ACTG A5372

Drug-Drug Interactions Between Rifapentine and Dolutegravir in HIV/LTBI Co-Infected Individuals

ClinicalTrials.gov Identifier: NCT 04272242

Primary Statistical Analysis Plan

Version 1.0

July 7, 2021

This is ACTG A5372 SAP Version 1.0 with names of authors, names of publication writing team members and analysis timeline redacted. Study objectives related to Arm 2 will be addressed if Arm 2 opens.

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1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary, secondary, and selected exploratory outcome measures of the A5372 study that will be included in the primary manuscript addressing the major primary and secondary objectives of the study, as well as the primary and secondary outcome measures for which results will be posted on ClinicalTrials.gov. The Primary SAP also outlines the general statistical approaches that will be used in the analysis of the study. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary statistical analysis report.

1.2 Version History

Version	Changes Made	Rationale	Effective Date
1.0	Original Version (For protocol version 2.0. Note that the original SAP was still in draft form when participants began enrolling under protocol version 1.0; no final version of the SAP was filed that corresponds to protocol version 1.0. Issue Tracking ID 40443 [deviation].)	N/A	7/7/2021

1.3 Abbreviations

Abbreviation	Full text
1HP	4-week (1 month) daily regimen of isoniazid and rifapentine
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
AUC	Area under the concentration-time curve
BID	Twice daily
Cmax	Maximum concentration observed over the dosing interval
Cmin	Minimum concentration observed over the dosing interval
DTG	Dolutegravir; may refer to antiretroviral drug administered as part of an ARV regimen, or to concentrations of the drug as measured in plasma by pharmacology assay
H	One-letter abbreviation for isoniazid, used in the one-letter-per-drug notation for TB regimens
HIV-1	Human immunodeficiency virus, type 1 (the predominate type world-wide)
INH	Isoniazid
LTBI	Latent TB infection
NRTI	Nucleoside reverse transcriptase inhibitor
P	One-letter abbreviation for rifapentine, used in the one-letter-per-drug notation for TB regimens
PK	Pharmacokinetic

PWH	People with HIV
QD	Once daily
RPT	Rifapentine

2 Study overview

2.1 Overview of Study Design

A5372 is an open-label, non-randomized, two-arm, multicenter PK study to investigate the potential interactions between DTG and steady state RPT when RPT is prescribed with INH daily for 4 weeks (1HP) in HIV-1 and LTBI co-infected individuals.

The *study regimen* will be as follows, days 1 through 28.

Arm 1

- DTG 50 mg orally BID (~12 hours apart)
  - 1st dose: DTG 50 mg each morning from non-study ARV supply
  - 2nd dose: DTG 50 mg each evening from study supply
- 1HP: INH 300 mg + RPT 600 mg orally orally each morning for 4 weeks

Arm 2 (upon opening; contingent on assessment of DTG PK data from participants in Arm 1)

- DTG 50 mg orally each morning from non-study ARV supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

All participants must also be on once-daily DTG-based ARV treatment with 2 NRTIs (excluding TAF) during the study. All participants must receive pyridoxine (vitamin B6) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines.

Initially, the study will open with Arm 1. Once DTG concentrations data from the first 32 evaluable participants in Arm 1 are available, the core team will review the DTG PK data to ensure sufficient plasma exposures of DTG (C_{tau}) are achieved with twice-daily DTG dosing. This review will consist summarizing data completeness, participant evaluability for PK, and observed minimum concentrations. Provided: (1) there are 32 evaluable participants with minimum concentrations, (2) these minimum concentrations are above 158 ng/mL, and (3) there are no worrisome outliers among these minimum concentrations, the PK data will be used to model the anticipated PK of QD DTG when coadministered with 1HP. Based on these models and simulations of QD DTG dosing with 1HP, a decision will be made on whether to open Arm 2 for enrollment. Details on the criteria for opening Arm 2 are given in the protocol (Section 7.4) and herein (Section 4.5).

Plasma PK profiles for DTG will be determined at two time points. At the first time point, plasma samples will be drawn in participants at steady state with respect to DTG when receiving once daily DTG prior to 1HP. At the second time point, DTG will be given BID in Arm 1 and QD in Arm 2 during the 1HP LTBI regimen; PK sampling for DTG will occur on day 28 of the 1HP regimen.

