

IMPAACT P1097

Raltegravir Pharmacokinetics and Safety in Neonates

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STATISTICAL ANALYSIS PLAN

Version 3.0

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This is IMPAACT P1097 SAP Version 3.0 with names of authors, names of publication writing team members and analysis timeline redacted

DOCUMENT ADMINISTRATION

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March 20, 2016	<p>IMPAACT P1097 SAP Version 2.0</p> <ul style="list-style-type: none"> • Updated to include analysis for Cohort 2 (low birth weight infants) which opened to accrual under Protocol Version 2.0. • Updated to reflect Cohort 2 SMC monitoring as specified under Protocol Version 2.0. • Updated to reflect changes in the Case Report Forms. • For final analysis, added table for descriptive statistics for infant RAL concentrations and half-life. • For final analysis, added tables for availability of maternal PK data, and duration of infant follow-up.
September 14, 2018	<p>IMPAACT P1097 SAP Version 3.0</p> <ul style="list-style-type: none"> • Primary SAP (this document) and Analysis Implementation Plan (AIP) were created based on specifications in SAP Version 2.0. • The following were added: <ul style="list-style-type: none"> ○ description of submission to ClinicalTrials.gov ○ wide visit windows for checking availability of safety data ○ sections on report contents, writing team roster, and timeline for Final Analysis Report and manuscript preparation. • Updated proposed analyses for Cohort 2 so that prematurity and growth restriction which are considered highly linked to LBW, will be considered baseline.

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1 Introduction

1.1 Purpose of the Statistical Analysis Plan

This Primary Statistical Analysis Plan (SAP) describes the primary and secondary outcomes measures of IMPAACT P1097 that will be included in the primary manuscript addressing the primary and secondary objectives of the study. This document outlines the general statistical approaches that will be used in the analysis for administrative and safety data. 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). SAP and AIP have been developed to facilitate discussion of the statistical analysis components amongst 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.

The SAP includes the components for the data analysis of P1097 Versions 1.0 and 2.0 for Cohorts 1 and 2, respectively. The pharmacology data will be analyzed separately by the protocol pharmacologist.

The primary 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 6 weeks of infant follow-up.

1.2 Key Updates to the SAP

- 1. Primary SAP (this document) and Analysis Implementation Plan (AIP) were created based on specifications in SAP Version 2.0. Primary SAP covers outcome measures, general analytic approaches, and overview of the analysis report content. AIP includes more specific coding details, data sources, validation requirements, and table/figure specifications. There were no changes to the planned analyses for the primary and secondary study objectives.**
- 2. The following were added:**
 - a. description of submission to ClinicalTrials.gov**
 - b. wide visit windows for checking availability of safety data**
 - c. sections on report contents, writing team roster, and timeline for Final Analysis Report and manuscript preparation.**
- 3. Updated proposed analyses for Cohort 2 so that prematurity and growth restriction, which are considered highly linked to LBW, will be considered baseline.**

1.3 Protocol Overview

P1097 is a multi-center clinical trial to determine the washout pharmacokinetics (PK) and safety of in utero/intrapartum exposure to raltegravir (RAL) in infants born to pregnant women with

HIV1 infection who received at least one dose of RAL 400mg within 2 to 24 hours prior to delivery.

The IMPAACT P1097 Protocol includes two cohorts of Mother-Infant (M-I) pairs:

- Cohort 1 (Fully accrued under Protocol Version 1.0): pregnant women with HIV1 infection receiving RAL 400mg twice daily for at least two weeks prior to delivery and continuing to receive ARVs during labor, and their infants.
- Cohort 2 (Opened to accrual under Protocol Version 2.0): pregnant women with HIV1 infection who received at least one dose of RAL 400mg within 2 to 24 hours prior to delivery and their low birth weight (LBW) infants.

