Pharmacology Statistical Analysis Plan

Version 3.0

IMPAACT 2007

Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

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This is IMPAACT 2007 Pharmacology SAP Version 3.0 with names of authors redacted.

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1. Introduction

This Pharmacology Statistical Analysis Plan (PK SAP) is complementary to the IMPAACT 2007 Primary SAP (version 2.0), the IMPAACT 2007 Population Pharmacokinetic Reporting Analysis Plan (Population PK RAP, version 1.0), and the IMPAACT 2007 PK Data Management Plan (version 1.0). This document describes the non-compartmental pharmacokinetic (PK) analysis to be performed by the IMPAACT 2007 protocol pharmacologist(s) at the end of study on the completed study dataset and included in the Clinical Study Report (CSR, for regulatory submission) and study manuscript(s).

2. PK-Related Study Background

IMPAACT 2007 is a Phase I safety and pharmacokinetic study of maraviroc (MVC) in HIV-1 exposed infants at risk of acquiring HIV-1 infection. This study has two sequential dosing cohorts stratified by maternal use of efavirenz (EFV). Cohort 1 infants receive two single doses of MVC – the first dose at study entry (days 0 – 3 of life) and the second dose at one week (7 – 14 days) of life, with PK evaluations around both single doses (refer to protocol sections 6.4.1 and 6.5.1 for sampling schedules). Once the dose is determined for each Cohort 1 Stratum, the corresponding Stratum will open to enrollment for Cohort 2. Infants enrolled in Cohort 2 will receive 6 weeks of daily MVC dosing (within day 3 of life up to day 42 of life). In Cohort 2, PK evaluations are performed at weeks 1 and 4 (refer to protocol sections 6.5.3 and 6.7.2 for sampling schedules). In Cohort 2, both strata, single random sparse PK samples are also drawn at week 6. Additional single samples were collected in Stratum 1B and 2B infants to assess EFV concentrations in the infants (from maternal dosing).

The starting dose for both strata in Cohort 1 is 8 mg/kg. Summary data were prepared to evaluate the dose in each Cohort 1 stratum after enrollment of at least 6 infants per stratum to confirm appropriateness of dose, and to confirm dose(s) to be used in Cohort 2. Refer to protocol sections 9.2, 9.6.2, and 10.3 for the dose-finding algorithm. For the dose-finding interim PK analyses, non-compartmental pharmacokinetic analysis methods were used to generate PK parameters, followed by pharmacokinetic modeling as needed to generate C_{avg} estimates for the real-time PK assessments that were needed to make dosing decisions, as per protocol section 10.5.

The MVC exposure target for this study is $C_{avg} \geq 75$ ng/mL at both PK evaluations (entry and week 1 for Cohort 1, and weeks 1 and 4 for Cohort 2).

3. Pharmacokinetic Population

PK Dose-Finding Evaluable participants are infants whose PK results provide data on the primary PK parameter of interest (C_{avg}) and are included in the dose-finding evaluations (See Section 10.1 of the protocol for additional details). Refer to the Primary SAP and the Analysis Implementation Manual for the Regulatory Submission (AIM) for a description of participants who are included for the dose-finding purposes in this study (i.e., eligible participants who are PK and/or safety

evaluable). The summary figures and tables and the listings will include all **PK Dose-Finding Evaluable** participants. Any infant who is not included in the **PK Dose-Finding Evaluable** group will be listed separately with a corresponding explanation or discussion of the reasons they are not included in the dose-finding group.

4. Pharmacokinetic Study Objectives

The primary PK objective for IMPAACT 2007 is to determine the pharmacokinetics of maraviroc solution during the first six weeks of life and to determine an appropriate dose over this time frame. The secondary PK objective for IMPAACT 2007 is to determine age-related changes in maraviroc pharmacokinetic parameters over the first six weeks of life.

5. Non-Compartmental Pharmacokinetic Analyses

The intensive PK sampling schedules are outlined in the IMPAACT 2007 protocol. Standard non-compartmental methods for PK parameter derivation will be performed using Phoenix (Certara USA, Inc). Where possible, the following PK parameters will be determined from maraviroc plasma concentrations following PK sampling:

Parameter	Definition
C_{max}	Observed maximum plasma concentration
t_{max}	Time of maximum plasma concentration
$AUC_{(0-\infty),\ pred}$	For Cohort 1: Area under the concentration-time curve from time zero to infinity
$AUC_{(0-\tau),\ pred}$	For Cohort 2: Area under the concentration-time curve from time zero to the end of the dose interval
CL/F	Apparent oral clearance
V_z/F	Apparent volume of distribution calculated as CL/λ_z
λ_z	Terminal elimination rate constant
$t_{1/2}$	Terminal half-life calculated as $\ln(2)/\lambda_z$
C_τ	Concentration at the end of the dose interval
C_{avg}	Average concentration calculated as AUC/τ

Additional PK parameters may be determined where appropriate. Pharmacokinetic analysis will be carried out using actual sampling times. Concentrations for PK analyses will be used as supplied by the analytical laboratory.

