Statistical Analysis Plan

Study ID: 218307

Official Title of Study: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitor Monotherapy in HIV-1 Infected Treatment-Naïve Adults

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TITLE PAGE

Protocol Title: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitor Monotherapy in HIV-1 Infected Treatment-Naïve Adults

Study Number: 218307

Compound Number: VH4004280 (also known as GSK4004280) and VH4011499 (also known as GSK4011499)

Abbreviated Title: Proof of concept treatment study of orally administered VH4004280 or VH4011499 in HIV-1 infected adults

Acronym: CINNAMON

Sponsor Name: ViiV Healthcare UK Limited

Regulatory Agency Identifier Number(s)

Registry	ID
Clintrials.gov	

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	03 Aug 2023	Version 1 (08 May 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 218307. Details of the planned End of Study analyses are provided. Selected End of Study outputs will also be provided at the planned Interim analyses (see also Section 4.7). See OPS for the list of outputs delivered at Interim and End of Study analyses.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
To evaluate the antiviral activity of orally administered VH4004280 and VH4011499 monotherapy over 10 days in HIV-1 infected Treatment-Naïve (TN) participants	Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 11.
Secondary	
To assess the safety and tolerability of orally administered VH4004280 and VH4011499	• Incidence of adverse events (AEs), severity of AEs and AEs leading to study treatment discontinuation • 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 characterize the pharmacokinetic profiles of orally administered VH4004280 and VH4011499	PK measures that include but are not limited to: • Maximum observed plasma drug concentration (Cmax), • Time to maximum observed plasma drug concentration (tmax), • Concentrations on Day 11 for VH4004280 and VH4011499
To determine the relationship between the exposure levels of orally administered VH4004280 and VH4011499 and change in plasma HIV-1 RNA	VH4004280 and VH4011499 PK parameters with maximum change in plasma HIV-1 RNA from baseline through Day 11
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1.1.1. Estimands

Table 1 Estimands Definitions

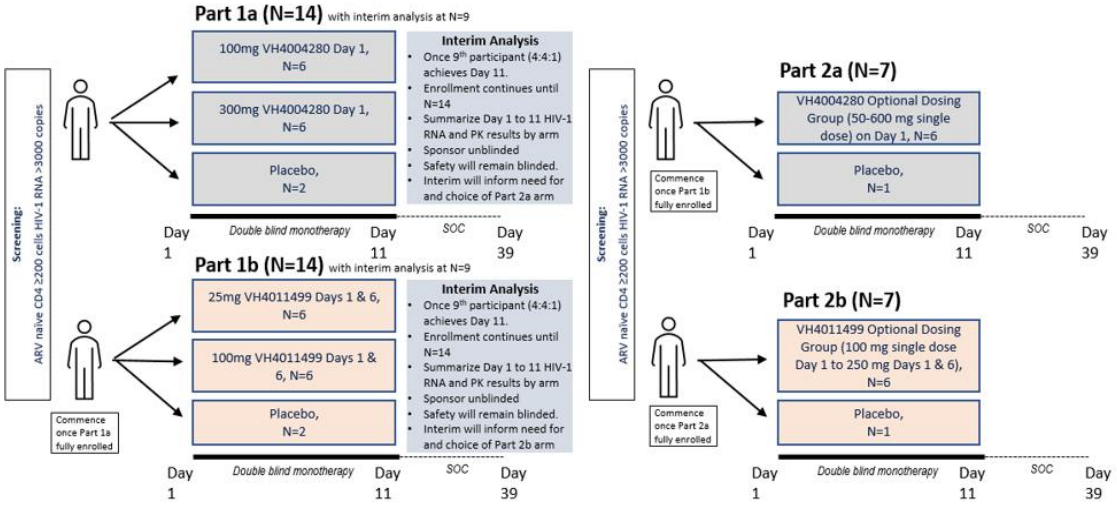
Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
Primary Objective: To evaluate the antiviral activity of orally administered VH4004280 and VH4011499 monotherapy over 10 days in HIV-1 infected Treatment-Naïve (TN) participants				
Maximum change from baseline (Day 1) in plasma HIV-1 ribonucleic acid (RNA) through Day 11.	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo single dose on Day 1, or VH4011499 or placebo single dose on Day 1 and Day 6	Mean of maximum change from Baseline in log10 HIV-1 RNA during Days 1-11	Discontinuation of study treatment due to any reason: **Treatment policy strategy,** i.e., any HIV-1 RNA data available after study treatment discontinuation day + 1 and prior to starting SoC will be used in calculation of max VLD Use of SoC medication prior to Day 11: **While on-treatment strategy**, i.e., HIV-1 RNA collected after initiation of SoC, if for any reason this takes place prior to Day 11 will be excluded from calculation of max VLD Use of prohibited medication: **Treatment policy strategy**, i.e., any HIV-1 RNA data available after use of prohibited medication will be used in calculation of max VLD Missed or incorrect doses of study treatment: **Treatment policy strategy,** i.e., HIV-1 RNA collected after missed or incorrect dose(s) will be used in calculation of max VLD *Rationale:* Interest is in evaluating efficacy irrespective of study treatment discontinuation or missed/incorrect doses, or use of prohibited medications, hence a treatment policy strategy is appropriate. Also, interest is to evaluate efficacy of VH4004280/VH4011499 monotherapy and not in combination with

Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
				other antiretroviral medication hence a while on-treatment strategy is appropriate. *Note: discontinuation or missed doses of VH4004280 is not possible as only a single dose on Day 1 is administered, hence these IEs apply only to VH4011499 and to placebo matched for VH4011499.*
Secondary Objective: To assess the safety and tolerability of orally administered VH4004280 and VH4011499				
• Incidence of adverse events (AEs), severity of AEs and AEs leading to study treatment discontinuation • Change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo CCI [redacted] or VH4011499 or placebo CCI [redacted]	• 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 ○ Summaries (mean, median, std, Q1, Q2, min, max) of change from baseline in liver	Discontinuation of study treatment: **Treatment policy strategy,** i.e., all data to be used regardless of whether the study treatment discontinuation has occurred Use of SoC medication prior to Day 11: **While on-treatment strategy**, i.e., Safety data collected after initiation of SoC, if for any reason this takes place prior to Day 11 will be excluded from monotherapy Safety summaries Use of prohibited medication: **Treatment policy strategy,** i.e., all data to be used regardless of whether prohibited medication has been used *Rationale:* There is interest in evaluating and reporting monotherapy safety events from the monotherapy period and regardless of whether participants have completed monotherapy treatment or received prohibited medication *Note: discontinuation of VH4004280 treatment is not possible as only a single dose on Day 1 is administered, hence this IE applies only to VH4011499 and to placebo matched for VH4011499.*

Endpoints	Estimand			
	Population	**Treatment**	**Summary Measure**	**Intercurrent event (IE) / strategy / rationale**
			panel laboratory parameters ○ Number and percentage of participants with maximum grade toxicity relative to Baseline	
Secondary Objective: To characterize the pharmacokinetic profiles of orally administered VH4004280 and VH4011499				
Concentration on Day 11 and PK parameters including ○ Cmax ○ tmax	Overtly healthy (other than HIV-1 infection) treatment naïve individuals	VH4004280 or placebo CCI [redacted], or VH4011499 or placebo CCI [redacted]	Summary statistics (e.g., arithmetic mean, median, std, minimum, maximum, geometric mean, sd (log), %CVb)	Discontinuation of monotherapy treatment with VH4011499: **While on-treatment strategy,** i.e., concentration values after study treatment discontinuation day + 1 will be excluded from analysis Use of prohibited medication: **treatment policy strategy**, i.e., all PK data to be used regardless of whether prohibited medication was used *Rationale:* Discontinuation of VH4011499 treatment may bias the evaluation of Pharmacokinetic behavior of VH4011499 as expected during and after the end of 10 days monotherapy period *Note: discontinuation of VH4004280 treatment is not possible as only a single dose on Day 1 is administered*
CCI [redacted]				

Endpoints	Estimand			
	Population	Treatment	Summary Measure	Intercurrent event (IE) / strategy / rationale
CCI [redacted]				

