Statistical Analysis Plan Amendment 1

Study ID: 212580

Official Title of Study: A Randomized, Double-Blind (Sponsor-Unblinded), Placebo-Controlled, Adaptive Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH3739937 in Treatment-Naïve Adults Living with HIV-1

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TITLE PAGE

Protocol Title: A Randomized, Double-Blind (Sponsor-Unblinded), Placebo-Controlled, Adaptive Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH3739937 in Treatment-Naïve Adults Living with HIV-1

Study Number: 212580

Compound Number: VH3739937

Abbreviated Title: PH2a, VH3739937 Proof-Of-Concept in TN HIV-1 Infected Adults

Acronym: PROCLAIM

Sponsor Name: ViiV Healthcare UK Limited

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	17 Oct 2023	Version 1 (01 June 2023)	Not Applicable	Original version
Amendment 1	30 Aug 2024	Amendment 1 (06 Oct 2023)	Section 1.2 study design updated to include Part 2 information Added a footnote in section 4.7 to indicate interim analysis has taken place Appendix 6.2 eCOA compliance added	To include Part 2 eCOA compliance requirement

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 212580. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the antiviral activity of VH3739937 in HIV-1 infected TN participants during 7 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 RNA through Day 8
Secondary	
• To assess the safety and tolerability of VH3739937 when administered as monotherapy over 7 days in HIV-1 infected TN participants	• Incidence of SAEs, Deaths and AEs leading to Discontinuation through Day 8
• To characterize the pharmacokinetics of VH3739937 in HIV-1 infected TN participants	VH3739937 PK parameters : Following QD dosing: • Day 1: Cmax, tmax, C24 and AUC(0-24) • Day 7: Cmax, tmax, C24, and AUC(0-24) Following single dose: Cmax, tmax, AUC(0-168) and C168
Exploratory	
• To assess the safety and tolerability of VH3739937 when administered as monotherapy over time in HIV-1 infected TN participants	• Incidence of AEs and severity of AEs through Day 25 • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters (consisting of total and direct bilirubin, ALT, ALP and AST)
• To assess the occurrence of Gag treatment emergent mutations or substitutions after 7 days of monotherapy with VH3739937	• Genotypic assessment to detect any change in the Gag gene sequence from Day 1 to Day 8
• To assess the immunologic effects of VH3739937 when administered over 7 days in HIV-1 infected adults	• Change from baseline in CD4+ T-cell count through Day 8
• To characterize the pharmacokinetics of VH3739937 in HIV-1 infected TN participants	Additional VH3739937 PK parameters:

Objectives	Endpoints
	• Following QD dosing (Day 7 only): CL/F, V/F and t1/2 will be determined if possible • Following single dose: AUC(0-24) and C24, In addition, AUCinfinity, CL/F, V/F and t1/2 will be determined where possible
• To explore relationship(s) between plasma concentrations of VH3739937 and pharmacodynamic, efficacy and/or safety endpoints.	• Appropriate VH3739937 PK parameters with pharmacodynamic, efficacy and/or safety endpoints (e.g., change in plasma HIV-1 RNA, CD4+ cell count etc) may be explored as deemed appropriate

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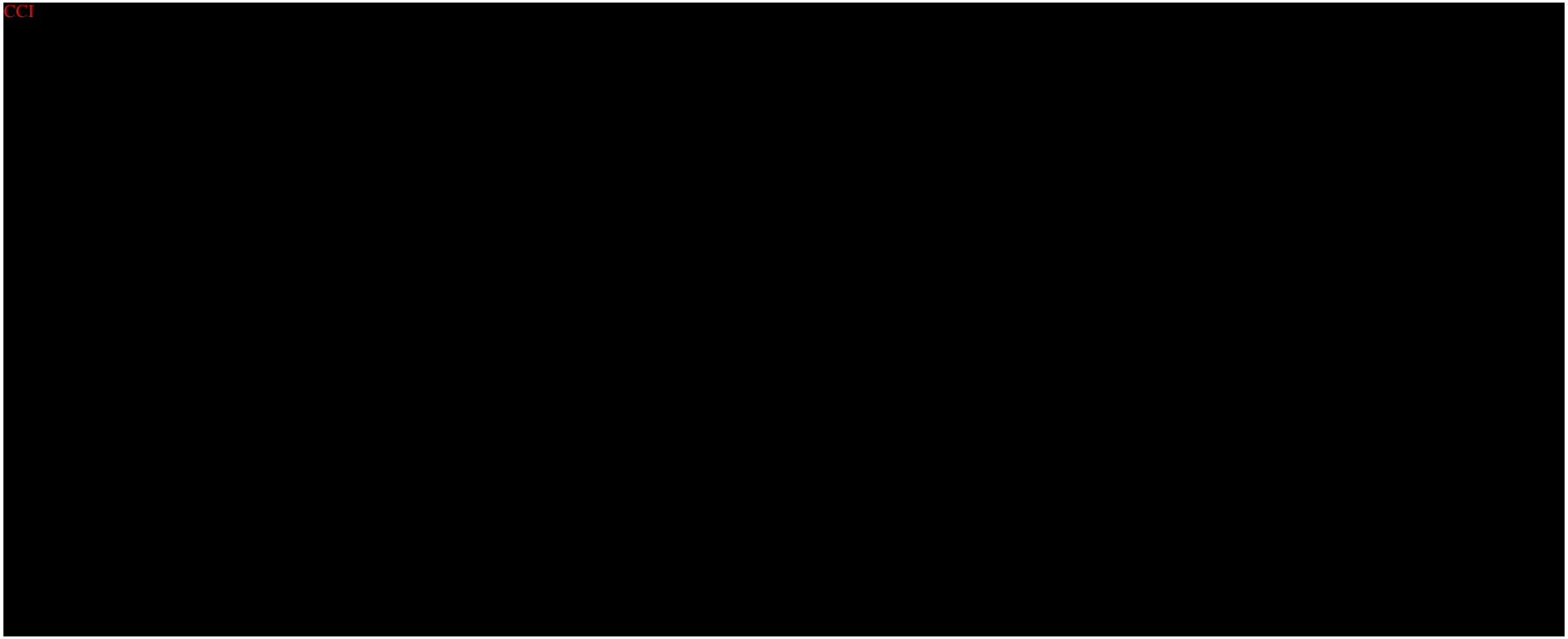