5.1. Below the Level of Quantitation

MVC concentration values that are below the level of quantification (BLQ), < 5 ng/mL, will be set to zero. If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis. If a pre-dose concentration is below the limit of assay detection, this value is set to zero. Any embedded BLQ value (BLQ value occurring between two quantifiable concentrations) in

a profile will be set to missing for the purposes of PK analysis. For regulatory submission purposes, in the analysis of the log transformed values of the PK parameter and concentration data, log (BLQ) was replaced with the value of 0.

5.2. Terminal Slope Estimation

The default settings for the analysis software will only estimate an elimination rate constant when the PK profile has three or more declining concentrations after the peak concentration in a non-compartmental analysis. For the infants in Cohort 2 whose peak concentration was at the 3 – 5 hour time point, only two more samples were drawn after the peak, and the default settings would not estimate the elimination rate constant in those infants. In those cases, the program was directed to calculate the elimination rate constant from the last two observed concentrations (the 6 – 8 hour concentration and the 11 – 13 hour concentration). Those infants whose elimination rate constants were calculated from only two points (instead of the three points used in the remaining infants) are indicted in the output tables.

5.3. AUC Values

AUC is calculated by the linear trapezoidal rule. For Cohort 1, predicted $AUC_{(0-\infty)}$ is used. For Cohort 2, predicted $AUC_{(0-T)}$ is used. Because the trough values are drawn over a range of times (either 11 – 13 hours post dose for twice daily dosing, or 20 – 24 hours post dose for once daily dosing) rather than right at the trough time post dose, the predicted $AUC_{(0-T)}$ to the exact proposed trough time (12 or 24 hours) will be reported, and used to calculate C_{avg}. For Cohort 1, if predicted $AUC_{(0-\infty)}$ is missing because the terminal elimination rate constant could not be estimated, then $AUC_{(ALL)}$ will be used. $AUC_{(ALL)}$ is the observed AUC through the time of the last sample. For Cohort 1 at Week 1 specifically, the limited sampling schedule and high number of BLQ MVC concentrations precluded the estimation of AUC (and hence C_{avg}) by non-compartmental methods. Therefore, the Tables/Figures/Listings (TFLs) summarizing this end-of-study non-compartmental analysis do not include C_{avg} values for Cohort 1 at Week 1. Results from the end-of-study Population PK analysis will be reported separately (see Population PK RAP). For Cohort 2, if predicted $AUC_{(0-T)}$ is missing (because terminal elimination rate constant could not be estimated), then $AUC_{(ALL)}$ will be used.

6. Summary Statistics

All individual concentrations and all pharmacokinetic parameters will be summarized using descriptive statistics. These will include the number of observations available,

geometric mean, geometric coefficient of variation (CV), geometric 95% confidence intervals, arithmetic mean, standard deviation (SD), CV, median, minimum, and maximum. For dissemination, selected descriptive statistics will be used as appropriate for the data distribution. Typically, this includes using geometric means to summarize the log-transformed parameters, such as AUC, C_{max}, C_{avg}, V_z/F, CL/F; median for t_{max} and arithmetic mean for $t_{1/2}$. PK parameters will be summarized by strata, cohort and study visit as listed in section 7.1 below.

7. Presentation of Data

Concentration time profiles (for individual infants, strata, and/or cohorts) will be presented graphically. For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used. The tables, listings and figures to be included in the CSR are listed below. The summary figures and tables will include all participants who are included in the **PK Dose-Finding Evaluable** population. MVC concentrations and PK parameters will be listed out separately for any participant not included in the **PK Dose-Finding Evaluable** population.