1.2. Study Design

Overview of Study Design and Key Features	
	

Design Features	• Phase IIa, PoC, multi-center, randomized, double-blind (sponsor unblinded), placebo-controlled (by each capsid inhibitor) study
	• Orally administered VH4004280 and VH4011499 monotherapy over 10 days in ART naive HIV-1 viremic adults
	• The study will evaluate the antiviral effect, safety, tolerability and PK/PD of VH4004280 and VH4011499
	• Participants have a Screening visit approximately 7 to 14 days prior to first dose on Day 1
	• On Day 1 randomized participants enter a monotherapy phase of 10 days (i.e. up to Day 11)
	• On Day 11, after collection of HIV-1 RNA sample, participants will start open-label SoC combination ART [redacted]
	• Total duration of study participation is approximately 45 to 66 days based on the following:
	  ○ 7 to 14 days, with a maximum of 28 days permitted in some cases for screening/qualification period,
	  ○ 10 days for treatment with the study intervention (monotherapy period) and
	  ○ 28 days for follow up visits (Follow-Up period)

Study intervention	• A single dose of orally administered VH4004280 or matched placebo for VH4004280 on Day 1 or

Overview of Study Design and Key Features	
	• A single dose of orally administered VH4011499 or matched placebo for VH4011499 on Days 1 and 6
Study intervention Assignment	• Part 1a: 100mg VH4004280, 300mg VH4004280 or placebo in a 6:6:2 ratio • Part 2a (if conducted): 50-600mg VH4004280 (exact dose to be decided after first Interim) or placebo in a 6:1 ratio • Part 1b: 25mg VH4011499, 100mg VH4011499 or placebo in a 6:6:2 ratio • Part 2b (if conducted): 100mg on Day 1 to 250mg on Days 1 & 6 VH4011499 (exact dose to be decided after second Interim) or placebo in a 6:1 ratio
Interim Analysis	• A first informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1a have completed their Day 11 visit. • A second informal interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1b have completed their Day 11 visit. • Conduct of parts 2a and 2b depend on results of first and second interim analysis, respectively

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 for each dose for both VH4004280 and VH4011499 CAIs.

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

Analysis Set	Definition	Analyses Evaluated
Randomized	• All participants who are randomly assigned to study treatment (i.e., VH4004280, VH4011499 or placebo) in the study	Study Population
Safety	• All randomized participants who take at least 1 incorrect or correct dose of study treatment • Participants will be analyzed according to the treatment they actually received	Study Population, Safety
Full Analysis Set (FAS)	• All randomized participants who received at least one correct dose of study treatment • Data will be reported according to the randomized study intervention	Efficacy, Study Population
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 The PP set will not be used for an 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 treatment	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.

Table 2 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 11 HIV-1 RNA assessment
04	Missed more than 1 post-Baseline HIV-1 RNA assessment, as per the protocol visit schedule, between Day 1 and Day 10 (inclusive)

Number	Exclusion Description
05	Started the SoC medication prior to Day 11
06	CCI [redacted]
07	Violated any of the inclusion criteria or met any of the 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

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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 11 (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, with the exception of SARS-CoV-2 scenarios (see protocol Section 7.2.1).

Data will be summarized by treatment (i.e., VH4004280, VH4011499, placebo matching VH4004280 and placebo matching VH4011499) and dose level, unless otherwise specified.

Data will be summarized either by visit, or separately for the monotherapy period, the Follow-Up period (i.e. AEs only), and/or overall (i.e., monotherapy period plus Follow-Up period), as appropriate for each endpoint, unless otherwise specified. For summaries focusing on the monotherapy period only (i.e. Day 1 – Day 11), if SoC medication for

any participant starts earlier than Day 11 (for any reason), data collected under SoC will be excluded from the monotherapy period (see respective IE in Estimands Section 1.1.1).

Unless, otherwise specified, summary tables will provide the following descriptive statistics:

- Continuous data: n (number of subjects used for data summary), arithmetic mean, standard deviation (SD), median, interquartile range, minimum and maximum. For PK parameters, geometric mean, SD of log-transformed data and geometric %CV_b may also be used. Confidence interval for the mean or geometric mean may also be used (e.g. check mock outputs in OPS).
- Categorical data: number and percentage of participants in each category.

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.

CCI [redacted] 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 monotherapy 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 SoC medication starts prior to Day 11 (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 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 monotherapy and prior to starting SoC will be used to calculate maximum VLD.

