IMPAACT 2001

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

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RATIONALE

- Pregnant/postpartum women with LTBI have a high risk of developing active TB.
- The newer regimen of 3 months of weekly INH + RPT (3HP) has improved completion rates and decreased hepatotoxicity (TBTC 26, n=7731).
  - Well-tolerated and safe in HIV-1-infected populations and children.
- **The intent of this this study is to provide data needed to extend use of this new regimen to pregnant women.**
  - Determine the impact of pregnancy on RPT PK
    - Compared to historical controls AND by trimester

Zenner AJRCCM 2011, Bergeron Curr Women Health Rep 2003; Sterling NEJM 2011, Sterling IAS 2012, Villarino JAMA 2015, Bliven-Sizemore IJTLD 2015

PRIMARY OBJECTIVES

- 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 INH (900mg) and once-weekly RPT (900mg*).

- To estimate the incidence of serious adverse events (SAEs) related to RPT + INH dosed once weekly for 12 weeks in pregnant women.

- To describe the infant safety outcomes among infants born to women receiving once-weekly RPT + INH.

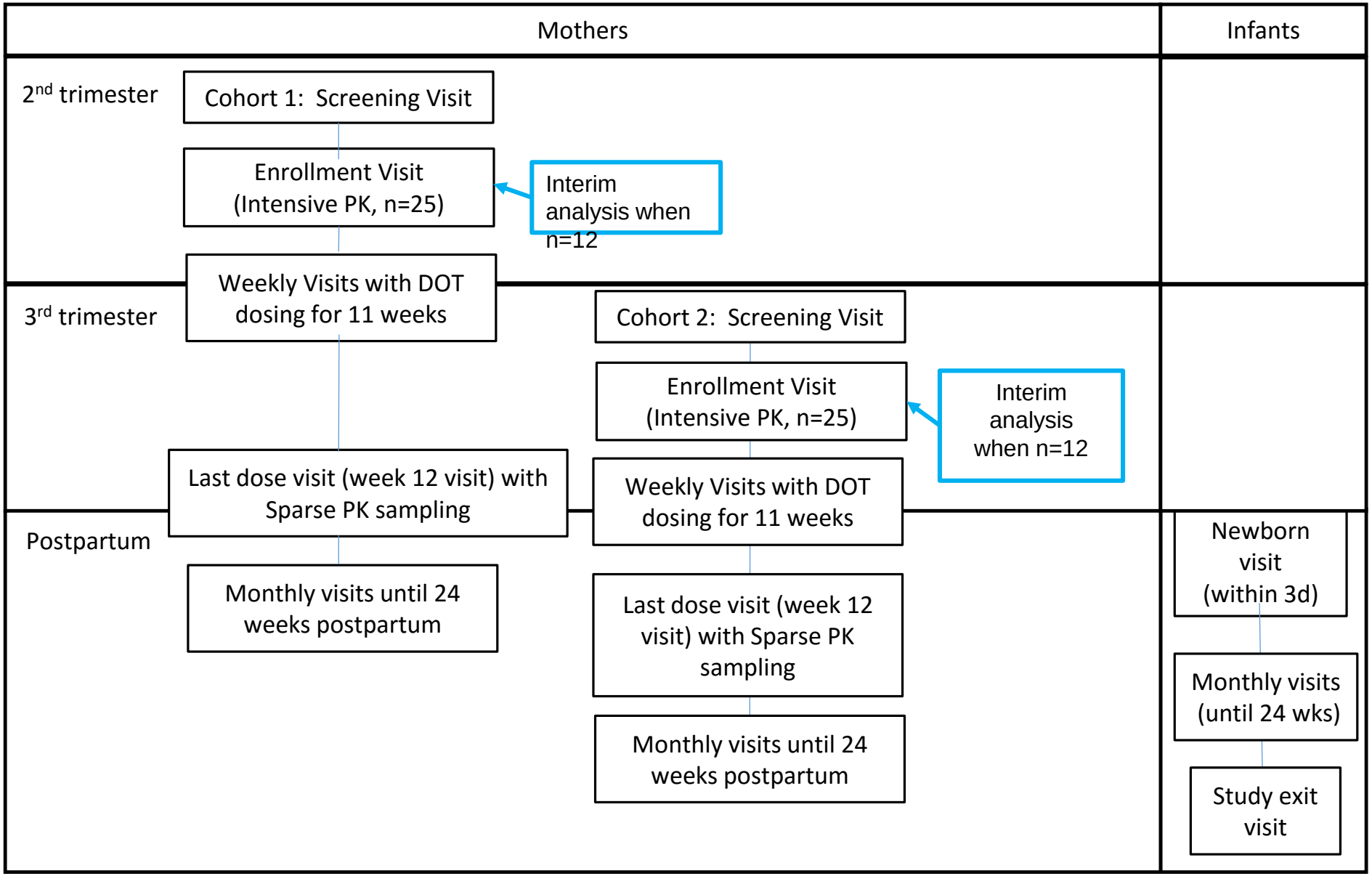
* or the new study dose, if a dose adjustment is indicated by the interim analysis

