DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

Division of AIDS (DAIDS) Pharmacokinetic Statistical Analysis Plan (PK SAP)

Protocol Name: IMPAACT P1093 - Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

PK SAP Version and Date: Reporting and Analysis Plan for Phase I/II, Multi-Centre, Open-Label Pharmacokinetic Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents, dated 08 April 2019

INTRODUCTION

The purpose of this RAP is to describe the PK analyses as outlined in the protocol only and will be used for submission of results for the Tivicay Pediatric global regulatory submissions. The tables, figures and listings of the Primary Statistical Analysis Report as well as those in this RAP will be shared with the industry sponsors and contribute to the CSR. This PK SAP covers only the intensive pharmacokinetic assessments and analyses conducted in P1093.

STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population PK analysis.	C24h, AUC0-24
To evaluate the steady-state pharmacokinetics of DTG in combination with OBT in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C24h and AUC024 PK parameters in this population.	C_0, C_{min}, C_{max}, CL/F, Vz/F and $t_{1/2}$
To evaluate the pharmacokinetic profile of DTG when dosed by weight bands.	Subgroup analysis for primary and secondary PK endpoints by weight band

PHARMACOKINETIC STUDY DESIGN

The overall safety and PK data of the first 4 participants on a given cohort will be evaluated with respect to the safety and guidelines per protocol. If the first 4 evaluable participants of this cohort meet both sets of guidelines, then accrual will continue, and no dose adjustments will be made. If the first 4 evaluable participants of the older cohort fail either the safety or the PK guidelines in this initial test, then the starting dose will be adjusted in the appropriate direction, (upwards for inadequate PK values; downwards for safety failure), if this is feasible. Four new participants will be treated at the new dose, and an initial evaluation of safety and PK will be made on the basis of data from these participants. The evaluation will proceed as described above. In the final assessment of Stage I results, the starting dose of a fully accrued cohort (minimum of N = 10) will be evaluated on the basis of safety

and PK guidelines. Failure with respect to the safety and/or PK guidelines will result in a dose adjustment within this cohort, with the starting dose adjusted in the appropriate direction, if this is feasible. New participants will be started on the new dose and evaluations will proceed as described above. If the Protocol Team deems a given participant's PK data to be unevaluable (e.g. because of reported non-adherence or PK results that would be physiologically implausible with good adherence), that participant will be replaced for dose finding purposes (but will continue in the study and contribute to the safety analyses). Note that the participant would be replaced for evaluating safety, as well as PK, criteria, if unevaluable PK data reflect uncertainty about appropriate exposure to the study medication. Once the dose finding procedures of Stage I have been completed for each cohort, the Protocol Team will review all safety and PK data and will make final recommendations concerning the doses. These recommendations will be reviewed by the Protocol Team. The purpose of this review process will be to take account of all available information in determining whether the dose finding algorithm has converged on the best dose for further study in Stage II or whether adjustments are needed. As part of this review process, safety and PK data will be broken down on the basis of the dosing adjustments that have been made because of the inducing or inhibiting effects of the background regimens. If there is evidence that some adjustments may have been associated with undesirable PK levels or with safety concerns, these adjustments may be modified for Stage II or further data may be gathered prior to opening Stage II. Under Version 5, the Stage I data from Cohorts III-DT, IV-DT and V-DT will also be examined by weight band. If this examination suggests that the dose under evaluation is not adequate for a given weight band and should not be used for that weight band in Stage II, then a new "weight band group" will be opened to determine an adequate dose for that weight band, and this weight band group will be evaluated like an age cohort, as described above. Participants accrued to Stage II of the study will be administered the doses determined for their age cohorts, with no individual dose adjustments on the basis of PK allowed. For purposes of analysis, data from these participants will be combined with the data from the Stage I participants who have been treated at the optimal doses determined for their cohorts and who have not required individual PK determined dose adjustments, such that their total exposure to the study drug has been at the optimal dose.

ANALYSIS POPULATIONS

Population	**Definition / Criteria**	**Analyses Evaluated**
Intensive Pharmacokinetic Concentration	All enrolled subjects who undergo intensive PK sampling, received at least 1 dose of DTG, where samples are collected according to the intensive sampling schedule and have been analyzed.	PK
Intensive Pharmacokinetic Parameter	All subjects in the Intensive Pharmacokinetic Concentration Population who provide at least one evaluable PK parameter and whose samples are not excluded for any reason.	PK

Sparse Pharmacokinetic Concentration	All enrolled subjects who undergo Sparse PK sampling, received at least 1 dose of DTG, where samples are collected according to the sparse sampling schedule and have been analyzed.	PK
Sparse Pharmacokinetic Parameter	All subjects in the Sparse Pharmacokinetic Concentration Population who provide at least one evaluable PK parameter and whose samples are not excluded for any reason.	PK

Sparse PK analyses will be conducted separately by the sponsor and not covered in this PK SAP

Weight Band and Cohorts

The following labels for Weight Band will be used on all tabulations where the results are displayed by Weight Band, in the following order:

- 3-<6kg
- 6-<10kg
- 10-<14kg
- 14-<20kg
- 20-<25kg
- 25-<35kg
- ≥35kg
- Overall

Note, the initial cohorts were not dosed by these weight bands. In the event that subjects are not dosed according to their weight band category they will be grouped according to the weight band for the dose they received.