Cohort 1 was fully accrued and closed to follow-up under Version 1.0. The protocol was amended to open a cohort for LBW infants (≤ 2500 grams at birth) in Protocol Version 2.0. The primary and secondary objectives of the protocol are the same for both cohorts. Data analysis will be done separately for the two cohorts and no across cohort analysis will be done.

Cohort 1 total accrual was 22 M-I pairs and there were 19 evaluable infants for the RAL washout PK analysis. The M-I pairs were enrolled prior to delivery. Infant blood samples for RAL assay were collected at 1-5, 8-14, 18-24 and 30-36 hours after birth. Maternal blood sample and cord blood sample were also collected during delivery. Team pharmacologists decided if infants were PK evaluable or not. PK unevaluable infants will still remain in the study and will be followed for safety.

Cohort 2 will enroll up to 20 M-I pairs to achieve 15 evaluable LBW infants for the washout PK of RAL. The M-I pairs will be enrolled prior to delivery or within 48 hours after birth. Infant blood samples for RAL assay will be collected at 1-6, 12-24, 36-48, 72-84 and 108-132 hours after birth, and on day 7-14. When possible, maternal blood sample and cord blood sample will be collected during delivery. The washout PK analysis will be based on infants from whom at least 3 neonate blood specimens were collected from the first 5 time points (PK analyses will be done by the protocol pharmacologist). PK unevaluable infants will still remain in the study and will be followed for safety.

Women will be followed until discharge from the labor/delivery unit. Cohort 1 infants were followed for 20 weeks. Cohort 2 infants will be followed for 6 weeks.

1.4 Study Objectives

- a) Primary Objective:
 - To evaluate the washout PK of RAL in infants born to pregnant women with HIV1 infection receiving RAL during pregnancy.
 - To evaluate bilirubin levels and the safety of in utero/intrapartum exposure to RAL in infants born to pregnant women with HIV1 infection receiving RAL during pregnancy.

- To develop a neonatal RAL dosing regimen to be evaluated in a follow-up study of this protocol.

b) Secondary Objective:

- To investigate the relationship between neonatal RAL elimination and UGT1A1 genotype.

1.5 Outcome Measures

a) For primary objectives:

- PK outcome measures:
 - Neonatal RAL elimination ($T_{1/2}$).
 - RAL maternal-cord blood ratio (for Cohort 1 only).
- Safety outcome measures:
 - Infant adverse events (AEs) of Grade 3 or 4 as defined in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance>.
 - **Adverse birth outcomes including stillbirth and low birth weight^a (for Cohort 1 only)**
 - Infant death
 - Total bilirubin
 - Direct bilirubin

^a **Prematurity and growth restriction are highly linked to LBW and will be considered baseline AEs for Cohort 2.**

b) For secondary objective:

- Neonatal RAL elimination (concentrations and $T_{1/2}$)
- UGT1A-1 genotype (presence or absence of *28/*28 genetic variant)

2 SMC Monitoring of Cohort 2

Cohort 1 was fully accrued under Protocol Version 1.0. The SMC report will not include any data from Cohort 1.

Cohort 2 will be monitored for accrual by a Study Monitoring Committee (SMC) to be appointed per IMPAACT Standard Operating Procedures. The SMC will assess accrual 6 months after Cohort 2 opens to enrollment and Protocol Version 2.0 has been approved by IRB/ ECs at 50% of eligible sites, and perform an independent review of the data. If Cohort 2 has not met the accrual target subjects (7 PK evaluable infants) by the 6-month timeframe, the protocol team will be required to provide a written plan to increase accrual prior to the SMC 6-month review at which time the SMC will consider whether to recommend closing the study to enrollment.

A summary of P1097 Cohort 2 administrative data will be included in the SMC report which will be prepared by the protocol statisticians. Other than the site activation summary table, the rest of the summary tables below will be generated by the protocol statisticians.

- Site activation
- Accrual (M-I pairs, Infants, PK evaluable infants)
- Eligibility verification
- Study status

3 Statistical Principles

3.1 General Consideration

Cohort 1 was closed under Version 1.0 with final analysis report for Cohort 1. Data analysis is done separately for the two cohorts and no across cohort analysis will be done.