In the final statistical analysis, inference will be based on geometric mean ratios for DTG PK parameters (with/without co-administered 1HP) where each participant serves as their own control (ie, within-subjects design).

In addition, sparse PK sampling will be performed on days 3, 14, and 21 of the 1HP regimen.

Leftover plasma from the DTG analysis will be used to determine RPT concentrations achieved from 1HP dosing to support exploratory study objectives.

A participant is considered ***evaluable*** (for PK) if they (a) have completed 28 daily doses RPT/INH within the 6-week study period, (b) have completed intensive PK sampling at both the day 0 and day 28 visits. Furthermore, each visit must have been conducted after 3 consecutive days of dosing, with at least 6 plasma samples collected and (for Arm 1) with both the 23- and 24-hour samples collected.

All participants must receive pyridoxine (vitamin B6) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines.

Participants enrolling to A5372 will not be randomized. Enrollment will not be stratified.

2.2 Hypothesis

Dolutegravir (DTG) concentrations, when given twice daily (BID) or once daily (QD) with coadministration of 4 weeks daily rifapentine (RPT) (600 mg) and isoniazid (INH) (300 mg) [1HP], will maintain steady-state plasma trough DTG concentrations above 158 ng/mL in 95% of study participants. The value 158 ng/mL is the 5^{th} percentile steady-state trough concentrations of DTG which has been demonstrated to be sufficient in maintaining virologic suppression.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives listed in the study protocol. The remaining study objectives in the protocol will be addressed in subsequent analysis plans.

2.3.1 Primary Objectives

1. To determine the dosing for DTG that, when given together with 1HP, achieves target exposures (C_{trough}) of standard-dose DTG when it is given without RPT [Objective 1.2.1; this objective will be addressed by the study pharmacologists].
2. To estimate the steady-state plasma pharmacokinetic (PK) parameters of DTG when DTG 50mg is dosed twice daily (BID) with 1HP [Objective 1.2.2].
3. If Arm 2 opens, to estimate the steady-state plasma PK parameters of DTG when DTG 50 mg is dosed once daily (QD) with 1HP [Objective 1.2.3].

2.3.2 Secondary Objectives

1. To evaluate the safety of coadministration of DTG-based ART with 1HP [Objective 1.3.1].
2. To evaluate the tolerability of coadministration DTG-based ART with 1HP [Objective 1.3.2].

3. To estimate the proportion of participants who maintain virologic suppression when DTG-based ART is coadministered with 1HP [Objective 1.3.3].

2.4 Overview of Sample Size Considerations

Sample size estimates are based on the desired precision model-based estimates of DTG PK parameters in the presence and absence of 1HP. These models, once validated, will further be used to determine recommended DTG dosing algorithms for the treatment of patients living with HIV and co-infected with LTBI, pending appropriate safety assessment.

The sample size determination was done by evaluating different study designs (varying the numbers of participants and time points, assuming the design where each participant is its own control) using clinical trial simulations. See protocol version 1.0, Section 10.4 for details of clinical trial simulations.

The effect of RPT on DTG PK parameters (bioavailability) was assumed to be a decrease of 30%-50%. Inter-participant variability in PK parameters (CL and F) was assumed to be 25-40%. The time course of RPT induction was considered.

Under these assumptions, data from ≥32 participants in Arm 1 will provide >80% power to detect the hypothesized drug-drug interaction effect on bioavailability, and to unbiasedly (relative bias <5%) and precisely (RSE<25%) estimate PK parameters and inter-participant variability.

These estimated unbiased parameters will be then used for simulations of Arm 2 and derivation of the median 5th percentile of DTG troughs by simulations. The probability of opening Arm 2 will be dependent on magnitude of both the decrease in bioavailability due to drug-drug interactions and the between-participant variability. Precise estimate of drug-drug interaction coupled with acceptable between-participant variability will provide 90% chance of making a correct decision if Arm 2 opens.

The proposed design requires at least 32 evaluable participants, each of whom has intensive PK sampling conducted at both visits, conducted after 3 consecutive days of dosing recorded in participant diaries, the third of which is observed being taken in the clinical research site, with at least 6 plasma sample collections (per visit) which must include the 23- and 24-hr samples. Such data is expected to provide estimated pharmacokinetic parameters with required the precision, defined as relative standard errors <10% for typical values, and RSE <25% for random effects (between subject variability).