Participants who withdraw 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 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 in Section 1.1.1 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 Table 2). All available HIV-1 RNA data from the monotherapy period on the PP analysis set will be used for the sensitivity analysis.

The maximum VLD calculated for each participant on the PP analysis set will be used for CCI [redacted].

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.

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4.3. Secondary Endpoint(s) Analyses

4.3.1. Definition of endpoints/estimands

Safety Endpoints
• Incidence of AEs • Severity of AEs • AEs leading to study treatment discontinuation • Change from baseline in liver panel laboratory parameters • Maximum toxicity grade increase from baseline in liver panel laboratory parameters
PK Endpoints
Derived VH4004280 and VH4011499 PK parameters including:

- Maximum observed plasma drug concentration (Cmax)
- Time to maximum observed plasma drug concentration (tmax)
- Concentrations on Day 11 for VH4004280 and VH4011499

For definition of secondary estimands see Section 1.1.1.

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 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 monotherapy 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
- 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 and a listing of reasons for considering as SAE 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 visit. Visits up to Day 11 (inclusive) will exclude any liver panel values assessed under SoC, if SoC starts earlier for any reason, in line with the Estimand definition (Section 1.1.1).

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 (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.

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

4.3.2.3. Pharmacokinetic Analyses

Pharmacokinetic parameters for VH4004280 and VH4011499 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 pharmacokinetic parameters described in Table 3 will be determined from the plasma concentration-time data, as data permits and they will be included in the final SDTM datasets.

As per the PK Estimand definition in Section 1.1.1, in case of discontinuation of VH4011499, only serum concentration data up to the time of discontinuation of VH4011499 will be used in derivation of VH4011499 PK parameters.

Table 3 Definition of PK parameters

Compound	PK Parameter	Definition
VH4004280 & VH4011499	C_{max}	Maximum observed plasma concentration
VH4004280 & VH4011499	T_{max}	Time to C_{max}
VH4004280 & VH4011499	C_{11}	Concentration on Day 11
VH4004280	$AUC_{0\text{-}inf}$	Area under the plasma concentration vs time curve from time zero hours to infinity
VH4011499	$AUC_{0\text{-}t}$	Area under the plasma concentration time curve from time zero to the last quantifiable time point
VH4004280 & VH4011499	$AUC_{0\text{-}11}$	Area under the plasma concentration time curve from time of first dose to Day 11

Note: Additional Parameters may be included as required

At Interim analyses, preliminary PK data will be analysed by CPMS to select appropriate doses for Part 2 of the study.

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:

For each compound, pharmacokinetic concentrations collected within the PK analysis visit window (see Section 6.2.4) 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.

For each compound, derived PK parameters (excluding AUC_{0-11}) will be summarised using descriptive statistics (AUC_{0-11} will be used only for analyses to explore relationship between PK exposure and safety/immunologic endpoints; see Section 4.6.3 and Section 4.6.4).

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 Table 1.

If a participant takes an incorrect dose or miss a dose, PK concentrations and 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 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, 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. Additional Estimands for PK analyses

In case prohibited medications have been used during the monotherapy period, the summary of PK concentrations by visit will be repeated using a "while on-treatment" strategy for the Intercurrent Event of prohibited medication use. This implies that PK concentrations derived after use of prohibited medication will be excluded from PK data summaries.

4.3.2.5. PD and PK/PD analyses

The relationship between dose and VLD, and the relationship between PK parameters and VLD will be explored separately by CPMS. These analyses will be described in a separate CPMS report.