The following labels for Cohort will be used on all tabulations where the results are displayed by Weight Band or Age, in the following order:

Cohort I	Adolescents ≥ 12 to <18 years of age (tablets)
Cohort IIA	Children ≥ 6 to <12 years of age (tablets)
Cohort IIB	Children ≥ 6 to <12 years of age (granules for suspension)
Cohorts III	Children ≥ 2 to < 6 years of age (granules for suspension)
Cohort III-DT	Children ≥ 2 to < 6 years of age (dispersible tablets)
Cohort IV	Children ≥ 6 months to < 2 years (granules for suspension
Cohort IV-DT	Children ≥ 6 months to < 2years of age (dispersible tablets)
Cohort V-DT	Infants ≥ 4 weeks to < 6 months (dispersible tablets)

Formulation

The following labels for Formulation will be used on all tabulations where the results are displayed by Weight Band or Age, in the following order:

- Film Coated Tablets (FCT) and Dispersible Tablets (DT)

PHARMACOKINETIC ANALYSES

All concentration-time samples will be registered in the Lab Data Management System (LDMS) database. All PK samples (including intensive and population PK) will be sent to the University of Alabama (UAB) Laboratory (see the Laboratory Processing Chart). The study database will be kept up to date by close tracking of samples. As part of Stage I, the intensive PK sample assays and pharmacokinetic calculations will be performed in real-time and the results will be reported and discussed with the Protocol Team.

Steady-state pharmacokinetic parameters will be determined from plasma concentration-time profiles using non-compartmental methods (Phoenix WinNonlin 8.0, Certara, Princeton, NJ). Calculated pharmacokinetic parameters will be: area-under-the-curve ($AUC_{0\text{-}24}$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), plasma concentration observed at end of 24 hour dosing interval (C_{24h}), plasma concentration observed immediately to dosing of 24 hour dosing interval (C_0), minimum plasma concentration (C_{min}), apparent clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half-life ($t_{1/2}$). $AUC_{0\text{-}24}$ will be determined using the linear-log trapezoidal rule. C_{max}, $T_{max,}$ C_0, C_{24h}, and C_{min} will be taken directly from the observed concentration-time data. Intensive PK sampling is conducted between days 5 and 10 after study drug initiation and over the course of approximately 24 hours. Sparse population pharmacokinetic evaluation is scheduled at Weeks 4, 12 and 24. This will be a separate analysis conducted by the sponsor and not covered in this PK SAP.

Derived Pharmacokinetic Parameters for subjects participating in the intensive studies

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin 6.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve (AUC) from time 0 (predose) to time of the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-24)	Area under the concentration-time curve (AUC) over time 0 (predose) to 24 hours after dose administration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax, Cmin C0, and $T_{max,}$	The maximum observed concentration (C_{max}) at steady-state and the time of its occurrence during a dosing interval (T_{max}) will be obtained directly from the observed concentration-time data. The minimum observed concentration at steady-state (C_{min}) is obtained directly from the observed concentration-time data.

	The predose concentration at steady state (C_0) is obtained directly from the observed concentration-time data.
C_{24}	The observed concentration at 24 hours after dose administration.
t½	Elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve (ln2), where λz stands for the apparent terminal phase elimination rate-constant. The λz will be estimated by linear regression of logarithmically transformed concentration versus time data in WinNonLin. A minimum number of three data points will be used in calculating λz. C_{max} should not be included among these data points. As a measure of evaluating the regression analysis, R-square values (square of the correlation coefficient) over 0.85 will be ideal, although lower R-square values may be acceptable, based on individual judgement: $t½ = \ln 2 / \lambda z$
λz	Terminal-phase rate constant.
V_d/F and CL/F	Vd is the distribution volume that is used as a conversion factor between the total amount of the drug in the body and the plasma concentration. The F stands for bioavailability, which is not known for each individual because it is variable between the children. The apparent clearance (CL/F) will be calculated by dividing the dose by the AUC0-12h/24h. Vd/F will be calculated by dividing CL/F by λz.

