

This is IMPAACT P1101 SAP Version 2.0 with names of authors, names of publication, writing team members, and analysis timeline redacted.

Primary Statistical Analysis Plan (for Protocol V3.0, LoA#1-2)

Version 2.0

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

1.1 Purpose of the Statistical Analysis Plan

This Analysis Plan outlines the components of the primary and secondary data analyses for IMPAACT P1101. The focus is on analyses of administrative, baseline and safety data, analyses needed to address the study's primary and secondary objectives, and the analyses to assess whether safety guidelines have been met at final accrual to all cohorts. This document focuses on analyses necessary for scientific purposes. The procedures and reports involved with protocol team monitoring of safety data during regular team calls are not described in this document (see the Study Monitoring Plan for details concerning monitoring). The pharmacology data will be analyzed separately by the protocol pharmacologist.

The purpose of this analysis plan is:

- to ensure that the protocol team is aware of all the major issues that will be in the proposed analyses, and agrees on the contents of these analyses; and
- to specify how the team intends to investigate the study questions listed in the protocol objectives, and how the data will be analyzed and presented.

This analysis plan includes the key analyses that will form the core of any presentation or publication used to disseminate the primary conclusions of the study. It is, however, recognized that this analysis plan may be modified by the core study team as new information becomes available outside of the study, or to reflect recommendations made by the Study Monitoring Committee (SMC).

1.2 Key SAP Updates

Version	Changes Made	Date Finalized
1	Original SAP Version (Per Protocol V1.0-3.0)	June 12, 2017
2	Protocol Amendment review (V3.0, LOA #1-2) Pearl Samson	March 28, 2019

Changes made under V2.0 of the SAP

- **Modified the title page (shows protocol version and LoAs), headers and footers.**
- **Removed the Team Roster, and replaced it with Key SAP Updates.**
- **Noted requirements for validation based on Risk Assessments.**
- **Bolded minor edits.**
- **Added a signature page.**

1.3 Study Design

This is a Phase I/II, dose-finding, safety, tolerability and pharmacokinetics study of raltegravir (RAL) in infants and children who have received ≥ 1 week and ≤ 20 weeks of Rifampicin (RIF)-based TB therapy prior to initiation of antiretroviral therapy.

Sample Size: Approximately 36 to 108 to achieve a target of 36 evaluable children at the final recommended dose.

Population: HIV-infected and TB co-infected infants and 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.

Stratification: 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 will enroll simultaneously. Each age cohort will start with a mini-cohort of 6 participants, followed by 6 additional participants to make up a full cohort.

Regimen: Chewable RAL tablet, starting dose of 12 mg/kg (up to a maximum dose of 800 mg) orally twice daily in addition to, as part of standard of care, two NRTIs plus RIF-containing regimen for treatment of TB.

Following an intensive PK visit, a fourth ARV drug will be added to the RIF-containing regimen per local standard of care.

Treatment Duration: The four drug ARV regimen (including RAL, 2 NRTIs plus an additional ARV drug per local standard of care) will be continued until TB treatment is completed and then RAL will be discontinued. The three drug ARV regimen will be continued per local standard of care after RAL is discontinued.

Study Duration: Participants will be followed for up to three months post discontinuation of RAL.

2 Study Objectives

2.1 Primary 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.
- To determine safety and tolerance of RAL-containing ART when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected infants and children.

2.2 Secondary Objectives

- To describe the short-term treatment outcomes of infants and children using a RAL-containing ART regimen co-treated with a RIF-containing TB treatment (see Sections 8.2.3 and 8.2.4 of the protocol).
- To explore whether infants and children receiving a RAL-containing ART regimen, co-treated with a RIF-containing TB treatment, develop ARV drug associated resistance mutations (see Section 6.2.3 of the protocol).

3 Outline of Planned Analysis

This section contains the details of the analyses for:

- Full cohort accrual safety/efficacy reports: at full accrual to each Cohort.
- SDAC final report: The final report will focus on safety, efficacy and treatment outcomes until the end of study follow-up. Summary tables will be generated by cohort and aggregated.

The full cohort accrual safety reports will be prepared for the core team. These reports will include information concerning Accrual/Screening, Participant and Study Status, Baseline Characteristics, Safety summary and Efficacy (HIV-RNA/CD4) tables. Unless otherwise noted the SDAC final reports will contain all summary tables.

Additional participant listings, not mentioned in this plan but which may be necessary in writing up the SDAC final report, will be generated and will be used internally at SDAC. Highlights of these listings will be included in the SDAC final report. These participant listings will be provided to the manuscript writing team. The manuscript writing team, which is a subset of the protocol team, will be identified by the protocol team.

The analysis of the PK data will be performed by the protocol pharmacologist, thus, not included in this document.

Validation requirements as per SDAC SOPs will be as follows:

- a. All dataset creation programs will be validated for the primary and secondary safety endpoints **as specified below**.
- b. All study-specific formats will be validated.
- c. Validation of analysis programs is specified in the subsections below.

For all analyses, the relative weeks of visit date/specimen date/onset date/other dates (“Assessment Window”) will be calculated using the following guidelines:

Assessment Window	Target Study Day of Window
Entry/Week 0	1
Day 5-8/Week 1	5-8
Day 14/Week 2	+/- 3 days
Week 4	+/- 1 week
Week 8	+/- 2 weeks
Every 4 weeks*	+/- 2 weeks
TB and/or RAL Treatment Discontinuation**	
4 Wks Off RAL treatment / On study	+/- 2 weeks
Early Discontinuation or End of Study	at 12 wks off RAL treatment ± 2 wks

* These visits will only be done if a participant will continue TB treatment and RAL after the Week 8 visit.