To protect against data loss after closure to accrual (e.g., lost specimens, assay problems), the study will enroll 36 participants in each arm. This is an increase of ~12% over the required sample size of 32 evaluable participants.

2.5 Overview of Interim Monitoring Reviews by the TB TSG Study Monitoring Committee (SMC): Reviews for Safety and Study Conduct

The SMC will provide independent oversight to safeguard the well-being of study participants and to ensure study integrity. Interim analyses of study progress and conduct as well as participant safety will be

reviewed by the SMC approximately every 6 months. The first interim review will occur no more than 6 months after the enrollment of the first study participant. (If accrual is rapid enough that only a short period of time – 1 month, say – would elapse between analyses for the SMC review and for the interim PK analysis for Arm 1 participants, the SMC review will not be conducted.) For all reviews, detailed information on safety (including treatment tolerability and mortality), and administrative aspects (including accrual, retention, compliance with study requirements) will be provided by study statisticians. The A5372 Study Progress, Data, and Safety Monitoring Plan (SPDSMP) provides details of the contents of reports to the SMC.

In the event that 3 or more participants experience Grade 3 or higher AEs deemed to be definitely, probably, or possibly related to DTG, RPT and/or INH, the study will be halted until an SMC review takes place. ("Related to" values will be assigned by the core team on regular calls or emails.)

An additional SMC review may also be convened if a concern is identified by the DAIDS clinical representative, study chairs, or study statisticians in consultation with the team.

To determine whether Arm 2 (QD dosing) will open to accrual, an interim analysis will be conducted by the study pharmacologist (see Section 4.5 herein). When this analysis has been completed, the team will inform the SMC of results and of the team's decision.

2.6 Interim Core Team Reviews

The core team will meet regularly to review safety data. Details can be found in the A5372 SPDSMP.

In addition, when DTG PK data from the first 32 evaluable participants in Arm 1 are available, an interim analysis of Arm 1 DTG PK data will be conducted by protocol pharmacologist and reviewed by the core team. The main purpose of this review is to determine whether Arm 2 should open, or the study should proceed with Arm 1 only. This analysis is described in Section 4.5 herein.

There will not be a formal SMC review to evaluate the interim DTG PK data; however, the SMC will be notified of the decision as soon as the PK interim review by the core team is completed.

3 Outcome measures

3.1 Primary Outcome Measures

The primary outcome measures are participant-specific estimates of the day 0 and day 28 plasma DTG PK parameters C_{max}, C_{min}, and area under the concentration-time curve over 24 hours ($AUC_{0\text{-}24h}$) while on the Arm 1 regimen and, if Arm 2 opens, the Arm 2 regimen. [Outcome Measure 10.2.1.1].

3.2 Secondary Outcome Measures

The secondary outcome measures for addressing the study's secondary objectives are listed in protocol Section 10.2.2 as:

1. Proportion of participants exhibiting each of the following events during administration of DTG with 1HP, by arm [Outcome Measure 10.2.2.1]
   a. Grade 3 adverse event(s) (AE(s))
   b. Grade 4 AE(s)
   c. Grade 3 or 4 AE(s)
   d. AEs of grade 2 or higher
   e. AEs that led to a change in study treatment regardless of grade
   f. AEs meeting the serious adverse events (SAE) definition or EAE reporting requirements.
2. Proportion of participants who discontinue study or study drugs during DTG and 1HP dosing, by arm [Outcome Measure 10.2.2.2]. This includes discontinuation of DTG, RPT, INH, and NRTIs.
3. Proportion of participants with HIV-1 RNA levels >50 copies/mL at day 28 (-2/+14 days) and/or at the Follow Up visit [Outcome Measure 10.2.2.3].

4 Statistical considerations

4.1 Times Used in the Primary and Secondary Outcome Measure Definitions

Day 0: The day of study enrollment and the first intensive PK sampling is conducted. At this point, participants have not taken any study provided medications.

Day 1: Start of study provided medications.

Day 3 (+2 days): First visit on study treatment. The first sparse PK sampling is conducted.

Day 14 (±2 days): Second visit on study treatment. The second sparse PK sampling is conducted.

Day 21 (±2 days): Third visit on study treatment. The third sparse PK sampling is conducted.

Day 28 (-2/+14 days): Last visit onstudy treatment. The second intensive PK sampling is conducted.

4.2 Analysis Populations

We define three analysis populations used for estimation of the estimands described in Section 4.8.