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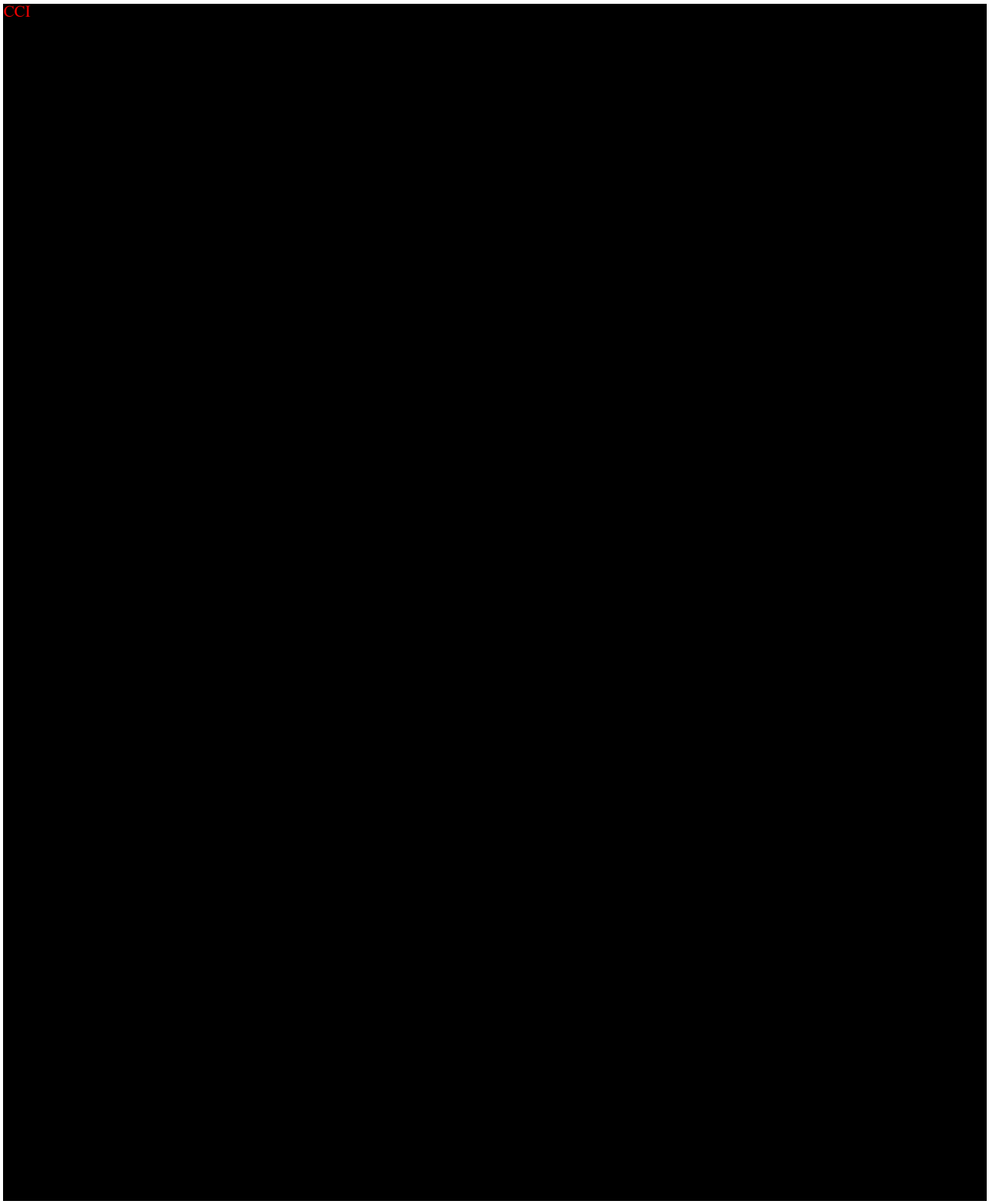

