Statistical Analysis Plan

Study ID: 218806

Official Title of Study: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH4524184 in HIV-1 Infected Treatment Naïve Adults

NCT number: NCT06214052

Date of Document: 11-Jan-2024

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Study to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of VH4524184 in HIV-1 Infected Treatment Naïve Adults
Study Number:	218806
Compound Number:	GSK4524184 (also known as VH4524184)
Abbreviated Title:	VH4524184 Proof-of-Concept in Treatment-Naïve Adults Living with HIV-1
Acronym:	INSIGHT

Sponsor Name: ViiV Healthcare UK Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**

TABLE OF CONTENTS

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	11 Jan 2024	Version 1 (29/SEP/2023)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 218806. 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 orally administered VH4524184 in TN participants with HIV-1 during 10 days of monotherapy	• Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 10.
Secondary	
• To assess the safety and tolerability of orally administered VH4524184	• Incidence of adverse events (AEs), severity of AEs and proportion of participants who discontinue treatment due to AEs. Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameter (Alanine Transaminase (ALT), Aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase, albumin and total protein)
• To characterize the pharmacokinetic profile of orally administered VH4524184	As data permits, PK measures that include: • Maximum observed plasma drug concentration (Cmax), • Time to maximum observed plasma drug concentration (tmax), • Concentration on Day 10
• To evaluate any relationship between VH4524184 exposure and change in plasma HIV1 RNA	• Correlation of VH4524184 PK parameters with maximum plasma HIV-1 RNA change from baseline through Day 10
• To assess the occurrence of emergent genotypic or phenotypic resistance after 10 days of monotherapy with VH4524184	• Genotypic and phenotypic data from baseline (Day 1) and Day 10 will be compared for amino acid substitutions and VH4524184 fold change IC50.
• To assess the immunologic effects of VH4524184 when administered over 10 days in participants living with HIV	• Change from baseline in CD4+ T-cell count to Day 10
Tertiary	

Objectives	Endpoints
• To further assess the safety and tolerability of orally administered VH4524184	• Post baseline values and changes over time of vital signs, electrocardiogram (ECG) parameters and suicidality scores. • Absolute values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation and remaining chemistry panels

Primary estimand

The primary objective is to evaluate the antiviral activity of orally administered VH4524184 in TN participants with HIV-1 during 10 days of monotherapy.

The estimand is described by the following attributes:

- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals

- **Endpoint:**

  Maximum change from baseline (Day 1) in plasma HIV-1 RNA through Day 10

- **Treatment:**

  VH4524184 or placebo CCI [redacted]

- **Intercurrent events:**
  - Discontinuation of study treatment due to any reason will be addressed using **while on-treatment strategy**, i.e. any HIV-1 RNA data available after study treatment discontinuation day + 1 and prior to starting standard of care (SOC) will be excluded from calculation of max VLD
  - Use of SOC or other antiviral medication prior to Day 10 will be addressed using **while on-treatment strategy**, i.e., HIV-1 RNA collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded from calculation of max VLD
  - Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., any HIV-1 RNA data available after use of prohibited medication will be used in calculation of max VLD
  - CCI [redacted]

- **Population-level summary:**

Mean of maximum change from baseline in log10 HIV-1 RNA during Days 1-10

Rationale for estimand: Interest lies in evaluating efficacy of orally administered VH4524184 CCI or use of prohibited medications and not in combination with other antiretroviral medication.

Secondary estimands

The secondary objective is to assess the safety and tolerability of orally administered VH4524184.

The estimand is described by the following attributes:

- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals

- **Endpoint:**
  - Incidence of AEs, severity of AEs and proportion of participants who discontinue treatment due to AEs
  - Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameter
- **Treatment:**

  VH4524184 or placebo CCI followed by SOC on Days 10-38
- **Intercurrent events:**
  - Discontinuation of study treatment due to any reason will be addressed using **treatment policy strategy**, i.e. all safety data after study treatment discontinuation will be used
  - Use of SOC or other antiviral medication prior to Day 10 will be addressed using **while on-treatment strategy**, i.e., safety data collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded from monotherapy safety summaries
  - Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., all safety data will be used regardless of the use of prohibited medication
  - CCI
- **Population-level summary:**

  AEs:

- Number and percentage of participants with AEs
- Number and percentage of participants with AEs by severity grade
- Number and percentage of participants with AEs leading to study treatment discontinuation

Liver panel laboratory parameters:

- Summary statistics (mean, SD, median, min, max, etc.) of change from baseline
- Number and percentage of participants with maximum toxicity grade increase relative to baseline

Rationale for estimand: Interest lies in evaluating safety and tolerability of orally administered VH4524184 irrespective of study treatment discontinuation, CCI [redacted], or use of prohibited medications and not in combination with other antiretroviral medication.

