IMPAACT 2001

Final Statistical Analysis Plan

Version 2.0

A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection

Protocol Version 1.0

ClinicalTrials.gov Identifier: NCT02651259

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This is IMPAACT 2005 SAP Version 2.0 with names of authors redacted

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1 Introduction

1.1 Purpose

This Final Statistical Analysis Plan (or Primary SAP) describes the primary and secondary outcomes measures of IMPAACT 2001 that will be included in the primary manuscript, which address the primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches that will be used in the analysis. It has been developed to facilitate discussion of the statistical analysis components among 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. It also describes the results for the primary and secondary outcome measures that will be posted on ClinicalTrials.gov. Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Statistical Analysis Report are included in the Analysis Implementation Plan (AIP). Data for the Final Statistical Analysis Report will be downloaded once all participants are off study and all queries have been resolved, and the database frozen for analysis.

This Final SAP is limited to analyses that will be conducted by the Statistical Data Analysis Center (SDAC) protocol statisticians; ***hence it will only address primary objectives (2) and (3), and secondary objectives (6) and (7), which are listed in Section 2.5 of this document***. The Final Statistical Analysis Report will be based on this Final SAP. The analyses for the PK objectives (primary objective (1) and secondary objectives (1), (2), (3), (4), (5), and (8) which are listed in section 2.5 of this document) will be performed by the protocol pharmacologists and the results will be reported in a separate PK analysis report,

The Final Statistical Analysis Report will be used for submission of results to ClinicalTrials.gov. Results for primary outcomes are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is based on when the last participant was off study.

1.1 Key SAP Updates

Version	Changes Made	Rationale	Effective Date
1.0	Original Version		20 October 2017
2.0	Modified as per SOP requirements	To align with CLIN.10070 Version 5.0.	25 June 2019

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2 Protocol Overview

2.1 Study design

IMPAACT 2001 is a Phase I/II, open-label, multi-center, intensive pharmacokinetic (PK) study to evaluate the pharmacokinetics, safety, and tolerability of rifapentine (RPT) and isoniazid (INH) dosed once weekly for 12 doses in HIV-1-infected and HIV-1-uninfected pregnant women with latent TB infection at high risk for development of TB. Infants were also enrolled, and breast milk samples from postpartum women who were still taking RPT/INH were collected.

Each enrolled woman received the study drug regimen and were followed until 24 weeks postpartum, regardless of when she delivered. Therefore, it is expected that some women were to continue the study drug regimen postpartum, while some women may have completed the study drug regimen prior to delivery. It is possible that a woman enrolled in Cohort 1 could continue the study drug regimen postpartum (e.g., if she delivers her infant pre-term).

Two study cohorts are planned:

Cohort 1: Pregnant women ≥14 weeks gestation through <28 weeks gestation (second trimester)

Cohort 2: Pregnant women ≥28 weeks gestation through ≤34 weeks gestation (third trimester)

An interim analysis to assess the PK of RPT was to be conducted, and a dose adjustment may be indicated for each cohort (see protocol Section 10). Dose adjustments indicated for Cohort 2 would be implemented for Cohort 1 women as they enter their third trimester of pregnancy. See Section 3.4 for accrual into the cohorts, and Section 10.3 (Interim Analysis and Dose Adjustment) for further details regarding the interim analysis and dose adjustment.

2.2 Sample size

Up to 82 pregnant women (and their infants) were to be enrolled to yield a minimum of 25 evaluable women in each cohort. Within each cohort, enrollment of at least 10 evaluable HIV-1-infected women were to be targeted. This sample size is selected to achieve a relative standard error (RSE) of five percent for estimation of clearance.

2.3 Study regimen

Twelve directly observed once-weekly doses of RPT (900mg) and INH (900mg) taken with pyridoxine (25 to 100mg). An interim analysis was to be performed to assess the clearance of RPT compared to non-pregnant historical controls, and a dose adjustment may be recommended based on this analysis.

2.4 Study duration

Approximately 24 months total. Accrual was expected to require approximately 12 months, and each enrolled woman would be followed through pregnancy and 24 weeks postpartum. Infants were to be followed for 24 weeks from birth.

2.5 Study objectives

Primary Objectives

1. To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the second trimester and third trimester who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).
2. To estimate the incidence of serious adverse events (SAEs) related to RPT + INH dosed once weekly for 12 weeks in pregnant women.
3. To describe the infant safety outcomes among infants born to women receiving once-weekly RPT + INH.