4.2.1 Primary PK Analysis Population

Primary PK Analysis Population (separately defined for Arm 1 and Arm 2 participants): The primary PK analysis population consists of those participants who: (1) met all study entry criteria, (2) initiated the 1HP TB regimen and completed 28 daily doses RPT/INH within the 6-week study period, and (3) took DTG twice-daily (Arm 1) or once-daily (Arm 2) for days 1-28 (that is, for the participant, both PK profiles are available (before initiating 1HP and while taking 1HP).

4.2.2 Secondary PK Analysis Population

Secondary PK Analysis Population (separately defined for Arm 1 and Arm 2 participants): The secondary PK analysis population consists of those participants who met all study entry criteria and for whom at least one DTG concentration is available where the dates, times and dose amounts of DTG doses in the three days leading up to the intensive PK sampling visit. Concentrations from all participants, not just evaluable participants, will be used (limited to those concentration for which the dates, times and dose amounts of DTG in the days leading up to the PK visit are available).

4.2.3 Safety Analysis Population

Safety Analysis Population: The Safety Analysis Population consist of all participants who have taken at least one dose of RPT, at least one dose of INH, and at least 2 doses of DTG (Arm 1) or at least 1 dose of DTG (Arm 2).

4.3 General Statistical Considerations

Confidence intervals (CIs) around geometric mean ratios will have 90% coverage probability; all other CIs will have 95% coverage. Hypothesis tests will have test size of 5%. No adjustments will be made for multiple comparisons. The justification for no such adjustment is as follows. Rationale for multiple comparisons generally emphasizes control of a family-wise error rate when there is a global null hypothesis. For example, in a multiple-arm clinical trial comparing different drugs to a placebo, a global null hypothesis would be of the form “at least one of the active arms performs better than the placebo” (Parker and Weir, 2020). The emphasis in A5372 is on estimation (CIs) not hypothesis testing (p-values). Furthermore, within an arm, PK micro parameters are jointly estimated through modeling, and descriptive summaries of PK parameters are not independent (participants with low C_{min} values are expected to have a low AUC values). Therefore it would be incorrect to adjust as if these are independent estimands. The same rationale holds across arms: the null hypothesis is not that at least one of the two doses is effective but to estimate PK parameters based on all available data.

4.4 PK Parameter Calculations (Conducted by Study Chair and Study Pharmacologist)

In separate final analyses for Arms 1 and 2, DTG plasma PK parameters (primary outcomes) will be determined for evaluable participants (the primary analysis population) using nonlinear mixed-effects population PK modeling. Participant-specific C_{min} values will be estimated both from the model and as the observed minimum plasma concentration.

4.5 Interim Analysis of DTG PK Data to Determine Decision for Opening Arm 2

Prior to opening Arm 2, when DTG drug concentrations are available for at least 32 evaluable participants from Arm 1, an interim analysis of DTG PK data will be conducted by the pharmacologist. Results will be reviewed by the core team. Arm 2 will open to enrollment if simulations based on Arm 1 PK data support the hypothesis that 50 mg DTG dosed QD in combination with 1HP will result in DTG trough concentrations that mimic reported plasma concentrations following a 10 mg DTG QD dose without RPT.

There will not be a formal SMC review to evaluate the interim DTG PK data; however, the SMC will be notified of the decision as soon as the PK interim review by the core team is completed.

Background. In the SPRING-1 study, a 10 mg daily dose of DTG was associated with virologic suppression [18] and, as such, the DTG PK parameters achieved for this dose in SPRING-1 are considered adequate targets. The 5th, 50th, and 95th percentiles for this dose were 158, 316, and 555 ng/mL, respectively.

4.5.1 Preliminary Interim Analysis (Conducted by Study Statisticians)

Initially, when DTG concentrations from the first 32 evaluable participants (ie, participants in the primary PK analysis population) in Arm 1 are available, the core team will review the DTG PK data to ensure sufficient plasma exposures of DTG (C_{tau}) are achieved with twice-daily DTG dosing. This review will consist of summaries of data completeness, participant evaluability for PK, and observed minimum concentrations. If: (1) there are at least 32 evaluable participants with minimum concentrations, (2) no more than 5% of these participants exhibit minimum DTG concentrations above 158 ng/mL, and (3) there are no worrisome outliers among these minimum concentrations, the PK data will be used to model the anticipated PK of QD DTG when coadministered with 1HP, as described in Section 4.5.2. Based on model simulations of QD DTG dosing with 1HP, a decision will be made on whether to open Arm 2 for enrollment. Details on the criteria for opening Arm 2 are given in the protocol (Section 7.4) and above (beginning of Section 4.5).