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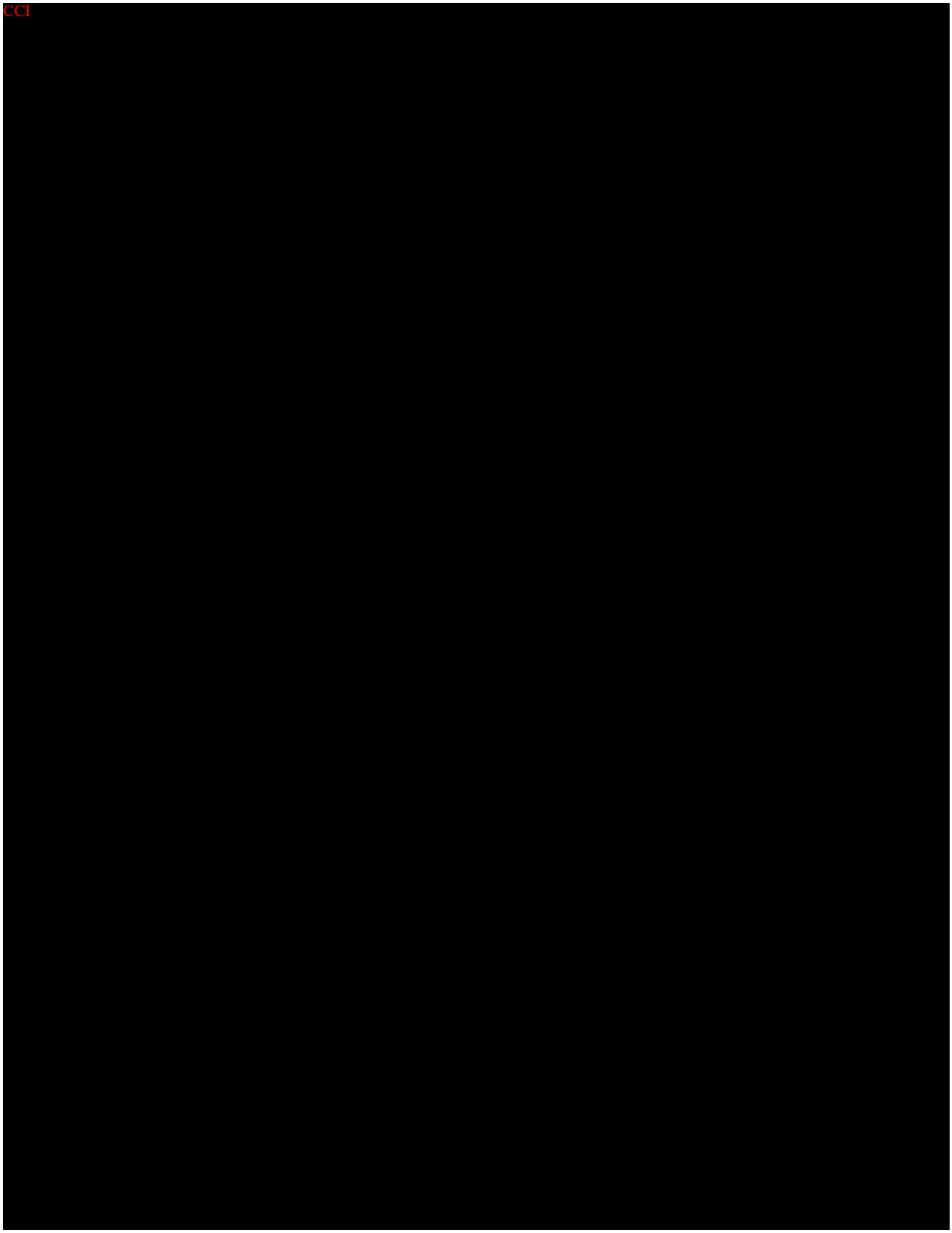