1.2. Study Design

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Design Features	• Phase IIa, PoC, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled adaptive study • Orally administered VH3739937 over 7 days in treatment naive HIV-1 infected adults • The study will evaluate the antiviral effect, safety, tolerability and PK/PD of VH3739937 • Participants have a Screening visit approximately 7 to 14 days prior to first dose on Day 1 • This study will be conducted in two parts: o Part 1: 20 TN HIV-1 infected adults will be randomized to one of 4 cohorts. o Part 2: 7 TN HIV-1 infected adults will be randomized to active treatment or placebo.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td>

Total duration of study participation is approximately 32 to 53 days based on the following:

7 to 14 days, with a maximum of 28 days permitted for screening/qualification period
7 days for treatment with the study intervention and assessment at all planned visits
18 days for post-study intervention follow up visits including the final follow up visit. Participants will take cART throughout this period.

</td></tr>
<tr><td>Study intervention</td><td>
<table>
<tr><th>Part</th><th>Cohort Number</th><th>Number of Participants</th><th>Intervention</th></tr>
<tr><td>1A</td><td>1</td><td>1</td><td>Placebo CCI [redacted]</td></tr>
<tr><td></td><td>2</td><td>6</td><td>VH3739937 CCI [redacted] CCI [redacted]</td></tr>
<tr><td></td><td>3</td><td>6</td><td>VH3739937 CCI [redacted] CCI [redacted]</td></tr>
<tr><td>1B</td><td>1</td><td>1</td><td>Placebo CCI [redacted]</td></tr>
<tr><td></td><td>4</td><td>6</td><td>VH3739937 CCI [redacted]</td></tr>
<tr><td>2</td><td>1</td><td>1</td><td>Placebo CCI [redacted]</td></tr>
<tr><td></td><td>5</td><td>6</td><td>VH3739937 CCI [redacted] CCI [redacted]</td></tr>
</table>
</td></tr>
<tr><td>Study intervention Assignment</td><td>

Part 1a: cohort 1 (placebo), cohort 2 or cohort 3 in a 1:6:6 ratio
Part 1b: cohort 1 (placebo) or cohort 4 in a 1:6 ratio
Part 2: cohort 1 (placebo) or cohort 5 in a 1:6: ratio.

</td></tr>
<tr><td>Interim Analysis</td><td>

An informal interim analysis will be conducted using available preliminary unvalidated in-stream unblinded clinical data once all participants (to include a minimum of 5 participants per active arm and 2 placebo participant) from Part 1 have, at a minimum, completed their Day 8 visit.

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</table>

2. STATISTICAL HYPOTHESES

The primary objective of this study is outlined in Section 1.1 and will be addressed using an estimation approach (descriptive statistics) with no hypothesis testing. The primary treatment effect to be estimated is the maximum change from Baseline in plasma HIV-1 RNA over 7 days of VH3739937 treatment.

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be made.

3. ANALYSIS SETS

Analysis Set	Definition	Analyses Evaluated
Screened	• All participants who are screened for eligibility	• Study Population
Randomized	• All participants who are randomly assigned to study treatment (i.e., VH3739937 or placebo) in the study	• Study Population
Safety	• All randomized participants who take at least 1 partial or full dose of study treatment • Participants will be analysed according to the treatment they actually received	• Safety
Full Analysis Set (FAS)	• All randomized participants who received at least one full dose of study treatment • Data will be reported according to the randomized study intervention	• Efficacy
Per-Protocol (PP)	• All participants in the full analysis set for whom there were no major protocol deviations that impact the primary analyses • Data will be reported according to the treatment actually received • Specific details of major protocol deviations that would exclude participants from the PP analysis set are provided in Section 3.1	• Efficacy
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 PK assessment (NQ values will be considered as non-missing values) • Data will be reported according to the actual study treatment	• PK

3.1. Exclusions from the Per Protocol Analysis set

A participant meeting any of the following criteria prior to the end of part 1 will be excluded from the primary analysis based on the PP analysis set.

Table 1 Criteria leading to exclusion from Per Protocol Analysis set

Number	Exclusion Description
01	Missed at least one dose
02	Took at least one incorrect dose
03	Missed the Day 1 or the Day 8 HIV-1 RNA assessment
04	Missed more than 1 post-Baseline HIV-1 RNA assessment between Day 1 and Day 7(inclusive)
05	Started the SoC medication prior to Day 8
06	Used strong or moderate CYP3A inducers (e.g., rifampin) or strong CYP3A/P-gp inhibitors (e.g., cobicistat, voriconazole) within 7 days (or 14 days if the drug is a strong CYP3A inducer) prior to Day 1 and through to Day 8*
07	Violated any of the inclusion or exclusion criteria.
08	Met other Important Protocol Deviations occurring during the monotherapy period meriting exclusion from the PP analysis set as they have the potential to significantly impact primary analysis. • Protocol deviations will be adjudicated throughout the study conduct and will be classified as important (yes/no), along with determination on whether they should trigger exclusion from the PP analysis set and finalised prior to DBL

*Medical monitor and PK lead will review the list of prior and concomitant medications used by participants in the study and determine which ones meet the criteria of strong/moderate inducers/inhibitors described here prior to DBL.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

If participants prematurely discontinue the study for non-safety reasons prior to Day 8 (primary endpoint), additional replacement participants may be enrolled at the discretion of the sponsor and investigator. These replacement participants will be assigned to the same treatment sequence and same dose as the corresponding participant who prematurely discontinued from the study. Participants will not be replaced if the reason for discontinuation from the study is due to a safety concern.

Data will be summarized by dose of VH3739937 and placebo, unless otherwise specified.

Data will be summarized either by visit or for the study intervention period and overall (i.e., study intervention period plus cART period) separately, as appropriate for each endpoint.

For all endpoints, except for ECG, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Day 1 pre-dose ECGs will be

performed in triplicate and the average of pre-dose triplicate measurements will be used as baseline.