Another secondary objective is to characterize the PK profile of orally administered VH4524184.

The estimand is described by the following attributes:

- **Population:**

  Overtly healthy (other than HIV-1 infection) treatment naïve individuals

- **Endpoints:**

  As data permits,

  - Maximum observed plasma drug concentration (Cmax)
  - Time to maximum observed plasma drug concentration (tmax)
  - Concentration on Day 10

- **Treatment:**

  VH4524184 or placebo CCI [redacted] followed by SOC on Days 10-38

- **Intercurrent events:**

  - Discontinuation of study treatment due to any reason will be addressed using **while on-treatment strategy**, i.e. PK data after study treatment discontinuation will be excluded from use in noncompartmental analyses.
  - Use of SOC or other antiviral medication prior to collection of HIV-1 RNA and PK specimens on Day 10 will be addressed using **while on-treatment strategy**, i.e., PK data collected after initiation of SOC, if for any reason this takes place prior to Day 10, will be excluded

- Use of prohibited medication will be addressed using **treatment policy strategy**, i.e., all PK data will be used regardless of the use of prohibited medication
- CCI of study treatment will be addressed using **while on-treatment strategy**, i.e. PK data collected CCI will be excluded from use in noncompartmental analyses.

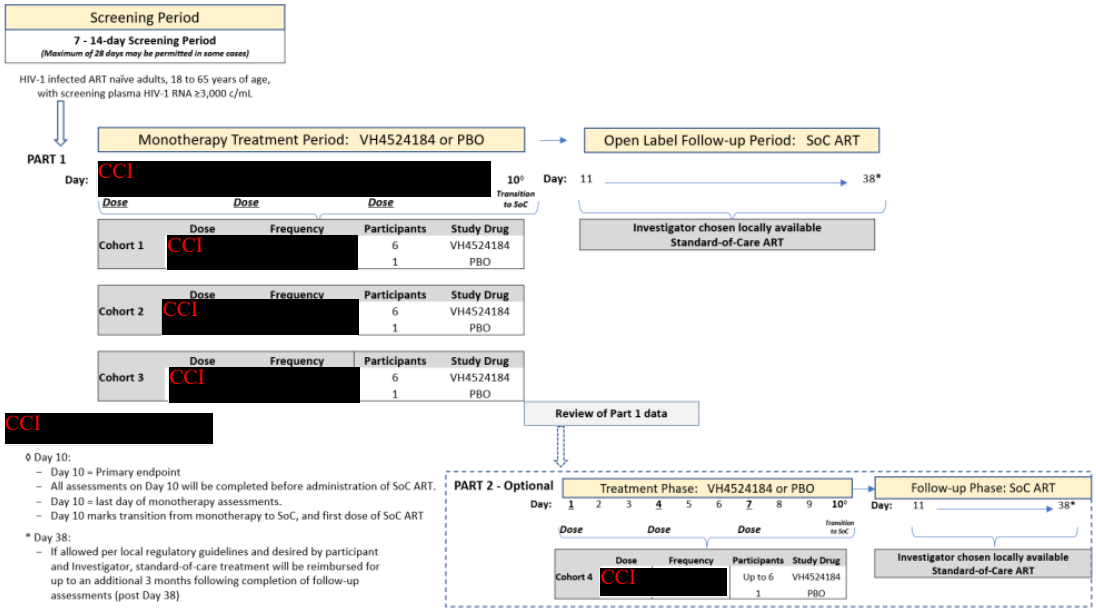
- **Population-level summary:**

  Summary statistics (e.g. arithmetic mean, SD, median, min, max, geometric mean, SD (log), %CVb, etc.)