4.5.2 Model-based Interim Analysis (Conducted by Study Pharmacologist)

Criterion for opening Arm 2. In addition to the three criteria above, when DTG concentrations from at least 32 evaluable participants (ie, participants in the primary PK analysis population) in Arm 1 are available, a model-based evaluation of DTG PK in these BID participants will occur. The study pharmacologist will develop a nonlinear mixed-effects population pharmacokinetic model, based on available concentrations from all Arm 1 participants (ie, participants in the secondary PK analysis population). From the developed and evaluated model, concentrations for 100 hypothetical participants will be simulated for Arm 2/QD dosing of DTG 1000 times. The parameter of primary interest is C_{24}, the expected DTG concentration at the end of the 24h dosing interval at steady state. For each simulated trial, the 5th, 50th, and 95th percentile of DTG trough concentrations, C_{24}, will be determined.

Of the 1000 simulated trials, the median value of the 5th percentile of DTG C_{24} will be compared to 158 ng/mL, which is the 5th percentile of DTG C_{24} observed for the 10 mg daily DTG dose in SPRING-1. If the median C_{24} value among simulated 5th percentiles is at or above 158 ng/mL, A5372 Arm 2 will open for enrollment, for evaluation of DTG 50 mg QD dosing with 1HP.

4.6 Analysis of the Primary Objective 1 (Conducted by Study Pharmacologist)

In order to determine the dosing for DTG that, when given together with 1HP, achieves target exposures (C_{24}) of standard-dose DTG when it is given without RPT, the distribution of simulated DTG C_{24} values (based on concentrations from Arm 1 and develop population pharmacokinetic model) will be compared

with the historical data from SPRING Study (e.g., C_{tau} in the DTG 10 mg dosing arm) to examine whether dosing of DTG 50 mg BID will maintain above the trough concertation necessary for virologic suppression.

The same analysis will be conducted for Arm 2 if it opens. For this objective, a separate population PK analysis will be conducted (as described in Section 4.5.2).

There is no specific outcome measure associated with this analysis. The "outcome" is the characterization (through modeling) of the relationship between dosing (amounts, frequencies) and CIs around predicted C_{min} values; this analysis will be performed by the study pharmacologist.

4.7 Analysis of Primary Objectives 2 and 3 (outcome measures listed in Section 3.1; conducted by Study Pharmacologist)

For all PK parameters, the following descriptive statistics will be reported by arm and visit: mean, standard deviation, coefficient of variation, median, 5^{th} and 95^{th} percentiles, minimum, and maximum, as well as mean and standard deviation on the natural log (base e) scale. This analysis is conducted using the primary PK analysis population. To assess the overall effect of 1HP on DTG PK parameters, geometric mean ratios (GMRs) and associated 90% CIs will be calculated by arm. The ratio is <u>with</u> (after initiation of 1HP; numerator) vs <u>without</u> (before initiation of 1HP; denominator) co-administered 1HP. The DTG PK parameters are C_{min}, C_{max}, and total daily exposure as measured by $AUC_{0\text{-}24h}$. (For Arm 1, day 28 (BID dosing), participant-specific $AUC_{0\text{-}24h}$ will be estimated by combining (summing) areas for the two BID dosing intervals. For Arm 1 day 0, and for Arm 2 days 0 and 28 (QD dosing), participant-specific $AUC_{0\text{-}24h}$ values will be estimated from concentrations collected over the single 24-hour dosing interval.)

4.8 Primary Estimands

The CBAR requirement of defining estimands was enacted after the protocol had been finalized. As a "grandfather clause" compromise, we are only defining estimands for primary objectives with analyses lead by statisticians.

4.8.1 First Primary Estimand

This objective will be addressed by the pharmacologist; the corresponding estimand is not defined in this analysis plan.