Continuous and categorical variables will be summarized using the following descriptive statistics, unless otherwise specified:

- Continuous data: n (number of participants used for the summary), arithmetic mean, SD, median, interquartile range, minimum and maximum. For PK data, geometric mean, SD of log-transformed data and geometric $\%CV_b$ may also be used.
- Categorical data: number and percentage of participants.

PK values collected outside analysis visit windows will be excluded from data summaries (applies to both Tables and Figures) but will be included in listings. Figures with subject level information will include all values (i.e. irrespective of being within/outside of analysis visit windows). Confidence intervals for PK data summaries will use 95% confidence levels, unless otherwise specified.

Only lab data from central laboratory will be included in lab data summaries. Lab data from local laboratories, if any, will be included in listings (and flagged appropriately).

No imputation for missing values will be performed.

Subject level data will be available through the Reporting & Analysis Plan Improving Design and Delivery of Outputs Data Viewer (RAPIDO DV) tool. Only selected listings required by regulatory agencies will be created in static fashion. See OPS for the list of selected listings.

4.1.2. Baseline Definition

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If Day 1 pre-dose ECG has been assessed more than once (e.g. in triplicate), the average of the available ECG measurements will be used as baseline value.

Unless otherwise stated, if baseline data is missing, no derivation will be performed, and baseline will be set to missing.

Baseline will not be rederived for the Follow-Up period.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoint(s)

Plasma HIV-1 RNA values (copies/mL) will be used for the primary efficacy analysis. Change from baseline at the time point where the HIV-1 RNA is minimum (nadir) during the treatment period will be calculated for each participant in the original and log10 scales. The change from baseline at nadir is the primary endpoint used to construct the primary estimand (see Section 1.1.1). According to primary estimand definition (Section 1.1.1), if cART medication starts prior to Day 8 (for any reason), change from baseline values after cART initiation will be excluded from calculation of change from baseline at nadir.

Note, the change from baseline at nadir during monotherapy is typically the maximum change from baseline in HIV-1 RNA, or in other words the maximum Viral Load Decline (VLD). However, for participants who have all their post-baseline HIV-1 RNA values during treatment higher than the baseline value (e.g. as is the potential with some participants randomized to

placebo) the change from baseline at nadir is the minimum change from baseline. Also, if a (placebo) participant has a high increase from baseline in HIV-1 RNA and then a smaller decrease from baseline (or vice versa), the maximum change from baseline is at the point where HIV-1 RNA is its peak (zenith); the change from baseline at nadir will be used in this case in the primary analysis. From now on, in this document by "maximum change from baseline in HIV-1 RNA" during treatment we will mean the "change in HIV-1 RNA at nadir".

The log10 transformation is used to allow for comparisons with data publicly available in the same scale from other compounds, and hence aid in interpretation.

4.2.2. Main analytical approach

The primary efficacy analysis will be based on the Full Analysis Set.

Maximum change from baseline in plasma HIV-1 RNA during monotherapy will be summarized in original and log10 scale using descriptive statistics as described in Section 4.1.1.

Any missing HIV-1 RNA data (e.g., due to missed visits in the clinic, LFU or for any other reason) will not be imputed and will remain missing. Whatever HIV-1 RNA data are available for a participant during part-1 study and prior to starting cART will be used to calculate maximum VLD. Participants who withdraw from study prior to the end of the treatment period, preventing assessment of primary endpoint, no imputation will be performed for missed assessments after their study withdrawal.

All HIV-1 RNA data from all participants will be included in a listing.

4.2.3. Sensitivity analyses

The primary analysis described in Section 4.2.2 will be repeated on the PP analysis set, and on the Safety analysis set if any participant receives treatment other than the one to which was randomized.

None of the IEs specified for the primary estimand are applicable for the PP analysis set, as none of them can occur in participants within the PP analysis set (because of criteria in Table 1). All available HIV-1 RNA data from the monotherapy period on the PP analysis set will be used for the sensitivity analysis.

4.2.4. Supplementary analyses

4.2.4.1. Summaries of HIV-1 RNA Change from Baseline by Visit

Change from baseline in plasma HIV-1 RNA will be calculated for each participant at each assessment time point during the monotherapy and Follow-Up periods in the original and log10 scales. Change from Baseline at each assessment time point during monotherapy and Follow-Up will be summarized in original and log10 scale using descriptive statistics as described in Section 4.1.1.

Mean and 95% CI of change from baseline in plasma HIV-1 RNA in the log10 scale will be plotted by visit for the monotherapy period.

These analyses will be performed on the FAS, PP analysis set, and Safety analysis set if any participant receives treatment other than the one to which they were randomized.

4.2.4.2. Modelling of HIV-1 RNA Change from Baseline

A mixed-effects linear model will be fitted using plasma HIV-1 RNA change from baseline (on log10 scale) during the Study Intervention Period Days 1-7 period from all treatment arms as the outcome measure, with day, treatment, day and treatment interaction and baseline HIV-1 RNA (on log scale) as main effects and participant as a random effect. Day will be treated as continuous variable. The Kenward & Roger (KR2) degrees of freedom approach will be used [Kenward & Roger, 2009]. The model will be used to estimate the rate of decline in HIV-1 RNA and its 90% CI for each treatment.

Model assumptions will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are departures from model assumptions, or if the model fails to converge, or if parameter estimates are at the boundary of parametric space (e.g. zero variance estimates), or if the model does not fit the data well, alternative models or data transformations may be explored. For example, if model fit is poor, as e.g. may be the case if the HIV-1 RNA does not decline linearly over time, the same model treating day as categorical (with an autoregressive order one (AR(1)) covariance structure for the residuals (R matrix) or simpler structure (e.g. $R = \sigma^2 I$)) may be used, or the same model using a variable transformation for day or a model using splines may be used. In case day is treated as categorical, mean estimates of change from Baseline at each (or selected) day for each treatment will be provided along with 90% CIs.