Rationale for estimand: Interest lies in characterizing the PK profile of orally administered VH4524184 which could be biased by study treatment discontinuation, CCI, or use of SOC medication prior to day 10.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• Phase 2a POC, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled, adaptive clinical study • Orally administered VH4524184 monotherapy over 10 days in antiretroviral therapy (ART) naive adults with HIV-1 and detectable viremia • Total duration of study participation is approximately 45 to 66 days based on the following:

Overview of Study Design and Key Features	
	• **Screening Period:** 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period • **Monotherapy Period:** 10 days for treatment with the study intervention and assessment at all planned visits • **Open Label Follow-up Period:** 28 days for follow up visits while on SOC ART including the final follow up visit
Study intervention	VH4524184 or placebo CCI [redacted] followed by SOC on Days 10-38
Study intervention Assignment	Participants will be randomly assigned to one of 3 dose levels (CCI [redacted]). Within each dose level, participants will be randomly assigned to receive VH4524184 or placebo in a 6:1 ratio.
Interim Analysis	An informal interim analysis will be conducted after all Part 1 participants complete their monotherapy phase.

2. STATISTICAL HYPOTHESES

The primary objective 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 the monotherapy period.

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be made.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Randomized	• All participants who were randomly assigned to study intervention in the study.	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety	• All randomized participants who received at least 1 partial or full dose of study intervention. • Participants will be analyzed according to the study intervention they actually received	• Study Population • Safety
Full Analysis Set (FAS)	• All randomized participants who received at least 1 full dose of study intervention. • Data will be reported according to the randomized study intervention.	• Study Population • Efficacy
Per-Protocol (PP)	• All participants in the FAS for whom there were no major protocol deviations that impact the primary analyses. • Data will be reported according to the study intervention actually received. • Specific details of major protocol deviations that would exclude participants from the PP analysis set are provided in Section 3.1.	• Efficacy • The PP set will not be used for analysis if it is the same as FAS
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	• PK

3.1. Exclusions from the Per Protocol Analysis Set

A participant meeting any of the following criteria prior to the end of monotherapy period will be excluded from the primary analysis based on the PP analysis set:

Number	Exclusion Description
01	Missed at least one dose or received a partial dose
02	Took at least one incorrect dose
03	Missed the Day 1 or Day 10 HIV-1 RNA assessment
04	Missed more than 1 post-baseline HIV-1 RNA assessment between Day 1 and Day 10
05	Started the SoC medication prior to Day 10
06	CCI [redacted]
07	Violated any of the inclusion criteria or met any of the exclusion criteria

Number	Exclusion Description
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

Note: participant-level data will be available interactively via Reporting & Analysis Plan Improving Design and Delivery of Outputs Data Viewer (RAPIDO DV) at SAC. Only selected listings specified in the Output and Programming Specifications (OPS) will be created in a static fashion. See OPS for the list of selected listings.

The term "Analysis Set" in the SAP will be referred to as "Population" in the displays. The term "Participant" in the SAP will be referred to as "Subject" in the displays of the OPS document.

4.1.1. General Methodology

If participants prematurely discontinue the study for non-safety reasons, additional participants may be recruited with randomization and assignment to the same cohort (to ensure a minimum of 5 evaluable participants in each of cohorts 1, 2 and 3, and optional cohort 4) at the discretion of the Sponsor in consultation with the Investigator. Participants will not be replaced if the reason for discontinuation is the original participant meeting stopping criteria. 'Discontinuation' of study intervention refers to any participant who has not received all planned doses of the study intervention. In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

Data will be summarized by study intervention (VH4524184 or placebo) and dose level, unless otherwise specified. In other words, placebos from each dose level will be grouped collectively, while active participants from each dose level will be grouped separately. As such, if optional Part 2 is not used, the following groups will be summarized: VH184 CCI, VH184 CCI, VH184 CCI, and PBO. If optional Part 2 is used, the following groups will be summarized: VH184 CCI, VH184 CCI, VH184 CCI, VH184 Dose Level 4 (to be determined by interim analysis) and PBO.

Data will be summarized either by visit or separately for the monotherapy period and overall (i.e., monotherapy period + follow-up), as appropriate for each endpoint, unless otherwise specified.

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center are unlikely to be informative and will not, therefore, be provided.

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, standard deviation (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

Confidence intervals will use 95% confidence levels unless otherwise specified.

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 participant level information will include all values (i.e. irrespective of being within/outside of analysis visit windows).

