The data from these participants will be combined with the previous 6 for evaluation of this dose using the same criteria.

If the initial mini-cohort of n = 6 fails either the safety or the PK guidelines in this initial test, then the dose will be adjusted in the appropriate direction, unless dose reduction is likely to result in inadequate PK values. An initial evaluation of the new dose level will be made on the basis of data from the first six new participants treated at this dose. If the first six participants of a cohort meet both sets of guidelines, then six additional participants will be accrued to this cohort. The additional six participants will be evaluated on both safety and PK; if the full cohort of n = 12 passes both safety and PK criteria, then the dose on which they have been treated will become the selected dose.

Note: Please see Section 8.5.1 of the protocol V3.0 for details regarding Safety Guidelines.

4. Primary Pharmacokinetic Study Objectives

To determine the pharmacokinetics and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children that generates PK parameters generally comparable to those seen in HIV-infected infants and children in the absence of RIF.

5. Non-Compartmental Pharmacokinetic Analyses

PK sampling was collected at pre-dose (0), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post dosing. A single 0.5 mL sample of whole blood was collected at each time point. Standard non-compartmental methods for PK parameter derivation will be performed using Phoenix WinNonlin 8.1 (or current, Certara USA, Inc.). Where possible, the following PK parameters will be determined from RAL plasma concentration-time data:

Parameter	Definition
C_{max}	Observed maximum plasma concentration
T_{max}	Time of maximum plasma concentration
$AUC_{(0-12)}$	Area under the concentration-time curve from time zero to the end of the dosing interval at 12 hours at steady-state

CL_{ss}/F	Apparent oral clearance at steady-state
V_z/F	Apparent distribution volume at steady-state
λ_z	Terminal elimination rate constant
$t_{1/2}$	Terminal half-life calculated as ln(2)/λz
C_{12h}	Concentration at the end of the dose interval at 12 hours

Additional PK parameters may be determined where appropriate. Pharmacokinetic analysis will be carried out using actual sampling times provided by the UAB PSL.

5.1. Below the Level of Quantitation

RAL concentration values that are below the level of quantification (LLOQ), < 10 ng/mL, will be set to ½ the LLOQ. If an entire concentration-time profile is LLOQ, the profile will be excluded from the PK analysis. If a pre-dose concentration is below the limit of assay detection, this value is set to ½ the LLOQ. Any embedded BLQ value (BLQ value occurring between two quantifiable concentrations) in a profile will be set to missing for the purposes of PK analysis.

5.2. Terminal Slope Estimation

The default settings for the analysis software will only estimate an elimination rate constant when the PK profile has three or more declining concentrations after the peak concentration in a non-compartmental analysis. In the case of only two terminal concentrations can be chosen for t1/2 determination, these points will be chosen by pharmacokineticist.

5.3. AUC Values

AUC is calculated by the linear trapezoidal rule. Since this study is evaluating RAL PK at steady-state, the only important AUC parameter is the 12 hour result, $AUC_{0\text{-}12h}$.

6. Summary Statistics

All individual concentrations and all pharmacokinetic parameters will be summarized using descriptive statistics. These will include the n, mean, standard deviation, CV%, median, range and geometric mean. For dissemination, selected descriptive statistics on evaluable participants will be used as appropriate for the data distribution. PK parameters will be summarized by cohort.

7. Presentation of Data

Concentration time profiles (for individual infants, strata, and/or cohorts) will be presented graphically. For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used. RAL concentrations and PK parameters will be listed out separately for any participant not included in the dose-finding population. Additional tables, listings or figures may be prepared upon request.