This analysis will be performed on the FAS, PP analysis set, and Safety analysis set if any participant receives treatment other than the one to which was randomized.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of secondary endpoint(s)

Safety Endpoints
• Incidence of SAEs, Deaths and AEs leading to Discontinuation through Day 8
PK Endpoints
Following QD dosing: • Day 1: Cmax, tmax, C24 and AUC(0-24) • Day 7: Cmax, tmax, C24 and AUC(0-24) Following single dose: Cmax, tmax, AUC(0-168) and C168

For definition of secondary estimands see Section 1.1.1.

4.3.1.1. Main analytical approach

All secondary Safety and PK analyses will be performed on the Safety and PK analysis set, respectively.

4.3.1.2. Adverse Events analyses

AEs will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) using the latest version at time of database release. AEs will be graded by the investigator according to the Division of AIDS (DAIDS) Criteria Version 2.1.

The number and percentage of participants reporting AEs during the treatment period will be summarised using the following categories and subcategories:

- AEs
  - By System Organ Class and Maximum Grade
- AEs leading to permanent discontinuation of study treatment
- Drug-related AEs
  - Overall
  - By Maximum Grade
- Drug-related Non-serious AEs
- Non-Serious AEs
- SAEs by System Organ Class and Maximum Grade
- Drug-related SAEs

The non-Serious AEs display will also include the number of events of an AE.

Selected displays from the above list will be repeated for AEs with onset during the Follow-Up period and during either the monotherapy or the Follow-Up period. AEs with onset in the treatment period which continue in the Follow-Up period will only be included in AE summaries for the treatment period. See OPS for the exact AE tables to be repeated for Follow-Up and monotherapy + Follow-Up.

A listing of all AEs and a listing of reasons for considering as SAE will be provided.

All planned AE displays are provided in the OPS document.

4.3.1.3. Pharmacokinetic Analyses

Pharmacokinetic parameters for VH3739937 will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters for the End of Study analysis will be based on actual sampling times. For the calculation of the Area under the concentration-time curve (AUC), the linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin

Professional). A minimum number of three data points (not including Cmax) should be used in calculating λz.

The adjusted correlation coefficient (R2 adjusted) should be greater than or equal to 0.80. Any value <0.80 should be considered for exclusion from descriptive summary. All derived parameters (half-life, $AUC_{0\text{-}inf}$, CL, V) will need to be flagged or excluded from statistical analysis but will be included in individual listings. The percent of $AUC_{0\text{-}inf}$ extrapolated ($\%AUC_{extrap}$) should not exceed more than 20%. Subject's $AUC_{0\text{-}inf}$ parameter with $\%AUC_{extrap}$ >20% will be flagged and excluded from statistical analysis but will be included in individual listings.

Table 2 Definition of PK parameters

PK Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time to C_{max}
C_{24}	Concentration at nominal time of 24 hours after dosing
C_{168}	Concentration at nominal time of 168 hours after dosing
CL/F	Apparent clearance
V/F	Apparent volume of distribution
$T_{1/2}$	Terminal half-life
$AUC_{0\text{-}inf}$	Area under the plasma concentration vs time curve from time zero hours to infinity
$\%AUC_{extrap}$	Percentage of $AUC_{0\text{-}inf}$ extrapolated from T_{last} to infinity
$AUC_{0\text{-}24}$	Area under the plasma concentration time curve from time of first dose to 24 hours after dosing
$AUC_{0\text{-}168}$	Area under the plasma concentration time curve from time of first dose to 168 hours after dosing

Note: Additional Parameters may be included as required

Summaries of PK concentration values and PK parameters

All pharmacokinetic analyses will be performed on the Pharmacokinetic Analysis Set. For the End of Study analysis, the following apply:

Pharmacokinetic concentrations collected within the PK analysis visit window (see Section 6.3.3) will be summarised at every scheduled time point using descriptive statistics. PK concentrations sampled outside the PK sampling windows will be included in listings and in subject level figures but will not be included in data summaries.

Derived PK parameters will be summarised using descriptive statistics and stratified by dose and frequency.

PK concentrations derived after discontinuation of study treatment will be excluded from PK data summaries, in accordance with the ‘while on-treatment’ strategy for IE.

If a participant takes an incorrect dose or misses a dose, PK concentrations and PK parameters inferred until the next dose (in case more than one dose is administered during the study intervention period) or until the end of study intervention period (if there is only one dose or if incorrect dose is the last one) may be excluded from PK data summaries, as instructed by CPMS prior to final database lock.

The following figures will be produced:

- A by-participant graph of concentration data over time, stratified by cohort, on linear and semi-logarithmic scales
- Graph of arithmetic mean of concentration data over time, stratified by cohort, on linear and semi-logarithmic scales

Listings of PK concentration and PK parameter values will be produced.

4.4. Exploratory Endpoint(s) Analyses

4.4.1. Adverse Events analyses

Analyses described in Section 4.3.1.2 will repeated up to and including day 25.

4.4.2. Liver panel laboratory analyses

Change from baseline values for liver panel laboratory parameters will be summarised by visit. Visits up to Day 8 (inclusive) will exclude any liver panel values assessed under cART, if cART starts earlier for any reason.

Laboratory toxicities will be graded according to the DAIDS Criteria Version 2.1.

For liver panel lab tests that are gradable by DAIDS (e.g. ALT, AST), summary of worst-case grade increase from baseline grade will be provided. This summary will display the number and percentage of participants with a maximum post-baseline grade increase from their baseline grade (e.g. for participants with maximum increase from Baseline to grade 4 the number and percentage of them will be displayed, same for increase to grade 3, 2 and 1). Also, maximum increase subtotals (i.e. max increase in grade to any grade between 1 and 4, max increase to grade 2-4 or max increase to grade 3-4) will be included. The grade increases are determined by comparing the baseline grade to the worst-case post-baseline grade (e.g., Increase to Grade 1, Increase to Grade 2 etc.) and maximum grade increase subtotals (e.g., Increase to Grades 1 to 4, Increase to Grades 2 to 4, Increase to Grades 3 to 4). The grading subtotals are determined by adding the counts for each worst-case grade change within the subtotal category, e.g., 'Increase to Grades 1 to 4' is a subtotal of all worst-case increases to Grade 1, to Grade 2, to Grade 3, and to Grade 4. Participants with missing baseline value are to be assumed to have a Grade 0 at baseline. The determination of the worst case during the post-baseline period takes into account both planned and unscheduled assessments.