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.

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)/estimands

See section 1.1 for definition of primary endpoint/estimand.

Change from baseline at the time point where the HIV-1 RNA is minimum (nadir) during the monotherapy period will be calculated for each participant in the original and $\log_{10}$ scales. The change from baseline at nadir is the primary endpoint used to construct the primary estimand (see section 1.1). According to primary estimand definition (section 1.1), if SoC medication starts prior to Day 10 (for any reason), change from baseline values after SoC 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 monotherapy 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 monotherapy we will mean the "change in HIV-1 RNA at nadir".

The $\log_{10}$ transformation is used to allow for direct comparisons with data from other compounds publicly available in the same scale, 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 $\log_{10}$ scales using descriptive statistics as described in section 4.1.1.

In addition, change from baseline in plasma HIV-1 RNA at each assessment time point during monotherapy will be summarized in original and log10 scales.

Any missing HIV-1 RNA data (e.g., due to missed visits in the clinic, loss to follow-up or for any other reason) will not be imputed and will remain missing. Whatever HIV-1 RNA data are available for a participant during monotherapy and prior to starting SoC will be used to calculate maximum VLD.

If a participant withdraws from study prior to the end of monotherapy 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 RAPIDO DV

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 they were randomized.

None of the IEs specified in section 1.1 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 section 3.1). 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 $\log_{10}$ scales. Change from baseline at each assessment time point during monotherapy and follow-up will be summarized in original and $\log_{10}$ scale using descriptive statistics as described in section 4.1.1.

Mean (95% CI) and median of change from baseline in plasma HIV-1 RNA in the $\log_{10}$ 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 $\log_{10}$ scale) during the monotherapy period from all dosing levels as the outcome measure, with day, dosing group, day and dosing group interaction and baseline HIV-1 RNA (on log scale) as fixed effects and participant as a random effect. Day will be treated as a continuous variable. The Kenward & Roger (KR2) degrees of freedom approach will be used [Kenward & Roger, 2009]. Data from placebos across dosing levels will be analyzed as a single placebo group. Thus, for Part 1, 4 dosing groups will be considered: VH4524184 CCI , VH4524184 CCI , VH4524184 CCI and Placebo. The model will be used to estimate the rate of decline in HIV-1 RNA and its 90% CI for each dosing group.

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 warranted, alternative models or data transformations may be explored.

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 Endpoints Analyses

4.3.1. Definition of endpoints/estimands

See section 1.1 for definition of secondary endpoints/estimands.

4.3.2. Main analytical approach

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

4.3.2.1. Adverse events analyses

AEs will be tabulated using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and 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 monotherapy period will be summarised using the following categories and subcategories:

- AEs
  - Overall
  - By System Organ Class and Maximum Grade
- AEs leading to permanent discontinuation of study treatment
- AEs leading to withdrawal from study
- Drug-related AEs
  - Overall
  - By Maximum Grade
- Drug-related Non-serious AEs
- Common (≥5%) non-Serious AEs
- SAEs by System Organ Class and Maximum Grade
- Drug-related SAEs

The Common (≥5%) 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 monotherapy period which continue in the follow-up period will only be included in AE summaries for the monotherapy period. See OPS for the exact AE tables to be repeated for follow-up and monotherapy + follow-up.

A listing of all AEs will be provided. All planned AE displays are provided in the OPS document.

4.3.2.2. Liver panel laboratory analyses

Change from baseline values for liver panel laboratory parameters will be summarised by assessment visit. Visits up to Day 10 (inclusive) will exclude any liver panel values assessed under SoC, if SoC starts earlier for any reason, in line with the Estimand definition (section 1.1).

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. 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 + follow-up).

For lab tests that are not gradable by DAIDS, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Liver panel data for participants with at least one abnormal lab value will be included in the listing of chemistry laboratory parameters.

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

4.3.2.3. Pharmacokinetic analyses

Pharmacokinetic analysis will be the responsibility of the CPMS Department at GSK. Plasma concentration-time data will be analyzed by non-compartmental methods with WinNonlin 8.1 or higher, Phoenix (Pharsight Corporation) or comparable software to derive the PK parameters. All calculations of non-compartmental parameters for the End of Study (EoS) analysis will be based on actual sampling times recorded during the study.