4.8.2 Second and Third Primary Estimands

Objectives 2 and 3 will use the same estimand. The principal stratum strategy is applied for the handling of intercurrent events in the primary analysis of this estimand. This strategy aligns with the definition of participant evaluability as specified in the protocol, and also agrees with the European Medicines Agency bioequivalence guideline, as interpreted in Ring and Wolfsegger (2020). (Bioequivalence is a way to assess drug-drug interactions.) The primary inference approach is estimation of geometric mean ratios, and associated 90% CIs, based on within-subject pairs of PK parameters, where the numerator condition is BID DTG dosed with 1HP, and the denominator condition is QD DTG without TB agents.

<table>
<tr><td colspan="2">Primary Objective 2: To estimate the steady state plasma pharmacokinetics (PK) of DTG when DTG 50 mg is dosed twice daily (BID) with 1HP.

Primary Objective 3 (Addressed only if Arm 2 opens): To estimate the steady state plasma PK parameters of DTG when DTG 50 mg is dosed once daily (QD) with 1HP.</td></tr>
<tr><td>Estimand description</td><td>Geometric mean ratio of steady state Cmax, Cmin, and AUC_{0-24h} of DTG taken as prescribed before and after completing the TB regimen 1HP in PWH with LTBI</td></tr>
<tr><td>Treatment</td><td><u>Arm 1</u>
• DTG 50 mg orally BID (~12 hours apart)
o 1st dose: DTG 50 mg each morning from non-study ARV supply
o 2nd dose: DTG 50 mg each evening from study supply
• 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks
<u>Arm 2 (upon opening; contingent on assessment of DTG PK data from participants in Arm 1)</u>
• DTG 50 mg orally each morning from non-study ARV supply
• 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks</td></tr>
<tr><td>Target population</td><td>Analysis set</td></tr>
<tr><td>PWH with LTBI taking DTG as prescribed and completing 28 doses of 1HP within 6 weeks</td><td>The primary PK analysis population (defined above in Section 4.2.1).</td></tr>
<tr><td>Variables</td><td>Outcome measure(s)</td></tr>
<tr><td>Steady-state (after 28 days) plasma DTG PK parameters:
• C_{max},
• C_{min},
• Area under the concentration-time curve (AUC_{0-24}).</td><td>Participant-specific estimates of the day 0 and day 28 steady-state plasma DTG PK parameters C_{max}, C_{min}, and area under the concentration-time curve (AUC_{0-24h}).</td></tr>
<tr><td>Handling of intercurrent events</td><td>Handling of missing data</td></tr>
<tr><td>IE: Failure to take DTG as prescribed (1) for 3 days prior to starting 1HP (Principal Stratum strategy)

IE: Failure to take DTG (1) and 1HP (2) as prescribed prior to steady state (Principal Stratum strategy)

(1) 6 BID 50 mg doses (Arm 1) or 3 QD 50 mg doses (Arm 2)
(2) 3 QD doses of 300 INH mg and 3 doses of 600 mg QD doses of RPT

For both intercurrent events the Principal Stratum is defined as having taken DTG and 1HP treatment as prescribed</td><td>Missing data may occur because of:
• Failure to appear at study visit (Day 0 or Day 28)
• Incomplete sampling (≥6 timepoints including both 23- and 24-hour samples)
• Incomplete/unevaluable concentrations when sampled (≥6 timepoints including both 23- and 24-hour samples)

Missing samples and PK concentrations for participants otherwise meeting the dosing criteria will be assumed missing completely at random and participants excluded from the analysis.</td></tr>
<tr><td>Population-level summary measure</td><td>Analysis approach</td></tr>
<tr><td>Geometric mean ratio of DTG Cmax, Cmin, and AUC_{0-24h} with (after initiating 1HP; numerator) and without (prior to initiating 1HP; denominator) 1HP</td><td>Geometric mean ratio with associated 90% CIs. See Section 8 for details.</td></tr>
</table>

<u>Sensitivity Analyses</u>

No sensitivity analyses are planned.

<u>Supplementary analyses</u>

No supplementary analyses are planned.

4.9 Analysis Addressing the Safety, Tolerability and Virologic Suppression Secondary Objectives (Conducted by Statisticians)

For the Safety Analysis Population (see Section 4.2.3), proportions of the events listed in **Section 3.2** will be reported by arm: (a) the proportion of participants with Grade 3 or 4 AE during administration of DTG with 1HP; (b) the proportion of participants who discontinue study or study drugs during administration of DTG with 1HP; and (c) the proportion of participants with HIV-1 RNA levels >50 copies/mL at the second intensive PK measure and/or at the Follow Up visit. Proportions will be reported along with 95% exact Clopper-Pearson CIs around the proportions.