This summary will be produced while participants are under the monotherapy period, as well as overall (i.e. monotherapy and Follow-Up periods).

Liver panel data for participants with at least one abnormal lab value will be included in the listing of chemistry laboratory parameters. No imputation will be performed for missed assessments while participants are on study or after study withdrawal.

More details of all planned displays are provided in the OPS document.

4.4.3. Immunology Analyses

The immunology analyses will be performed using the Safety analysis set.

Change from baseline values for CD4 will be summarised at every assessment visit.

Visits up to Day 8 (inclusive) will exclude any values assessed under cART, if cART starts earlier for any reason, in line with the Estimand definition (Section 1.1.1).

4.4.4. Virology Analyses

Changes in the gag gene sequence from baseline through day 8 will be explored separately by the study virologist. These analyses will be performed after SAC, when the genotypic and phenotypic data become available.

4.5. Other Safety Analyses

Other safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.5.1. Extent of Exposure

If more than one study treatment dose is administered in the study intervention period (e.g. Part 1b) or if actual dosing data is available (i.e. drug accountability and whether each container includes active drug vs. placebo), summary of exposure will be provided and will include number and proportion of participants received one/two/more doses and/or summary of cumulative actual dose.

A listing of Exposure Data will also be created.

See OPS for further details.

4.5.2. Additional Safety Assessments

Vital Signs

Change from baseline values of vital signs (e.g. temperature, systolic and diastolic blood pressure, pulse rate etc.) will be summarized by assessment visit.

All vital signs data will be included in a listing.

ECG

If multiple ECG records are available for a visit/timepoint (e.g. in case of triplicate ECG), then the average for continuous ECG variables and the worst case for categorical will be used for data summaries for that visit/timepoint.

Change from baseline in continuous ECG parameters (e.g. heart rate, PR, QRS, QT, QTc intervals) will be summarized by assessment visit.

A summary of the number and percentage of participants with ECG findings will be summarized by assessment visit. The ECG findings to be summarized are the ECG interpretation and clinical significance (yes/no) of abnormal ECGs.

The number and percentage of participants with maximum QTc values (i.e., worst case) post-baseline relative to baseline will be summarized by ECG parameter (e.g., QTcF Interval, Aggregate), treatment, planned time, and category (the standard categories are: no change or post-baseline increase to <=450 msec, any increase to >450 msec, increase >450 to <=480 msec, increase >480 to <=500 msec, and increase >500 msec). The maximum value category is determined by comparing the baseline value category to the worst-case post-baseline value category for each subject. The determination of the worst-case post-baseline considers both planned and unscheduled assessments.

Participants will be summarized (i.e. number of participants and percentage) by a categorization of their maximum increase in QTc value (e.g., QTcF Interval, Aggregate) (i.e., worst case) post-baseline relative to baseline. The standard categories for the worst-case shifts of QTc in msec are: Increase <=30 msec, Increase of 31-60 msec, and Increase of >60 msec change from baseline in QTc interval. Participants with missing baseline values are excluded from the display.

These summaries will be produced while participants are under the monotherapy period, as well as overall (i.e. monotherapy and Follow-Up periods).

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced. The figure will have reference lines at 450 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45-degree line), at equality plus 30 msec, and at equality plus 60 msec.

All ECG data will be included in a listing.

Suicidality Score

Baseline suicidality data assessed electronically via the C-SSRS questionnaire will be summarised. Number and percentage of participant with suicidal ideation or behaviour during lifetime and currently (i.e. within the past 2 months of screening) will be presented.

Post baseline (and baseline) participant-level suicidality data will be available via RAPIDO DV.

Hematology, coagulation, urinalysis and remaining chemistry lab parameters

Change from baseline values for hematology, coagulation, urinalysis (e.g. specific gravity) and remaining (i.e. non-liver panel) chemistry laboratory parameters will be summarised at each assessment visit. For urinalysis parameters assessed with the dipstick method (categorical parameters), number and percentage of participants in each outcome category will be summarised at each assessment visit.

For graded lab parameters by DAIDS, the number and percentage of participants with maximum post-baseline grade increase from their baseline grade will be presented for each laboratory parameter. The maximum grade increase categories and maximum increase subtotals will be included in the display (same as for liver lab parameters in Section 4.4.2). There are some lab parameters which are graded for both low values and high values. Summaries of these lab tests will be differentiated by term, e.g. sodium will be summarized as "hyponatremia" and "hypernatremia", potassium as "hyperkalemia" and "hypokalemia" etc. Check Section 4.4.2 for more details; analysis is the same as for graded liver panel lab parameters.

For lab parameters which are not graded by DAIDS, the number of participants with worst case laboratory results relative to normal range criteria which are post-baseline relative to baseline will be summarized by laboratory parameter and category. Check Section 4.4.2 for more details; analysis is the same as for non-graded liver panel lab parameters.

For urinalysis parameters assessed with the dipstick method, summaries of worst-case post-baseline relative to baseline will be created. The categories for which summaries (i.e. number and percentage of participants) will be provided are based on the actual values within the data, e.g. 'No Change/Decreased', 'Increase to TRACE', 'Increase to 1+ or Increase to +', 'Increase to 1+ or to 1/4 G/DL', etc. 'Decreased' indicates a "lesser" result including change to a negative result. The categorization is determined by comparing the baseline category to the worst-case post-baseline category. The determination of the worst-case post-baseline takes into account both planned and unscheduled assessments. Subjects with a missing baseline value are to be assumed to have a negative baseline value.

A summary, i.e. number of participants and percentages for each of the following bile acid categories "≤1 xULN", ">1x to ≤1 xULN", ">3x to ≤5 xULN", ">5x to ≤10 xULN", ">10x ULN", will be provided at worst case post-baseline record.

A summary of participants with shifts in laboratory grade from Baseline to worst case post-baseline will also be created for selected gradable lab parameters (e.g. lipids etc.). For selected non-gradable lab parameters (e.g. bile acid), shifts from baseline to worst-case post-baseline relative to categories defined based on xULN (see paragraph above) will be created.

