IMPAACT 2001

Final Pharmacokinetic Statistical Analysis Plan

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

OBJECTIVES

Primary

Pharmacokinetic (PK, concentration-time) data and safety data of rifapentine (RPT) and desacetyl-rifapentine (des-RPT, metabolite) in pregnant women

Secondary

PK data of RPT and des-RPT in postpartum women and infants; PK data of isoniazid (INH) in pregnant and postpartum women

DATA

Dataset checking

Source datasets provided to UCSF will be checked by IMPAACT against the original database. Datasets may need to be subsequently manipulated during the PK analysis. Each time manipulations are performed the new dataset will be checked against the original dataset. The following checks will be performed:

- Comparison of number of subjects in the new dataset to those expected to be retained from the initial dataset
- Number of observations per subject in the new dataset to those expected to be retained from the initial dataset
- Check of dosing history (PK sampling times relative to dosing, missing dosing or sampling times).

Any discrepancies/errors found in the dataset will be corrected and documented.

Exclusion of data points

All evaluable data will be used for analysis. All data exclusions will be documented.

Identification of outliers

Individual data points that are clearly aberrant and/or with residuals (weighted, conditional weighted, and/or individual weighted) greater than 6 will be considered for omission. An assessment of their impact on the analysis will be documented.

Handling of missing data

The population median value at each time point may be used for missing data from a continuous variable (e.g. age, weight, and serum creatinine level) for a particular subject. If any value is missing at baseline, screening values may be used for imputation, if available.

METHODOLOGY

RPT and des-RPT

Adults

Approach

Population-based estimates of PK parameters for RPT (CL/F, absorption, volume of distribution) and des-RPT ($CL_{metabolite}/F$) will be derived for

(1) pregnant women in the second and third trimesters of pregnancy and

(2) women after delivery (postpartum).

Secondary PK parameters for RPT and des-RPT (area under the curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min})) will be derived from the model for pregnant women in the second and third trimesters of pregnancy.

The study data, which provide a mix of longitudinal and cross-sectional observations, will be combined and modeled using nonlinear mixed effects approaches that are widely used in pharmacology research. Nonlinear mixed effects modeling will be performed using NONMEM v7.4. Dataset manipulation and data visualization will be performed using R v3.5.1 and Microsoft Office Excel. Perl-speaks-NONMEM (PsN) v4.8.1 and Xpose4 v4.6.1 will be used for model evaluation.

Exploratory data analysis

Prior to beginning modeling analyses, the following exploratory data analyses will be performed:

- Scatterplots of dependent variable (DV) versus time, stratified by treatment outcome, cohort, or disease status
- Summary statistics including the number of patients, samples, samples per patient, and number of patients with samples at each visit.

Structural model development

The absorption and disposition kinetics of RPT and des-PRT will be described by a one compartment model with first-order (linear) elimination and first-order oral absorption. More complex models with respect to absorption (e.g. transit compartments), distribution, and elimination will be explored if necessary.

Goodness-of-fit diagnostic plots will be used to assess the structural model:

- Observations versus population and individual predictions
- Population, individual, and conditional weighted residuals versus time

Stochastic model development

Exponential error models will be used to characterize the between-subject-variability of the model parameters. A diagonal sigma-structure will be used, and off-diagonal elements may be included.

For continuous data, additive, proportional, and combined (additive and proportional) error models will be used to characterize the residual variability.

The appropriateness of the random error models will be assessed using diagnostic plots:

- Observations versus population and individual predictions
- Population, individual, and conditional weighted residuals versus time
- Observations versus time with population and individual fits
- Histogram of ETA estimates

Model evaluation

Visual predictive checks will be used to evaluate how well the model describes the data.

Infants

Approach

Summary statistics will be compiled for plasma and cord blood RPT and des-RPT concentrations in infants collected within 72 hours following birth.

Dataset manipulation and data visualization will be performed using R v3.5.1 and Microsoft Office Excel.

Summary statistics

Cord blood and plasma concentration data for RPT and des-RPT will be summarized by

- Count
- Minimum concentration and maximum concentration
- Mean and median
- First quantile and third quantile.

INH

Adults: Approach

Population-based estimates of PK parameters for INH (CL/F, absorption, volume of distribution) will be derived for all pregnant women irrespective of pregnancy trimester or pre-/post-partum status.

The study data, which provide a mix of longitudinal and cross-sectional observations, will be combined and modeled using nonlinear mixed effects approaches that are widely used in pharmacology research. Nonlinear mixed effects modeling will be performed using NONMEM v7.4. Dataset manipulation and data visualization will be performed using R v3.5.1 and Microsoft Office Excel. Perl-speaks-NONMEM (PsN) v4.8.1 and Xpose4 v4.6.1 will be used for model evaluation.

Exploratory data analysis

Prior to beginning modeling analyses, the following exploratory data analyses will be performed:

- Scatterplots of dependent variable (DV) versus time, stratified by treatment outcome, cohort, or disease status
- Summary statistics including the number of patients, samples, samples per patient, and number of patients with samples at each visit.

Structural model development

The absorption and disposition kinetics of INH will be described by a one compartment model with first-order (linear) elimination and first-order oral absorption. More complex models with respect to absorption, distribution, and elimination (e.g. mixture models) will be evaluated if necessary.

Goodness-of-fit diagnostic plots will be used to assess the structural model:

- Observations versus population and individual predictions
- Population, individual, and conditional weighted residuals versus time

Stochastic model development

Exponential error models will be used to characterize the between-subject-variability of the model parameters. A diagonal sigma-structure will be used, and off-diagonal elements may be included.

For continuous data, additive, proportional, and combined (additive and proportional) error models will be used to characterize the residual variability.

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- Observations versus population and individual predictions
- Population, individual, and conditional weighted residuals versus time
- Observations versus time with population and individual fits
- Histogram of ETA estimates

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