5 Report components

5.1 Flow Diagram

- The flow diagram will include, but not be limited to, the following:
    - Number of screened patients
    - Summary of reasons not enrolled
    - Number of enrolled participants by arm
    - Summary of off-treatment and off-study reasons
    - Number of participants in primary and secondary analysis populations.

5.2 Accrual

- Summary of participants enrolled by month (and arm).
- Summary of participants enrolled by site (and arm).

5.3 Baseline Characteristics

The following characteristics (day 0) will be summarized by arm

- Summary of age, sex, race, and ethnicity.
- Summary of body weight and body mass index (BMI).
- Summary of plasma HIV-1 RNA (number below lower limit of quantification and, for participants with detectable viral load, statistical summary of $\log_{10}$ copies); ARV regimen.

5.4 Study Retention

- Summary of off-study reasons.

5.5 Study Treatment

- Summary of reasons for not starting study treatment.
- Summary of days from study entry to first dose of study drug.
- Summary of days from study entry to permanent discontinuation of study drug.
- Summary of the reasons for permanently discontinuing study drug, sorted so discontinuations due to treatment-related AEs are together.

5.6 Pregnancies (If Any)

- Summary of women who become pregnant while on study, including weeks from study entry, pregnancy outcome if known, and maternal AE if any. (Safety analysis population.)

5.7 Mortality (If Any)

- Summary of the number of deaths and the primary and contributing causes of death, with weeks from study entry. (Safety analysis population.)

5.8 Primary Analysis Results

- Descriptive summary of DTG PK parameters (C_{max}, $AUC_{0\text{-}24h}$, and C_{min}) at each of the two PK intensive time points, by arm. (Primary analysis population.)
- Geometric mean ratios of DTG PK parameters (C_{max}, $AUC_{0\text{-}24h}$, C_{min}), day 28 relative to day 0, and associated 90% CIs, by arm. (Primary analysis population.)

5.9 Secondary Analysis Results (Safety, Tolerability, Day 28 Viral Load)

- Summary of all new, post-entry reportable AEs by MedDRA high-level term and grade occurring during administration of DTG with 1HP, by arm. (Safety analysis population)
- Summary of SAEs by MedDRA code, by arm. (Safety analysis population)
- Discontinuation of study drugs during DTG and 1HP dosing, by arm (study drugs to include RPT, INH, DTG and NRTIs). (Safety analysis population)
- Discontinuation of study during DTG and 1HP dosing, by arm. (Safety analysis population)
- HIV-1 RNA levels >50 copies/mL at Day 28 (-2/+14 days) and/or at the Follow Up visit. (Safety analysis population)
- Analyses done for the Safety Analysis Population. Proportion of participants exhibiting each event is reported, along with the associated exact, 95% Clopper-Pearson binomial confidence intervals (CIs). For the AEs, each participant is counted only once, in the highest grade observed for the participant.

6 Calculation of geometric mean ratio and associated confidence interval

6.1 Introduction

A log-normal distribution is often used for analyzing positive, right-skewed data, including AUCs and other concentrations-based pharmacokinetic parameters (C_τ, C_0, C_{max}) (Van Belle, 2002). For a variable X that is assumed to be log-normally distributed, we write $X \sim LN(\mu, \sigma)$; here, μ and σ are considered location and scale parameters, but do not denote expected value or variance. For log-normally distributed X, if a new variable Y is defined as the natural (base e) log of X, written $Y = \ln(X)$, then Y is normally distributed – written $Y \sim N(\mu, \sigma^2)$ – with mean (expected value) μ and variance σ^2.

In order to exploit theorems that apply to normally distributed data (eg, sums and differences of normally distributed random variables are also normally distributed), analyses of PK parameters are often conducted on the log scale. For example, one might calculate and report the sample mean $\bar{Y}$ and sample standard deviation s on the log scale, and use the standard formula:

$$(\bar{Y} \pm t_{1-\frac{\alpha}{2}, n-1} \frac{s}{\sqrt{n}}) \quad \textbf{[1]}$$

to estimate 100*(1 - α)% CI around the log-scale PK parameter. The question then arises of how to convert findings back to the original scale, the scale with which pharmacologists and others are most familiar.