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 following pharmacokinetic parameters will be determined from the plasma concentration-time data, as data permits, and they will be included in the final SDTM datasets:

PK Parameter	Definition
C_{max}	Maximum observed plasma concentration (CCI [redacted])
t_{max}	Time to first occurrence of C_{max} (CCI [redacted])
C_{10}	Concentration on Day 10
$AUC_{(0-\infty)}$	Area under the plasma concentration time curve from time zero to infinity (CCI [redacted]) calculated as $AUC_{(0-\infty)} = AUC_{(0-t)} + {C_{last}}/{\lambda z}$
$AUC_{(0-tlast)}$	Area under the plasma concentration vs time curve from time = 0 hours to the last observed quantifiable concentration CCI [redacted])
$AUC_{(0-10)}$	Area under the plasma concentration vs time curve from time = 0 hours to Day 10

Note: Additional Parameters may be included as required

At interim analysis, preliminary PK data will be analysed by CPMS to select appropriate doses for Part 2 of the study (if used).

Pharmacokinetic concentrations collected within the PK analysis visit windows 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 participant level figures but will not be included in data summaries. For each compound, derived PK parameters (excluding AUC_{0-10}) will be summarised using descriptive statistics (AUC_{0-10} will be used only for analyses to explore relationship between PK exposure and immunologic endpoints; see section 4.3.2.6).

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, as described in section 1.1.

If a participant takes an incorrect dose or misses a dose, PK concentrations and PK parameters inferred until the next dose or until the end of monotherapy period (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-subject graph of the concentration data over time, on linear and semi-logarithmic scales
- Graph of geometric mean of concentration data over time, on linear and semi-logarithmic scales
- Individual and box plot of PK parameters

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

4.3.2.4. PD and PK/PD analyses

Pharmacokinetic-pharmacodynamic analyses will be the responsibility of the CPMS Department at GSK. The relationship between selected PK parameters (e.g., concentrations on Day 10) and selected PD parameters (e.g., maximum change from baseline in log10 plasma HIV-1 RNA) will be explored separately by CPMS. These analyses will be described in a separate CPMS report.

4.3.2.5. Virology analyses

Genotypic assessments will be analyzed separately by the study virologist. These analyses will be performed after SAC, when the genotypic data become available.

4.3.2.6. Immunology analyses

Change from baseline in CD4+, CD8+ and CD4+/CD8+ (if collected) will be summarized descriptively at every assessment visit. Visits up to Day 10 (inclusive) will exclude any values assessed under SoC, if SoC starts earlier for any reason.

To further explore the relationship between VH4524184 exposures and CD4+ T-cell counts, a scatter plot of change from baseline on Day 10 (within the monotherapy period) in CD4+ counts and Cmax after each administration, AUC_{0-10} and C_{10} will be created for all participants receiving active drug. A LOWESS line will be included in the scatter plot.

Further analyses may be conducted post SAC if any signals or trends are identified in this univariate analysis.

4.4. Tertiary Endpoints Analyses

4.4.1. Vital Signs

Post-baseline values of vital signs (temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate) and change from baseline over time will be summarized by assessment visit.

The number of participants with worst case vital sign results relative to Potential Clinical Importance (PCI) criteria which are post-baseline relative to baseline will be summarized.

The change categories for PCI criteria are: To Low, To w/in Range or No Change, To High. 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. Participants with missing baseline value are to be assumed to have a within range baseline value.

This summary will be produced while participants are under the monotherapy period, as well as overall (i.e. monotherapy + follow-up).

All vital signs data for participants with at least one value of potential clinical importance will be included inRAPIDO DV. PCI values for vital signs are defined in section 6.2.1.

4.4.2. 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.

Post-baseline values of ECG parameters (heart rate, PR, QRS, QT, and QTc intervals) and change from baseline will be summarized by assessment visit.

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. All ECG data for participants with a value of potential clinical importance occurring during either the monotherapy or follow-up period will be included in RAPIDO DV. PCI values for ECG parameters are defined in section 6.2.1.

4.4.3. Suicidality Scores

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.

Participant-level suicidality data will be available via RAPIDO DV.

4.4.4. Hematology, coagulation, urinalysis and remaining chemistry lab parameters

Post-baseline values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation, urinalysis and remaining chemistry panels will follow the same approach as liver panel laboratory analyses, detailed in section 4.3.2.2.

