Statistical Analysis Plan

ACTG A5338*:* An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

ClinicalTrials.gov Identifier: NCT02412436

Version 1.0
November 28, 2018

Introduction

This Statistical Analysis Plan addresses the following secondary objectives listed in the study protocol.

1.3.1. To estimate the area under the concentration-time curve (AUC), trough concentration (C_{min}), maximum concentration (C_{max}), apparent clearance (CL/F), and half-life ($t_{1/2}$) of MPA in HIV and TB coinfected women taking EFV-based cART and RIF-containing TB treatment.

1.3.2. To estimate time and variability in time to MPA C_{min} reaching 0.1 ng/mL or less in HIV and TB coinfected women taking EFV-based cART and RIF-containing TB treatment.

Statistical Analysis Plan

- The concentration vs. time data for DMPA will be analyzed using nonlinear mixed-effects (NLME) modelling using the software NONMEM (version 7.4.2) (S. Beal, Sheiner, Boeckmann, & Bauer, 2009) pooling the data from the available studies A5338, A5238 and A5093.
- The modelling approach followed a stepwise procedure to first identify the structural model best describing the data, and then incorporate the effect of the study covariates such as weight, age, and effect of concomitant anti-retroviral and anti-tuberculosis treatment.
- Various structural pharmacokinetic models were evaluated, focusing on correctly characterizing the absorption after intra-muscular injection. The tested models included one and two compartments disposition, with first-order elimination and zero-, first-order, two parallel first order absorption.
- Model selection was be based on changes in the NONMEM objective function value (ΔOFV), and visual inspection of conditional weighted residuals (CWRES) versus time, visual predictive checks, and basic goodness of fit plots (GOF).
- Statistically significant variability and correlation estimates for the PK parameters were included and the covariates of interest were retained in the final model with respect to their impact on the PK parameters and their variability. Covariate selection was be based on the drop in objective function value (assumed to be χ-square distributed and thus using 3.84 points drop as significant at $p<0.05$ for the inclusion of a single parameter), while scrutinizing the physiological plausibility of the effect.
- Allometric scaling (Anderson & Holford, 2008) was USED to account for the effect of body size on the pharmacokinetic parameters, using total body weight.

References

1. Beal, S., Sheiner, L. B. L., Boeckmann, A. & Bauer, R. R. J. NONMEM User's Guides. (1989-2009). (2009).
2. Anderson, B. J. & Holford, N. H. G. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. *Annu. Rev. Pharmacol. Toxicol.* **48**, 303–332 (2008).