Additional parameters may be included as required.

Terminal Slope Estimation

Data permitting, the terminal slope, λ_z, of DTG will be determined from the log-linear portion of the curve and the terminal half-life ($t_{1/2}$) calculated as $0.693/\lambda_z$. The default settings for the analysis software will be used to estimate λ_z when appropriate. Appropriateness of the estimated values will be assessed by reviewing the length of sampling time relative to half-life and the goodness of fit line through the observed data (adjusted R^2). If the adjusted R^2 was found to be less than 85% or the estimated $t_{1/2}$ was found to be relatively long compared to the sampling time, a statement highlighting that caution should be used in interpreting the $t_{1/2}$ results will be included in the report. In general, at least three consecutive time points in the terminal phase excluding T_{max} will be used for terminal half-life determination. Oftentimes, depending on the shape of the profile and limited pediatric sampling strategy, only two consecutive time points (excluding T_{max}) may be used for terminal half-life determination, which will be noted in the report. If less than two time points are available, then λ_z, $t_{1/2}$ and V_z/F will not be calculated or reported.

AUC Values

DTG AUC0-24h will be determined using the linear up-log down trapezoidal method. Pharmacokinetic analyses will be carried out using actual sampling times. AUC0-tau with tau (dosing interval) set to 24 hours will be reported as AUC0-24h since these participants are at steady-state.

Below the Level of Quantification

Concentrations for PK analyses will be used as supplied by the analytical laboratory. The lower level of quantification in the CPQA approved and validated PK assays for DTG and RPV are 5.0 ng/ml and 1.0 ng/ml, respectively. Concentration values that are below the level of quantification (BLQ) will be handled as follows for performing NCA:

- If a pre-dose concentration is below the limit of assay detection, this value will be set to zero.
- If a concentration is BLQ after dosing at time zero and before the first measurable concentration, this value will be set to zero.
- Any embedded BLQ value (BLQ value occurring between two quantifiable concentrations) will be set to missing.
- If a concentration at 24h (C_{24h}) is BLQ and λ_z is estimable, C_{24h} will be estimated. If λ_z is not estimable, then the BLQ C_{24h} will be set to zero.
- Two or more BLQ values in succession after C_{max} (for both DTG and RPV) or BLQ values at the end of collection interval (8h and 10h for RPV), the PK profile will be considered non-evaluable and the participant either repeats the PK or a new one is enrolled.

The above approach, rather than using half the limit of quantification or some other extrapolated value is the most conservative approach when assessing if overall exposure is lower than expected/acceptable in the patient population. In data listings, BLQ values will be shown as less than the quantification limit, "< [limit]" or BLQ. For summary tables, plots and figures, BLQ values will be set at 0.001 (as zero cannot be log-transformed for depiction in logarithmic plots and calculation of summary statistics such as geometric mean). If an entire concentration-time profile is BLQ, the profile will be reported separately and excluded from the PK analysis.

Profiles with Missing or Unexpected Concentrations

For profiles with a C_{24h} value higher than the prior post-dose concentration, C_{24h} may be set to the value of the pre-dose concentration (C_{0h}) for PK parameter calculations or C_{24h} will be extrapolated to 24 hours where feasible. If either the C_{0h} or C_{24h} is missing, then one may be used in substitution for the other. PK parameter summaries (tables) will use the parameters calculated with the substituted values, and this substitution will be noted in any tables and figures. The listings of concentrations, descriptive summaries of concentrations, and figures/plots should include the originally observed concentration, along with a note on how values were substituted for PK parameter calculations. If the NCA PK parameters cannot be estimated from a given participant's intensive PK samples for any reason, intensive PK sampling will be repeated (either in the same participant or in a different participant) to achieve the quota per protocol.

Presentation of Data

Graphical representations of concentration plots by sampling time will use the nominal PK sampling for summary results, and actual PK sampling time for individual results. Graphical results of PK parameters (i.e., $AUC_{0\text{-}24h}$, C_{max}, C_{24h} [C_{min}]) by weight band, HIV subtype and/or in comparison to historical data in adults may also be generated. Additional graphical representations may also be prepared per CMC/SMC request.

Summary Statistics

All individual concentrations for the intensive PK evaluations at week 4 and PK parameters from intensive PK assessments may include, but are not limited to, the following descriptive statistics: number of observations available, geometric mean, geometric standard deviation (geoSD), geometric coefficient of variation (geoCV), geometric 95% confidence intervals, arithmetic mean, standard deviation (SD), CV, median, interquartile range (IQR), 5^{th} and 95^{th} percentiles, minimum, maximum and number of BLQ samples imputed.