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”, calcium as “hyperkalemia” and “hypokalemia” etc.

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.

These summaries will be produced while participants are under the monotherapy period, as well as overall (i.e. monotherapy + follow-up).

A listing of hematology, coagulation and chemistry laboratory data will be created. For each laboratory category (i.e. chemistry, hematology etc.), the listing will include participants with at least one abnormal lab value (i.e. DAIDS grade ≥1 for graded parameters or outside normal range for non-graded) during either the monotherapy or the follow-up period in any lab parameter within a lab category. All data for all lab parameters within the lab category in which an abnormal value was observed will be included in the listing; no lab parameters from another lab category in which no abnormal values were observed will be included (e.g. if a participant has an abnormal ALT value then all data from all chemistry lab parameters will be included in the listing and none of the lab parameters from hematology and coagulation).

A listing of urinalysis data will be created. The urinalysis listing will include only participants with at least one abnormal value (i.e. outside normal range) for specific gravity or pH or if there is an increase from Baseline in Protein or in Occult Blood or if microscopy is performed, during either the monotherapy or the follow-up period.

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

Extent of exposure in cumulative actual dose (mg) will be summarized and exposure will be listed for all participants.

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 and will follow the IE strategies outlined for the secondary PK objective in section 1.1.

4.6.2.1. Dose proportionality assessment

Dose proportionality may be assessed following guidance from CPMS prior to final database lock.

Power Model

The analysis will be based on selected available PK parameters. No imputation will be done for missing PK parameters for any participant.

Endpoint / Variables
$AUC_{(0\text{-}t)}$ and C_{max}, as the data permit, at first, second, and third dose, separately
Model Specification
• Power model $$y = \alpha * dose^{\beta}$$ where y denotes the PK parameter being analyzed and dose denotes the dose administered to a subject. • Dose proportionality implies that $\beta = 1$ and will be assessed by estimating β along with its confidence interval by regressing the $\log_e$ transformed PK parameter on the $\log_e$ dose as shown below: $$\log_e y = \log_e \alpha + \beta \log_e dose$$
Model Checking & Diagnostics
• Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. • If there are any important departures from the distributional assumptions, alternative models may be explored using appropriately transformed data.
Model Results Presentation

- Estimates of slope β will be reported along with corresponding 90% CIs. If the CI contains 1 then we shall assume Dose Proportionality to hold.

ANOVA Method

If power model does not show dose proportionality, dose proportionality may be assessed by an analysis of variance (ANOVA) model.

PK parameters will be dose-normalised prior to $\log_e$-transformed by multiplying by reference dose / dose. Dose-normalised PK parameters will be analysed separately using a fixed effects ANOVA model for dose. Point estimates for the adjusted means on the $\log_e$ scale, the mean difference between each dose (test) and the reference dose and associated 90% confidence interval will be constructed using the residual variance. The point estimate and confidence interval will then be exponentially back-transformed to obtain adjusted (least square) geometric means for each dose, and point estimates and associated 90% confidence intervals for the ratio test/reference. The reference dose will be chosen based on the lowest clinically relevant dose over which PK can be adequately described, with each other dose as the test doses in the construction of the ratio μ(test)/μ(reference).

4.6.2.2. Estimation of Accumulation Ratios

Accumulation ratios may be estimated for C_{max} following guidance from CPMS prior to final database lock. These are defined as the ratio of PK parameters from last administration to first administration on Day 1, as follows:

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

To estimate the accumulation ratios for each dose level, a mixed effects ANOVA model will be used on the $\log_e$-transformed C_{max}. Participant will be treated as a random effect in the model, while day will be treated as fixed effect categorical variable. 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 means of PK parameters between last administration (e.g. CCI [redacted]) and first administration (Day 1) and the corresponding 90% CI. No imputation will be done for missing PK parameters.

Model assumptions for the analyses outlined in sections 4.6.2.1 and 4.6.2.2 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 warranted, alternative models or data transformations may be explored.

4.7. Interim Analyses

An informal planned interim analysis will be conducted after all participants in Part 1 have completed their monotherapy period.

The planned interim analysis will evaluate the PK and pharmacodynamic (antiviral activity) of VH4524184 and inform the need for Part 2, as well as future clinical development of VH4524184.

