IMPAACT 2001 STUDY TRAINING

VERSION 1.0, 10 NOVEMBER 2015

WITH LOA 1-2, CM 1-3

IMPAACT 2001
RATIONALE AND OBJECTIVES

RATIONALE

- Pregnant and postpartum women with LTBI have a high risk of developing TB.
- The standard LTBI regimen is 6-9 months of daily INH. The newer regimen of 3 months of weekly INH + RPT has shown improved completion rates and decreased hepatotoxicity (TBTC 26, n=7731). It is also 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.
- This study targets a sample of 50 pregnant women, 25 in their second trimester and 25 in their third trimester, for estimation of RPT CL/F.
  - We will test for effect of pregnancy on RPT PK (comparison to historical controls) and effect of trimester within pregnancy (internal comparison).
  - Comprehensive safety monitoring will be conducted for all enrolled women and their infants

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 RPT (900mg or the new study dose, if a dose adjustment is indicated by the interim analysis) and once-weekly INH (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.

SECONDARY AND EXPLORATORY OBJECTIVES

Secondary Objectives:

- To estimate the population 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 INH (900mg) and once-weekly RPT (900mg*).
- To assess the impact of covariates (e.g. gestational age, weight, age, HIV status) on primary PK parameters using population PK modeling.
- 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.
- To determine the RPT dose in pregnancy that achieves similar estimated exposure (AUC) of RPT as non-pregnant adults at standard doses.

SECONDARY AND EXPLORATORY OBJECTIVES

Secondary Objectives

- To quantify RPT and desRPT concentrations at delivery among infants born to women receiving once-weekly RPT + INH.
- To describe the tolerability of RPT + INH dosed once weekly for 12 weeks in pregnant and postpartum women.
- To assess incidence of active TB in mother-infant pairs up to 24 weeks postpartum.
- To explore the population 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

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

IMPAACT 2001 STUDY DESIGN

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