A summary of hepatobiliary laboratory abnormalities will also be provided to identify participants, in particular possible Hy's Law participants, for further clinical review.

All the summaries above will be produced while participants are under the monotherapy period, as well as overall (i.e. monotherapy and Follow-Up periods).

A listing of all laboratory data and a listing of all urinalysis data will be created.

All displays on hematology, coagulation, urinalysis and chemistry laboratory parameters are included in the OPS.

4.6. Other Analyses

4.6.1. Subgroup analyses

No subgroup analyses are planned.

4.6.2. Other Pharmacokinetic Analyses

All other pharmacokinetic analyses will be performed on the Pharmacokinetic analysis set.

For other pharmacokinetic statistical analyses:

- If any PK parameters are derived after discontinuation of study treatment, these will be excluded from statistical analyses in accordance with the "while on-treatment" strategy for IE.
- If a participant takes an incorrect dose or miss a dose, PK parameters inferred until the next dose (in case more than one dose is administered during the monotherapy period) or until the end of monotherapy period (if there is only one dose or if incorrect dose is the last one) may be excluded from the statistical analyses, as appropriate.

4.6.2.1. Estimation of Accumulation Ratios

Accumulation ratios may be estimated for C_{max} and $AUC_{0\text{-}24}$ when more than one dose is administered during the monotherapy period, following guidance from CPMS prior to final database lock.

Accumulation ratios are defined as the ratio of PK parameters from the last administration to Day 7 as follows:

$$R(PK\ parameter) = \frac{\text{PK parameter on Day of last administration}}{PK\ parameter\ \text{on Day 1}},$$

$$\text{e.g. } R(C_{max}) = \frac{C_{max}\ \text{on Day of last administration}}{C_{max}\ \text{on Day 1}}.$$

To estimate the accumulation ratios for each treatment, a mixed-effects ANOVA model will be used on the loge-transformed PK parameters, with a random intercept (for each participant) and fixed effects for the day. Day will be treated as a categorical variable in the model. The Kenward & Roger (KR2) degrees of freedom approach will be used

[Kenward & Roger, 2009]. The accumulation ratio will be estimated by calculating the ratio of the geometric least squares (GLS) means of PK parameters between last administration and first administration and the corresponding 90% CI. The GLS means of PK parameters on first administration and last administration, along with the estimated accumulation ratio and its 90% CI will be displayed. No imputation will be done for missing PK parameters.

For each of the statistical models distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from model assumptions, alternative models or data transformations may be explored.

4.7. Interim Analyses[1]

An informal interim analysis will be conducted using available preliminary unvalidated in-stream unblinded clinical data once all participants (to include a minimum of 5 participants per active arm and 2 placebo participant) from Part 1 have, at a minimum, completed their Day 8 visit. GSK/ViiV Healthcare CPMS (and associates) may be provided individual participant level plasma drug concentration and viral load information at one or more time points prior to all participants in Part 1 having completed their Day 8 visit, to refine the population PK model and develop a PK/PD model that will be used to explore the exposure-response relationship between PK and viral load to determine whether additional doses need to be evaluated in optional Part 2 of the study.

The interim analyses will evaluate the PK and PD (antiviral activity) of each respective VH3739937 dose and inform if additional optional dosing arm(s) for VH3739937 will be evaluated in Part 2. Depending on the Part 1 results, a higher dose, lower dose, or a dose between the 2 QD doses evaluated in Part 1 may be evaluated in Part 2, CCI [redacted] CCI [redacted]. It is also possible that Part 2 will not be conducted if the doses evaluated in Part 1 adequately describe the exposure response of VH3739937. The interim results will also inform future clinical development of VH3739937.

The interim results are not intended for public dissemination. Criteria for data quality for data used in the interim analyses will be described in the study data management plan. Throughout the conduct of the study ViiV Healthcare/GSK (and associates) will be

[1] The informal interim analysis described in this section has taken place and the decision was taken to proceed to part 2.

blinded to the assignment for individual participants except for key roles necessary to prepare for and conduct the interim analyses. These roles will minimally include the clinical lead physician/medical monitor, safety physician/scientist, team lead, statistician, programmer, clinical pharmacologist(s), modeller(s) and clinical virologist who will have access to unblinded data. Moreover, unblinded data may be shared with GSK/ViiV Healthcare Medical Governance Committees (at their request and consistent with internal SOPs).

After the interim analysis, a final EoS analysis will be conducted after the completion of the study (i.e., when all participants complete the Day 25 visit, discontinue or are withdrawn) and final datasets authorization. At the EoS analysis all primary, secondary and exploratory endpoints will be evaluated with the exception of viral resistance and any exposure-responses analyses, which will be evaluated at a later stage and reported separately.

Additional interim analyses may be performed during the course of the study to inform internal decision-making activities. No changes to the conduct of the study will be implemented as a result of these analyses.

5. SAMPLE SIZE DETERMINATION

The sample size is based on feasibility and no formal calculation of power or sample size has been performed. The sample size is based on feasibility and no formal calculation of power or sample size has been performed. Further details on sample size considerations are included in protocol Section 9.5

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety analysis set, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, will be based on GSK Core Data Standards. Details of the planned displays are included in the OPS.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who enrolled or failed screening will be provided. For screen failures, number and percentage of participants overall and by screen failure reason will be also provided.

A summary of the number and percentage of participants who entered, completed, are ongoing or withdrew from study at each study period (i.e. Monotherapy, Follow-Up) will be provided. A participant will be considered to have completed the study intervention

period if has completed Day 8 visit and has not started cART prior to Day 8. If a participant has started cART treatment prior to Day 8 visit and has performed Day 8 visit, he/she will be classified as 'Not Completed' the study intervention phase. A participant is considered to have entered the Follow-Up period if there is a recorded concomitant antiretroviral treatment start date.

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from study will be provided. Reasons for study withdrawal will be summarized. A participant is considered to have completed the study if he/she has a "Completed" status in the Study Conclusion eCRF page.

The number and percentage of participants who withdrew from study due to an AE will be summarised by the outcome (fatal versus non-fatal) of the AE.

A listing of reasons for study treatment discontinuation and a listing of reasons for study withdrawal will be provided.