Secondary Objectives

1. To estimate the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of RPT and its desacetyl-rifapentine metabolite (desRPT) among pregnant women during the postpartum period who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).
2. To assess the impact of covariates (gestational age, weight, age, HIV status) on primary PK parameters using population PK modeling.
3. To compare RPT and desRPT exposure pharmacokinetic parameters (AUC, C_{max}, C_{min}) for RPT in pregnant and postpartum women versus non-pregnant historical controls, using noncompartmental analyses.
4. To determine the RPT dose in pregnancy that achieves similar estimated exposure (AUC) of RPT as non-pregnant adults at standard doses.
5. To quantify RPT and desRPT concentrations at delivery among infants born to women receiving once-weekly RPT + INH.
6. To describe the tolerability of RPT + INH dosed once weekly for 12 weeks in pregnant and postpartum women.
7. To assess incidence of active TB in mother-infant pairs up to 24 weeks postpartum.

8. To explore the population pharmacokinetics (PK) (CL/F, absorption, volume of distribution) of INH in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women (i.e., women who are and are not taking efavirenz (EFV)) who are receiving once-weekly RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (900mg).

Exploratory Objectives

1. To quantify RPT and desRPT concentrations in breast milk of postpartum women receiving once-weekly RPT + INH.

2.6 Protocol History

Protocol Version 1.0 was finalized in November 10, 2015. Letter of Amendment (LoA) #1 was issued on January 22, 2016, and was to incorporate clarifications to 1) the number of maternal weekly visits and 2) initiation of the maternal intensive pharmacokinetic (PK) on the day of enrollment. LoA #2 was issued on October 18, 2016 and incorporated modifications to the inclusion criteria, toxicity management, case report form requirements, reporting requirements for expedited adverse events (EAEs), and the sample ICF to provide additional safety guidance and participant management regarding hepatotoxicities. Other corrections and updates were made to the inclusion criterion 4.1.3, procedures for premature discontinuation of the study drug regimen, and the schedule of evaluations. The first two LOAs required IRC approval at the sites before site activation to enroll. LoA #3 was issued on May 7, 2018 and the key changes was to clarify 1) study drug management for general grade 3 and 4 adverse events (AEs) for consistency with baseline values permitted at entry, 2) clarify PK and tolerability outcomes measures and 3) as per ICH and DAIDS requirements it is mandatory that all DAIDS-sponsored and/or supported trials include language that informs participants that other US, local, and international regulatory entities may also review study records. There were three Clarification Memos also issued on 8 April, 2016, 1 June 2016 and 8 February 2017 to clarify details in the protocol.

2.7 Monitoring

It is the responsibility of the protocol team to interpret safety data and make decisions regarding adverse events that are needed to protect participants from undue risk. The safety and tolerability of the study agent was to be monitored by means of adverse event and toxicity reports summarizing laboratory and clinical events. The data required for the toxicity reports must be entered into the database within 48 hours of when the results of the laboratory tests or clinical examinations become available. Reports compiled by the DMC were to be reviewed and discussed by the team on conference calls held at least monthly. The attribution of relationship of ≥ Grade 2 AEs to RPT/INH were to be determined by the protocol team, and any discrepancies of assessments between site investigators and the IMPAACT 2001

protocol team would be reconciled during the conference calls. For safety monitoring, a drug-related AE is an AE that is judged to be definitely, probably, or possibly related to study drug (RPT/INH). Data on participant accrual, pharmacokinetics, and toxicity would be reviewed.

2.8 Study Monitoring Committee (SMC) reviews

The study was monitored by an SMC according to standard IMPAACT procedures. The committee was to meet via conference call to review relevant data as described below and in Section 7.1 of the protocol to ensure participant safety. The SMC could meet at least once annually and more frequently if indicated by the SMC, the protocol team or the study sponsor. The study was to be reviewed for the quality of study conduct and participant safety, including [but not limited to]:

- Study progress and safety
- Participant accrual
- Retention (study/participant summary report)
- Data specimen and completeness
- Pharmacokinetics (as available given the general batching strategy)

The protocol team could also request ad hoc SMC reviews if any potential safety concerns arise. For example, if a potential concern was identified during a routine protocol team review of safety data, the team could request an ad hoc SMC review to further evaluate that potential concern. Based on any of its reviews, the SMC could recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued.

Data on accrual, pharmacokinetics (when made available by the protocol pharmacologist) and toxicity were to be reviewed by the study's SMC:

1) When the consensus among the site investigator, the protocol team and the DAIDS medical officers regarding to relationship of AEs to the study drug cannot be established.

2) When there is any specific safety concern.