In what follows, we define the sample mean and variance for the normally distributed, log-transformed PK parameter Y:

$$\bar{Y} = \Sigma_{i=1}^{n} \frac{Y_i}{n} \quad \textbf{[2]}$$

$$s^2 = \Sigma_{i=1}^{n} \frac{(Y_i - \bar{Y})^2}{n-1} \quad \textbf{[3]}$$

6.2 Geometric Mean (GM) and Associated CI

An approach to calculating a CI around the GM would be to exponentiate (take the antilogarithm of) the mean $\bar{Y}$ and the CI endpoints (Equation **[1]**). This approach is standard in the literature, and it is the approach taken here.

6.3 Geometric Mean Ratio (GMR) and Associated CI

In assessing drug-drug interactions, pharmacologists and clinicians often characterize the effect of co-administered drug(s) (inhibitor or inducer; “perpetrator”) on the PK parameter of another, target, drug (substrate; “victim”) as the ratio of a PK parameter when measured under 2 different conditions. Generally, the *numerator* of the ratio represents PK parameter of the target drug *when taken with the co-administered drug(s)*, and the *denominator* represents the target drug PK parameter when the target drug

is taken alone. Estimates near 100% indicate co-administered drug has no effect; estimates significantly below 100% indicate that the co-administered drug up-regulates the metabolism of target drug thereby decreasing systemic exposure to the target drug; and estimates significantly above 100% indicate that the co-administered drug down-regulates the metabolism of target drug thereby increasing exposure.

The geometric mean ratio (GMR) is used to estimate the effects of the interacting drug, with the corresponding CI providing inference. To estimate the ratio on the original scale, the sample mean and standard deviation on the log scale are used, along with the logarithmic identity $\log\left(\frac{\mathrm{B}}{\mathrm{A}}\right) = \log(\mathrm{B}) - \log(\mathrm{A})$ **[4]**.

6.4 GMR, Within-subject Design

In the within-subjects design, PK parameters are estimated for an individual participant under both conditions of interest. For the individual participant i, PK parameter differences on the log scale $\mathrm{Y_i}$ are calculated: $\mathrm{Y_i} = \log\left(\mathrm{X_i^B}\right) - \log(\mathrm{X_i^A})$, where $\mathrm{X_i^B}$ and $\mathrm{X_i^A}$ are untransformed PK parameters for participant i for conditions B and A, respectively. The sample mean and sample standard deviation of the $\mathrm{Y_i}$ are calculated. With $\bar{Y}$ and s defined as the sample mean and sample standard deviation of the within-participant differences on the log scale (Equations **[2]** and **[3]**), the GMR is estimated by exponentiating **[2]** and the corresponding CI is given by exponentiating the endpoints of **[1]**.

6.5 Rationale for Use of 90% Coverage for CIs Around the GMR

Schuirmann (1987) presents the “two one-sided tests” procedure to assessing average pharmacokinetic bioequivalence as follows:

$$H_0: \ \mu_T - \mu_R \leq \theta_1 \text{ or } \mu_T - \mu_R \geq \theta_2$$

$$H_1: \ \theta_1 < \mu_T - \mu_r < \theta_2$$

(subscripts *T* and *R* denote “test” and “reference” conditions). The null hypothesis, H_0, states that μ_T and μ_R are not equivalent. The alternative hypothesis, H_1 states that they are equivalent. If, on the basis of the study data, we reject H_0, then we may conclude that H_1 is true, ie, that μ_T and μ_R are equivalent. (If we do not reject H_0, we do not conclude that H_1 is true. Rather, we say that it has not been shown that H_1 is true. Further studies of the two conditions could conceivably establish that μ_T and μ_R are equivalent, even though the study in hand does not.) The statistical hypotheses H_0 and H_1 given above are referred to as the "interval hypotheses." The interval $[\theta_1.\theta_2]$ may be called the “equivalence interval.” The limits θ_1.and θ_2 (θ_1.< θ_2) may be stated as known numbers, expressed in the same units as the bioavailability variable of interest, or θ_1.and θ_2 may be defined as proportions of the unknown reference μ_R.

The “two one-sided tests” procedure with test size α for each subtest is operationally identical to the procedure of declaring equivalence if and only if the ordinary (1-2α)% CIs for $\mu_T - \mu_R$ is completely contained in the equivalence interval $[\theta_1.\theta_2]$. For this reason, it is sometimes referred to as the CIs approach.

7 References

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