Subject-level disposition information will be available via RAPIDO DV.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, race, height, weight and BMI at baseline will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 18-64, 65-84 and >=85 based on the Enrolled Analysis Set.

Demographic data will be listed.

Other baseline characteristics data such as medical history, CDC HIV-1 classification will be available at participant-level via RAPIDO DV. Participant-level HIV-1 associated conditions and pregnancy data will also be available via RAPIDO DV.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the Per Protocol analysis set will be available at participant level via RAPIDO DV.

- Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. A listing of concomitant medications based on GSK Drug dictionary will be produced.

6.1.5. Medical Conditions

Medical occurrences beginning after obtaining informed consent but before the start of study intervention will be recorded as medical history/current medical conditions, not as AEs, and will be available via RAPIDO DV.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

6.2.1. Electrionic Columba Suicidality Severity Rating Scale (e-CSSRS) Compliance

The target compliance for the study is 90%. The study e-CSSR compliance will be reported for each cohort.

A participant is considered to be compliant with their e-CSSRs if at least 90% of their e-CSSRs are complete (have no missing data), i.e, a participant is e-CSSR compliant if they meet the following criteria:

$$\frac{Total\ number\ of\ complete\ e-CSSRs}{Expected\ number\ of\ complete\ e-CSSRs} \times 100 \geq 90\%$$

An e-CSSR is considered complete if there is no missing data within the assessment.

The number of participants who are 0-<60% compliant, 60-<90% compliant and ≥90% compliant with e-CSSR assessments will be summarized.

6.3. Appendix 2 Data Derivations Rule

6.3.1. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Treatment is defined as time prior to the first dose of study intervention.

On-Treatment Period Days 1-8 is defined as time from first study intervention dose (typically Day 1) to start of cART treatment (typically Day 8).

- If time of assessment or time of study intervention is not collected, Day 1 assessments other than AEs are considered to have occurred prior to study intervention dose and therefore considered on Pre-Intervention period, whereas AEs with Day 1 onset are considered to have occurred after study intervention dose and therefore considered on Monotherapy period.

Post-Treatment Period Days 8- 25 is defined as time from first dose of cART treatment until study completion or withdrawal

- If time of assessment or time of cART initiation is not collected, Day 8 assessments other than AEs are considered to have occurred prior to cART initiation and therefore considered on on-treatment period, whereas AEs with Day 8 onset are considered to have occurred after cART initiation and therefore considered on Follow-Up period.

For concomitant medications, study periods will be defined as follows:

	Pre-Treatment	Monotherapy		Follow-Up		Pre-Treatment	cART	Follow-Up
(a)	x———x	Study Intervention Start Date		cART Start Date		Y	N	N
(b)	x———		———x			Y[1]	Y[1]	N
(c)	x———		———		———x	Y[2]	Y[2]	Y[2]
(d)			x———x			N	Y[3]	N
(e)			x———		———x	N	Y	Y
(f)					x———x	N	N	Y
(g)	?———x					Y	N	N
(h)	?———		———x			Y*	Y	N
(i)	?———		———		———x	Y*	Y*	Y*
(j)	x———		———		———?	Y	Y**	Y**
(k)			x———		———?	N	Y	Y**
(l)					x———?	N	N	Y
(m)	?———		———		———?	Y***	Y***	Y***
(n)	x———	x				Y	Y	N
(o)	?———	x				Y	Y	N
(p)		x	———x			N	Y	N
(q)		x	———	x		N	Y[4]	Y
(r)				x	———?	N	N	Y**
(s)				x	———x	N	N	Y
(t)			x———	x		N	Y	Y

x = start/stop date of medication
? = missing start/stop date of medication
* If a medication is stopped during the Monotherapy period or during the Follow-Up period and no start date is recorded it will be assumed that the medication was ongoing from the Pre-Intervention period
** If a medication is started Pre-Intervention or on Monotherapy and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the Pre-Intervention period to the Follow-Up period
[1]A medication which started before Study Intervention start date and stopped before the cART start date it will be classified as 'Pre and Monotherapy Treatment'.
[2]A medication which started before Study Intervention start date and stopped after the cART start date it will be classified as 'Pre and Monotherapy and Follow-Up Treatment'.
[3]A medication which started after Study Intervention start date and stopped before the cART start date it will be classified as "Monotherapy Treatment"
[4]A medication which started on the Study Intervention start date and stopped on the cART start date it will be classified as "Monotherapy and Follow-Up Treatment"
Similarly, for other cases.

6.3.2. Study Day and Reference Dates

The study day for all endpoints is calculated as below:

- Assessment Date = Missing:
  - Study Day = Missing

- Assessment Date < Study Intervention Start Date:
  - Study Day = Assessment Date – Study Intervention Start Date
- Assessment Date ≥ Study Intervention Start Date:
  - Study Day = Assessment Date – Study Intervention Start Date + 1

6.3.3. Assessment Window

For data summaries by visit, all visit assessments (including those from planned, unscheduled and withdrawal visits) will be slotted into a target visit based on visit window defined in the table below. Within each study period, if there are multiple assessments within the same analysis visit window, the following hierarchy will determine which assessment will be used:

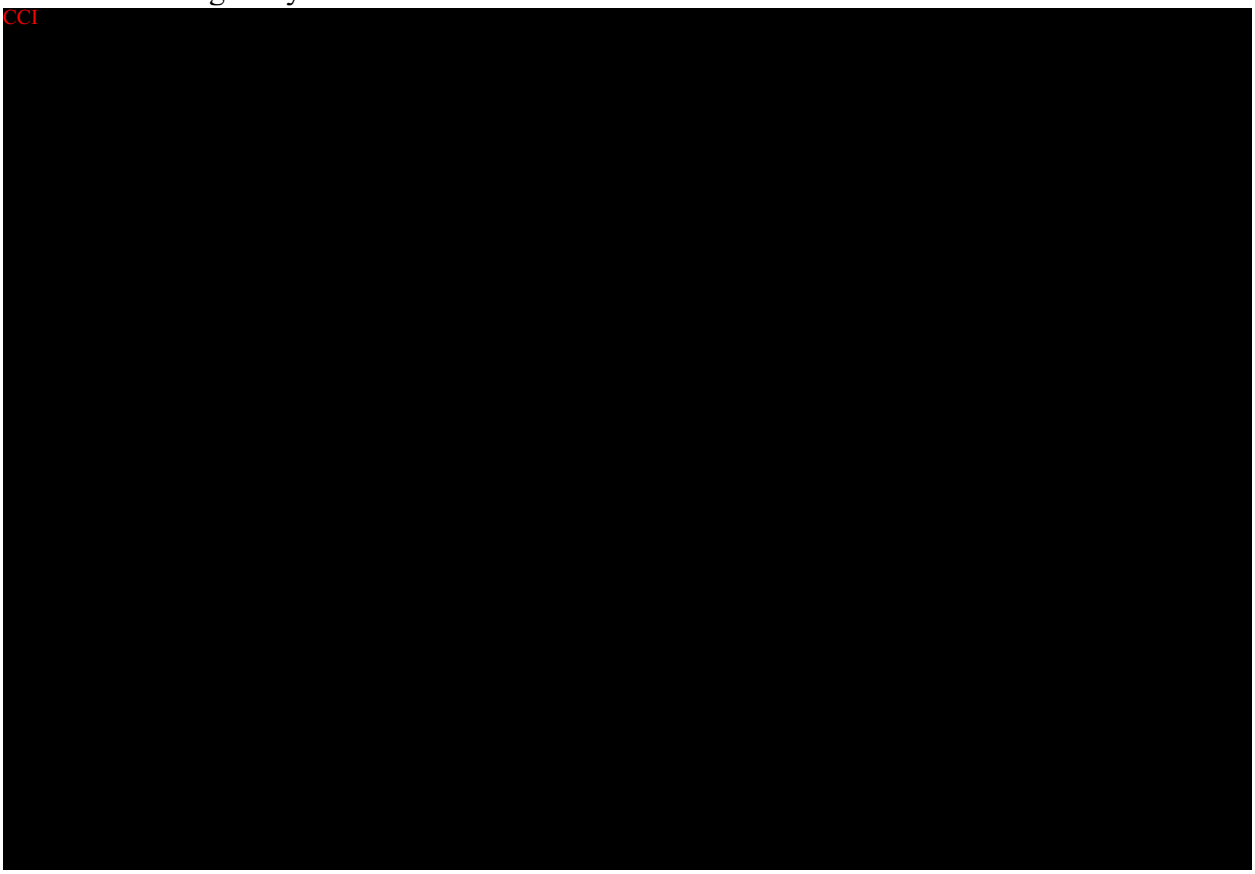
1. The assessment that is closest to the target day.
2. If there are multiple assessments equidistant from the target day, then:
   a. for continuous parameters the average of the values will be used
   b. for categorical parameters the worst assessment will be used.

The following analysis visit windows will be used for all but PK data.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
All but PK	All	Study Day 1	≤ Study Day 1		Visit 1
		Study Day 2	Study Day 2	Study Day 2	Visit 2
		Study Day 3	Study Day 3	Study Day 4	Visit 3
		Study Day 5	Study Day 5	Study Day 6	Visit 4
		Study Day 7	Study Day 7	Study Day 7	Visit 5
		Study Day 8	Study Day 8	Study Day 8	Visit 6
		Study Day 14	Study Day 13	Study Day 15	Visit 7
		Study Day 21	Study Day 20	Study Day 22	Visit 8
		Study Day 25	Study Day 24	Study Day 26	Visit 9

The following analysis visit windows will be used for the PK data.

CCI



6.3.4. Multiple measurements at One Analysis Time Point

If ECG has been assessed more than once (e.g. in triplicate) at an analysis time point, the average of the available ECG measurements will be calculated and summary statistics will be based on the calculated average. This applies to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab on a study day, the worst case will be used.

Other Safety Endpoints
Columbia Suicide Severity Rating Scale (C-SSRS)
• Missing data will not have any imputation performed. • A positive alert is triggered if a subject has reported suicidal ideation/behaviour in categories 4-9. • Questions in categories 3-5 will be triggered if suicidal ideation is reported in categories 1 or/and 2. • Incomplete calls: o when no complete call is databased on the same day, the data from the incomplete call will be used

Other Safety Endpoints
Columbia Suicide Severity Rating Scale (C-SSRS)
○ if a subject has only an incomplete call, and it resulted in a positive alert, the relevant pages in the CRF should be completed, even though the call was incomplete ○ when a complete call is databased on the same day, the data from the complete call will be used in the summaries. • Duplicate calls, ○ if they occur on the same day: ▪ Both calls will be reported in the listings. ▪ For summary tables, the entry with latest time record will be used. ▪ For summary tables at baseline, unscheduled repeat visits will not be summarised. ▪ Relevant CRF pages will be completed based on the latest entry (if it was a positive alert). ○ If they occur on different days ▪ take the entry closest to the target visit date • Visit 1 (Screening) assessments performed after study treatment initiation will not be included in Baseline summaries

6.3.5. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study periods or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions: **Missing start day:** If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: • If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.

Element	Reporting Detail	
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	No Imputation
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: • If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).

Element	Reporting Detail	
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation

6.3.6. Trademarks

Trademarks of the GlaxoSmithKline / ViiV Healthcare Group of Companies
RAPIDO DV

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6.3.7. Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ART	Antiretroviral Treatment
BLQ	Below the limit of quantification
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling and Simulation
CSR	Clinical Study Report
DAIDS	Division of AIDS
DBL	Database Lock
ECG	Electrocardiogram
HIV	Human Immunodeficiency Virus
IE	Intercurrent Event
LFU	Lost to Follow-Up
LOWESS	Locally Weighted Scatterplot Smoothing
LSR	Layperson Summary of Results
PCI	Potential Clinical Importance
PoC	Proof of Concept
PD	Pharmacodynamic
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
PreP	Pre-Exposure Prophylaxis
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

TN	Treatment Naive
ULN	Upper Limit Normal
VLD	Viral Load Decline
VH	ViiV Healthcare group of companies

7. REFERENCES

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