Adverse events were to be monitored from screening onward throughout the follow-up period. If any Grade 4 AEs that were possibly, probably, or definitely related to the study regimen or deaths occur, or if the protocol team identifies any potentially treatment-related toxicities that could compromise participant safety, the study could be paused, and the SMC was to review all relevant data and would determine whether, and under what conditions, the study would be allowed to proceed.

3 Selected Outcome Measures

The primary outcome measures for pregnant women during the second trimester, third trimester, and postpartum period who were receiving a dose of RPT 900mg once weekly together with once-weekly INH (900mg) are detailed below.

3.1 Primary Outcome Measures

- Estimates of CL/F, absorption, and volume of distribution of RPT and its desacetyl-rifapentine metabolite (desRPT) during the second trimester and third trimester among pregnant women receiving study drug.
- Safety (maternal)
  - Incidence of related serious adverse events (SAEs) in pregnant and postpartum women taking once-weekly RPT + INH (during treatment period)
  - Grade 2 or higher adverse events (AEs) judged to be related to study drug regimen up to week 24 pospartum
  - All Grade 3 or 4 AEs up to week 24 postpartum
  - All serious AEs up to week 24 postpartum
  - All AEs leading to permanent discontinuation of study drug regimen (i.e., RPT, INH, and pyridoxine)
- Safety (infant)
  Incidence of related serious adverse events (AEs) in infants born to women taking once-weekly RPT + INH.

3.2 Secondary outcome measures include:

- Vd, CL/F, Ka of RPT and desRPT, AUC, Cmax, and Cmon for pregnant women in their second or third trimester
- RPT and desRPT concentrations in infants born to women receiving once-weekly RPT + INH.
- Tolerability
  - Permanent discontinuation of study drug regimen due to intolerance (i.e., RPT, INH, and pyridoxine)
- RPT and des-RPT concentrations in breast milk of postpartum women receiving once-weekly RPT + INH.
- Incidence of active TB in mother-infant pairs up to 24 weeks postpartum.
- Estimates of CL/F, absorption, and volume of distribution of INH in pregnant and postpartum women taking the study drug.

4 Statistical methods

4.1 General statistical considerations

a. This is not a randomized study. Tables and figures in the primary report will be presented by cohort.

b. The primary analyses in this study are: (i) to estimate PK parameters cross-sectionally and longitudinally, and (ii) to describe safety outcomes of the women and their infants during the course of the study. The fundamental concern is to assess maintenance of drug levels between second and third trimesters of pregnancy along with assessment of postpartum drug levels in women and infants.

c. This is a Phase I/II single arm study and not subject to NIH requirements of primary analyses of treatment comparisons.

4.2 Analysis Approaches

The primary maternal safety analysis will include all women who have been exposed to RPT/INH at any dose in the study. Women whose doses have been adjusted for inadequate PK will be included in the primary safety analysis. Women who have discontinued treatment due to toxicities will be included and treated as safety failures in the primary safety analysis. Each woman's safety data will be summarized as: the worst grade of adverse event experienced during study treatment and the worst grade of adverse event judged to be at least possibly related to study treatment during this time period.

Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by cohort. Listing of all ≥ Grade 3 or ICH defined serious events will be provided. The proportions of participants experiencing ≥ Grade 3 or ICH defined serious events will be presented in aggregate and broken down by cohort, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of participants exhibiting ≥ Grade 3 or ICH defined serious events which have been judged (based on team attribution) to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

The primary infant safety analysis will include all infants whose mothers were included in the primary safety analysis (that is, all women who have been exposed to RPT/INH at any dose in the study). Infants were followed for 24 weeks post-delivery. The analysis of tolerability outcome will also include all women in the primary maternal analysis. Analysis of TB incidence will include all mother-infant pairs, except women who were determined to have TB at study entry. Analyses of infant serious adverse events judged to be related to study treatment, tolerability and incident TB will follow the analyses described above for the primary maternal safety outcomes.

For primary objective 2, Poisson regression will be used to estimate the incidence of serious adverse events, related to treatment, adjusting for important cofactors if data allows and for primary objective 3 (analyses of safety for infants), and secondary objectives 6 (analyses of tolerability) and 7 (analyses of incidence of active TB) will employ standard descriptive techniques.

NOTE: All objectives/outcome measures related to PK parameters will be conducted by the protocol pharmacologist

5 Report Components

Detailed descriptions of the content of each of the following sections are given in the AIP.

1. Enrollment
2. Eligibility Violations
3. Protocol Deviations
4. Baseline Characteristics
5. Study Status
6. Safety
7. TB assessment
8. Tolerability