CCI

Any safety outputs provided at the interim analysis will summarise data by dosing levels, with placebo participants grouped with active participants at the corresponding dose level. In other words, safety data summaries will be blinded to study intervention, but not to dose level. Any 'by visit' outputs could include data from the follow-up period, if available.

The tables, figures and listings that will be provided at the planned interim analysis are described in the OPS.

CCI

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

4.8. Final Analyses

The final EoS analysis will be conducted after the completion of the study (i.e., when all participants complete the follow-up period with the Day 38 visit) and final datasets authorization. At the EoS analysis all primary, secondary and tertiary objectives will be

evaluated with two exceptions: the analysis of (i) viral resistance and (ii) pharmacogenetics (if done), may be evaluated at a later stage and each of these outcomes will be reported separately.

4.9. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 29 September 2023).

5. SAMPLE SIZE DETERMINATION

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 9.5.1.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Safety Analysis Set.

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, the 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 Monotherapy period if they have completed Day 10 visit and have not started SoC prior to Day 10. If a participant has started SoC treatment prior to Day 10 visit and has performed Day 10 visit, he/she will be classified as having 'Not Completed' the Monotherapy 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.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the scheduled study intervention or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

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 withdrawal will be provided.

Participant-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 and CDC HIV-1 classification will be available at the 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. 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.

Participant-level protocol deviations which result in exclusion from the Per Protocol analysis set will be available 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. However, the listing of concomitant medications will be based on GSK Drug dictionary only.

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 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). A high or low abnormal laboratory value is not necessarily of clinical concern.

The Division of AIDS (DAIDS) grading for severity of laboratory toxicities and clinical adverse events, version 2.1, July 2017 will be used to assign grades to laboratory values as specified in the protocol.

In addition, the following criteria will be used to flag potential clinical importance:

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval (QTcF)	msec	< 320	> 450 (Males) > 470 (Females)

Change from Baseline		
Increase from baseline QTc	Msec	> 60*

*On-treatment triplicate averaged QTcF value > 60 msec over baseline regardless of sex

Vital Sign Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Systolic Blood Pressure	mmHg	< 85	> 140
Diastolic Blood Pressure	mmHg	< 45	> 90
Heart Rate	bpm	< 45 (Males) < 50 (Females)	> 100

Note: PCI values for Respiratory Rate & Temperature are not applicable.

6.2.2. Study Period

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

Screening is defined as time prior to the first dose of study intervention.

Monotherapy is defined as the time from first dose of study intervention (Day 1) to the start of standard of care ART (Day 10)

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

Follow-up is defined as any time after the transition to standard of care ART on Day 10.

- If time of assessment or time of SoC initiation is not collected, Day 10 assessments other than AEs are considered to have occurred prior to SOC initiation and therefore considered part of the Monotherapy period, whereas AEs with Day 10 onset are considered to have occurred after SOC initiation and are therefore considered part of the Follow-up period.

For concomitant medications, study periods will be defined as follows (please note that the screening period is used interchangeably with pre-treatment in descriptions):

	Screening	Monotherapy		Follow-Up		Screening	Monothe-rapy	Follow-Up
(a)	x———x	Study Intervention Start Date		SoC 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 SoC 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 SoC 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 SoC start date it will be classified as "Monotherapy Treatment"
[4]A medication which started on the Study Intervention start date and stopped on the SoC start date it will be classified as "Monotherapy and Follow-Up Treatment"
Similarly, for other cases.

6.2.3. Study Day and Reference Dates

The study day 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 Data ≥ Study Intervention Start Date

  → Study Day = Assessment Date – Study Intervention Start Date + 1

6.2.4. Assessment Window

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data 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 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

CCI

CCI

6.2.5. 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.

6.2.6. 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 phases 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). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions:

Element	Reporting Detail	
	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).
	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

Element	Reporting Detail	
		– 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).
	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

6.2.7. Trademarks

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

Trademarks not owned by the GlaxoSmithKline / ViiV Healthcare Group of Companies
WinNonlin

7. REFERENCES

Kenward, M. G., and Roger, J. H. (2009). “An Improved Approximation to the Precision of Fixed Effects from Restricted Maximum Likelihood.” Computational Statistics and Data Analysis 53:2583–2595.