KEY SECONDARY OBJECTIVES

- To compare RPT and desRPT PK parameters (AUC, C_{max}, C_{min}) in pregnant and postpartum women versus non-pregnant historical controls, using noncompartmental analyses.
- To determine the RPT dose in pregnancy that achieves similar estimated exposure (AUC) of RPT as non-pregnant adults at standard doses.
- To estimate the population PK of RPT and desRPT in postpartum women
- To quantify RPT and desRPT concentrations at delivery among infants born to women receiving once-weekly RPT + INH.

* or the new study dose, if a dose adjustment is indicated by the interim analysis

IMPAACT 2001 Study Design



STUDY STATUS*

6 participating sites

n= 8 mother-infant pairs enrolled as of 25 May 2017

United States	**Zimbabwe**	**Kenya+**
Haiti	**Malawi+**	**Thailand**

**as of 13 March 2017; +will be activated in July 2017*

PHARMACOKINETICS

- An interim analysis will be conducted for each cohort to determine whether a dose adjustment is indicated.
  - Cohort 1: when the first 12 women of Cohort 1 have completed the intensive PK sampling or after the first 12 women have enrolled into Cohort 2, whichever event occurs first.
  - Cohort 2: when 12 women have enrolled into Cohort 2 and completed the intensive PK sampling.

- For each cohort, the dose of RPT will be "acceptable" if median CL/F is within 25% of CL/F of non-pregnant historical controls

- Prior to the interim analysis, all women will be started at a 900mg RPT dose. If a dose adjustment is indicated by the interim analysis, all women enrolled thereafter will be started at the adjusted dose.

STATISTICAL CONSIDERATIONS

- Target enrollment is 25 women per cohort (n=50) at highest tested dose
  - Max enrollment of 37 per cohort (n=74) if both cohorts require a dose increase at interim analysis

- The primary tool for estimation of PK parameters is the single compartment model for RPT absorption and disposition kinetics

Interim Analysis:

- The power for a sample of size of 12 per cohort was computed assuming a difference in clearance between the 2nd and 3rd trimesters (Table 2).
- With this sample size, we will have >80% power to estimate if a dose change is required

Table 1. Sample size calculations and power estimates based on detecting a difference between 2nd vs 3rd trimester

Number of subjects	RSE (CL) (%)	RSE, CL_3rd (%)	RSE (V) (%)	RSE (ka) (%)	RSE (BSV-CL) (%)	RSE (BSV-V) (%)	Power (%)
10	9	39	9	12	36	41	82.2
15	8	33	8	10	33	35	91
20	7	27	7	9	29	32	94.6
30	6	23	6	7	25	27	98.2
40	5	20	5	6	22	24	99.5
50	5	18	4	6	20	22	99.9
60	4	17	4	5	18	19	100
70	4	14	4	5	17	18	100

*Keizer CPT Pharmacometrics Syst. Pharmacol 2013

SAFETY ASSESSMENT AND MONITORING

- Safety and tolerability monitored by AE reports (laboratory and clinical events) on all enrolled women
- Data on accrual, PK, toxicity reviewed by SMC, when:
  1. The consensus among the site investigator, the protocol team, and the DAIDS medical officers regarding relationship of AEs to the study drug cannot be established
  2. There is any specific safety concern

Table 2. Minimum sample sizes required to encounter one or more safety events (or two or more safety events) for given event rates, regarding safety events as independent, counts governed by the Poisson distribution.

Cell entries are minimum sample size required to detect 1 or more safety events at the given rates			
	Safety Event Rates		
Power	0.05	0.1	0.15
0.8	33	17	11
0.9	47	24	16
Cell entries are minimum sample size required to detect 2 or more safety events at the given rates			
	Safety Event Rates		
Power	0.05	0.1	0.15
0.8	60	30	20
0.9	78	39	26

TIMELINE

All sites will be activated and will begin enrollment

Interim analysis when Cohort 2, n=12

Complete interim analysis/ Dose adjustment?

Complete enrollment

Complete study analysis