**At any of the on-treatment visits that coincide with the discontinuation of TB treatment and/or RAL or when a participant has met the criteria for virologic failure and early treatment discontinuation as defined in Sections 6.2.2 and 6.7, respectively.

4 Data Summaries

4.1 Administrative Data

Purpose: To give a summary of accrual and retention progress of the study during interim and final analyses.

Data: Date and institution (with country) of enrollment and eligibility status will be from the STATUS table; comments related to eligibility deviations will be from COMENT table. Comments related to PK exclusion will be from COMENT table. Reasons for screening failures and non-enrollment will be from the SCR0049 CRF. Off-study reasons are from Off-Study (F1601) CRF. Off-treatment reasons are from Permanent Discontinuation of Study Drug (PE4005) CRF.

Analysis Program Validation: Not required.

Analyses (tables and listings presented by cohort and aggregated):

4.1.1 Recruitment and Accrual

- Summary table of accrual by site (dates of first and last enrollment will be indicated in the text or a footnote.)

4.1.2 Participants Deemed Ineligible and Analysis Status

- Listing table of violations of eligibility criteria, and details of reasons for exclusions from analyses

4.1.3 Study Status

- Summary table [number (%)] disposition of participants;
- Summary table [number (%)] and listing of participant off-study reasons
- Summary table [number (%)] and listing of off-study treatment reasons

4.2 Baseline Characteristics

Purpose: To describe participant baseline characteristics

Data: Demographics are from DMC’s STATUS derived dataset; Health status will also include HIV-RNA and CD4 data.

Analysis Program Validation: Not required

Analyses (tables and listings presented by cohort and aggregated):

4.2.1 Demographics

- Gender: number (%)
- Race: number (%)
- Ethnicity: number (%)
- Age (yrs): median (interquartile range), min/max, q1/q3
- Weight (kg): median (interquartile range), min/max, q1/q3

4.2.2 Health Status

- Baseline HIV-1 RNA and CD4%: median (interquartile range), min/max, q1/q3

5 Primary Analyses

5.1 Primary Safety Data Analyses on Final-Dose Participants for Final Analysis Reports (Data through the final study visit)

Purpose: To list the endpoints and tables of primary and secondary safety analyses on final dose participants for the SDAC final analysis reports.

Data: Safety data are adverse clinical and laboratory events reported on the following CRFs: Clinical: Signs/Symptoms (PE6833/PE6832/**PE6831**), Diagnoses (PE6853/PE6852), Death (PE1414); Laboratory: Hematology (PE6813/PE6812), Chemistries (PE6818/PE6817). The following variables in the SDAC SAS datasets will be used: EVENTDSC, EVNGRDE, FORMNM, FORMTYP in TRAC table; TRACKCD (team's drug attribution assessment variable) in TRAC table; and Code =40 (Subject reached protocol-defined toxicity endpoint) of Reason for Treatment Discontinuation of PE4005 CRF.

Analysis Program Validation: Code review is required. Primary analysis for primary safety endpoints will require **validation**.

Analyses (tables and listings presented by cohort and aggregated):

The following section includes information on: outcome measures, statistical methods and contents of the corresponding analyses.

- Safety endpoints by cohort and aggregated (worst grade per AE per participant):
 - Primary safety endpoint for the final analysis (by cohort and aggregated):
 - Summary table [number (%), with 95% Exact CI] and listing of adverse events which lead to termination of study treatment
 - Specifically, due to adverse events of \geq Grade 3 deemed at least possibly related to RAL.
 - Summary table [number (%), with 95% Exact CI] and listing of adverse events of Grade 3 or 4 severity
 - Summary table [number (%), with 95% Exact CI] and listing of adverse events of Grade 3 or 4 severity judged by the protocol team to be at least possibly related to RAL
 - Summary table [number (%), with 95% Exact CI] and listing of participant deaths and those who experienced Grade 4 life-threatening events (with focus on possibly RAL related).
 - Summary table [number (%), with 95% Exact CI] and listing of participants who experienced Grade 4 non-life-threatening events deemed probably or definitely related to RAL.
 - Summary table [number (%), with 95% Exact CI] and listing of participants' worst grade of adverse event experienced while on the selected dose RAL and the worst grade of adverse event judged to be at least possibly due to RAL.

6 Secondary Analyses

6.1 Short Term Efficacy and Other Treatment Outcomes of Final-Dose and All-Treated Participants for Final Analysis Reports

Purpose: To describe the short term efficacy and other treatment outcomes in children for the final analysis reports.

Data: HIV-RNA, CD4, Clinical Response (weight, height, BMI), genotypic resistance (from virologic failures only).

Analysis Program Validation: Code review is required for programs creating derived datasets.

Analyses (tables and listings presented by cohort and aggregated):

The following section includes information on: outcome measures, statistical methods and contents of the corresponding analyses.

- Summary table [number (%), bounded with 95% exact confidence interval] and listing of participants who have exhibited virologic response at week 8 (i.e., virologic success is defined as achieving at least 1- log₁₀ drop from baseline OR HIV RNA ≤ 400 copies/mL; A secondary, more stringent definition of virologic response is to achieve HIV RNA ≤ 50 copies/mL). This will be in an as-treated analysis. Note that participants who discontinue RAL due to TB-drug cessation will be excluded from the analysis.
- Summary tables and listings showing changes from baseline in: HIV-RNA (to week 8 and other time points), CD4 percent and count (to week 8, and other time points), weight, height, BMI.
- Listing of participants who had both virologic failures and developed genotypic resistance.
- Listing of participants who developed opportunistic infections.