For Cohort 1, team pharmacologists decided if infants were PK evaluable or not. For Cohort 2, the washout PK analysis will be based on infants from whom at least 3 neonate blood specimens were collected from the first 5 time points (PK analyses will be done by the protocol pharmacologist). PK unevaluable infants will still remain in the study and will be followed for safety.

3.2 Infant Safety Data Collection Schedule and Visit Windows

Table 1 shows the Schedule of Evaluations (SoE) for safety data and includes definition of “wide” visit windows to be used for checking availability of safety data. **Any AEs after the cut-off day for the last study visit will not be in summary tables, but will be mentioned in the report.**

Table 1: Infant Safety Data Collection Schedule and Visit Windows

Evaluation	Scheduled visits					
	Entry/Birth (0 hour after birth)	36 - 48 hours after birth	72 - 84 hours after birth	Week 1 (7 – 14 days after birth)	Week 6 (34 - 49 days after birth)	Off Study
	0-1 day	2 days	3-4 days	5-21 days	22-56 days	
Hematologies and liver chemistries (LBW0093) ³		X ¹	X ²	X		
Signs and Symptoms (PE6831)	X	X		X	X	X
Diagnoses (PE6851)	X	X		X	X	X

¹ Required at this visit: hematology and bilirubin. Hematology to include CBC with differential and platelet count. Bilirubin to include Total and Direct.

² Required at this visit: chemistry. Chemistry includes AST, ALT, Creatinine, Total Bilirubin and Direct Bilirubin.

³ Hematologies and liver chemistries have specimen date and time records. Detailed specimen time data would contribute to data completeness analysis if needed.

3.3 Statistical Tests and Analytic Approaches

3.3.1 Safety Analysis

The safety analysis will consist of descriptive statistics summarizing the safety data from all enrolled infants, including infants who were not evaluable for the washout pharmacokinetic analysis.

The composite infant primary toxicity endpoint has the following components:

- Infant AEs of Grade 3 or 4; or
- **Adverse birth outcomes including stillbirth and low birth weight (for Cohort 1 only)^a ;**
or
- Infant death

^a **Prematurity and growth restriction are highly linked to LBW and will be considered as baseline events for Cohort 2. Cohort 2 baseline events will be summarized separately and will be excluded from the AE tables.**

The primary safety analysis will be the calculation of the point and 2-sided 90% confidence interval (CI) using the Clopper-Pearson exact method estimates of the proportion of infants meeting the composite toxicity endpoint.

To show additional details relating to the analysis of the composite infant safety endpoint, the following will be generated: (1) point and 90% Clopper-Pearson CI estimates of infants meeting each component of the composite toxicity endpoint; (2) frequency tabulations of worst grade adverse events for each subject; and (3) listing of reasons for infant death.

To summarize bilirubin-related data, the following will be generated: (1) summary statistics for total and direct bilirubin at each required sampling time; and (2) point and 90% Clopper-Pearson CI estimates of proportion of infants requiring therapy (e.g. phototherapy, exchange transfusion) to reduce bilirubin.

3.3.2 Secondary Study Objective Analysis

Neonatal RAL elimination ($T_{1/2}$) for infants with versus without polymorphisms on UGT1A1 will be summarized using summary statistics and the comparison of median for these groups will be done using the Wilcoxon Sum Rank Test ($\alpha=0.05$). Analysis will be limited to infants with non-missing RAL elimination and UGT1A1 polymorphism data. There may be limited statistical power for this analysis if there is small sample size.

4 Report Contents

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

- 1) Accrual (M-I pairs, Infants, PK evaluable infants) and eligibility criteria violations**
- 2) Baseline characteristics**
- 3) Study status**
- 4) Data completeness**
- 5) Safety data**
- 6) Neonatal RAL elimination and UGT1A1 genotype**