7.1. Tables/Listings

- Plasma Maraviroc Concentration (ng/mL) versus Time Summary (Descriptive Statistics), By Visit, Strata and Cohort
    - Entry, Stratum 1A
    - Week 1, Stratum 1A
    - Entry, Stratum 1B
    - Week 1, Stratum 1B
    - Entry, pooled Cohort 1
    - Week 1, pooled Cohort 1
    - Week 1, Stratum 2A
    - Week 4, Stratum 2A
    - Week 6, Stratum 2A
    - Week 1, Stratum 2B
    - Week 4, Stratum 2B
    - Week 6, Stratum 2B
    - Week 1, pooled Cohort 2
    - Week 4, pooled Cohort 2
    - Week 6, pooled Cohort 2
        - These tables include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Maraviroc Concentration versus Time Listing, By Cohort
    - Cohort 1, Stratum 1A listings for each participant

    - Cohort 1, Stratum 1B listings for each participant
    - Cohort 2, Stratum 2A listings for each participant
    - Cohort 2, Stratum 2B listings for each participant
        - These tables include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Listing and Descriptive Summary of Maraviroc PK Parameters, By Visit, Strata and Cohort)
    - Entry, Stratum 1A
    - Week 1, Stratum 1A
    - Entry, Stratum 1B
    - Week 1, Stratum 1B
    - Entry, pooled Cohort 1
    - Week 1, pooled Cohort 1
    - Week 1, Stratum 2A
    - Week 4, Stratum 2A
    - Week 1, Stratum 2B
    - Week 4, Stratum 2B
    - Week 1, pooled Cohort 2
    - Week 4, pooled Cohort 2
        - In Cohort 2, include Week 1: Week 4 C_{avg} Ratio, and a Yes/No Column for C_{avg} Target met (C_{avg} for both Week 1 and Week 4 ≥ 75 ng/mL), in addition to PK parameters noted in section 5.
        - Notate in these tables the PK profiles for which only two concentrations (instead of three) were used for estimation of the terminal elimination rate constant.
        - The tables above include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Concentration versus time listing, and PK parameters listing, by Visit, Strata and Cohort
    - For each participant who was not included in the **PK Dose-Finding Evaluable** population.

<u>Figures</u>

- Mean Plasma Maraviroc Concentration-Time Plot (Linear and Semi-Log), By Visit, Strata and Cohort
    - Entry Stratum 1A, Week 1 Stratum 1A, Entry Stratum 1B, Week 1 Stratum 1B, Entry Pooled for Cohort 1, Week 1 Pooled for Cohort 1
    - Week 1 Stratum 2A, Week 4 Stratum 2A, Week 1 Stratum 2B, Week 4 Stratum 2B, Week 1 Pooled for Cohort 2, Week 4 Pooled for Cohort 2
        - These figures will include all participants who were included in

the **PK Dose-Finding Evaluable** population.

- Median Plasma Maraviroc Concentration-Time Plot (Linear and Semi-Log), By Visit, Strata and Cohort
    - Entry Stratum 1A, Week 1 Stratum 1A, Entry Stratum 1B, Week 1 Stratum 1B, Entry Pooled for Cohort 1, Week 1 Pooled for Cohort 1
    - Week 1 Stratum 2A, Week 4 Stratum 2A, Week 1 Stratum 2B, Week 4 Stratum 2B, Week 1 Pooled for Cohort 2, Week 4 Pooled for Cohort 2
        - These figures will include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Summary Plasma Maraviroc C_{avg}, By Visit, Strata, and Cohort
    - Entry Stratum 1A, Week 1 Stratum 1A, Entry Stratum 1B, Week 1 Stratum 1B, Entry Pooled for Cohort 1, Week 1 Pooled for Cohort 1
    - Week 1 Stratum 2A, Week 4 Stratum 2A, Week 1 Stratum 2B, Week 4 Stratum 2B, Week 1 Pooled for Cohort 2, Week 4 Pooled for Cohort 2
    - Include reference line at 75 ng/mL
        - These figures will include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Maraviroc Concentration-Time Plot (Linear), By Visit and Strata
    - Include all individual profiles in one summary figure for each Visit
    - Entry Stratum 1A and 1B
    - Week 1 Stratum 1A and 1B
    - Week 1 Stratum 2A and 2B
    - Week 4 Stratum 2A and 2B
        - These figures will include all participants who were included in the **PK Dose-Finding Evaluable** population.
- Maraviroc Concentration-Time Plot (Semi-Log), By Visit and Strata
    - Include all individual profiles in one summary figure for each Visit/Stratum
    - Entry Stratum 1A and 1B
    - Week 1 Stratum 1A and 1B
    - Week 1 Stratum 2A and 2B
    - Week 4 Stratum 2A and 2B
        - These figures will include all participants who were included in the **PK Dose-Finding Evaluable** population.

Additional tables, listings or figures may be prepared upon request.