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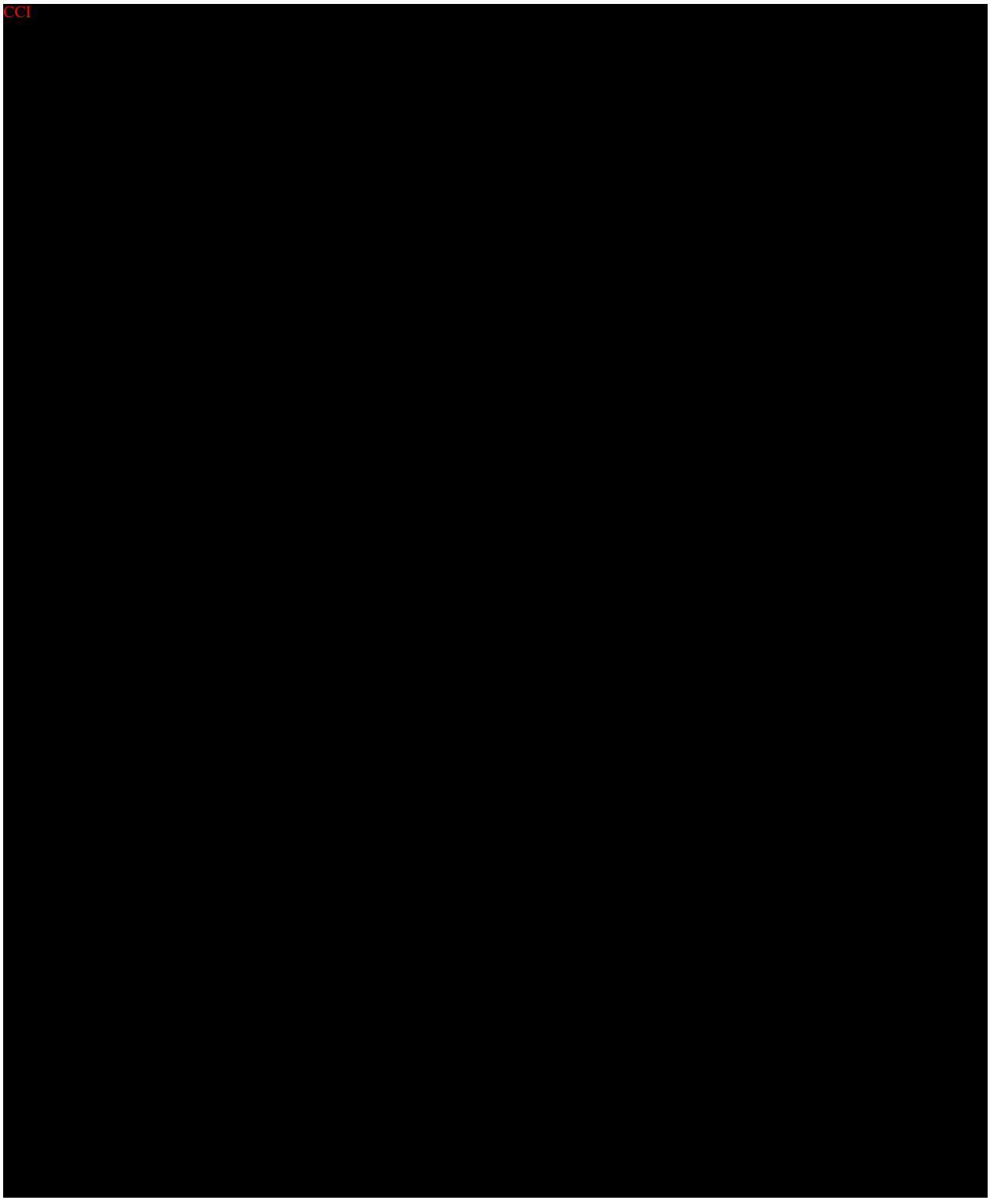

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4.5. Other Safety Analyses

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 monotherapy 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.

4.6. 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 as described in Table 1.
- 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. Dose Proportionality Assessment

Dose proportionality may be assessed if Part 2 is activated for a compound, 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

• For VH4004280: C_{max}, $AUC_{0\text{-}inf}$
• For VH4011499:
  ○ First dose (Day 1): C_{max}, $AUC_{0\text{-}t}$
  ○ Second dose (Day 6): C_{max}, $AUC_{0\text{-}t}$

Model Specification
• Dose proportionality of PK parameters will be assessed using the following 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 it will be assessed by estimating β along with its confidence interval. • β will be estimated by regressing the $\log_e$ transformed PK parameter on the $\log_e$ dose as shown in the following fixed effects model below:

$log_e y = log_e \alpha + \beta log_e dose$
Model Results Presentation
Table: Estimates of slope β will be reported in a Table along with corresponding 90% confidence intervals and number of participants corresponding to the analysis. Figure: Comparative plots will be provided showing individual subject values by dose for each of the PK parameters, together with the predicted PK parameter value from the Power Model.

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 treatment (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 treatment (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).

Plots will be provided showing individual subject dose-normalised PK parameters versus treatment and will also include the geometric mean and 95% CI for each treatment.

4.6.2.2. Estimation of Accumulation Ratios

Accumulation ratios may be estimated for C_{max} 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 (e.g. Day 6 for VH4011499 in Part 1b) to first administration (Day 1) 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 (e.g. Day 6 for VH4011499 in Part 1b) and first administration (Day 1) and the corresponding 90% CI. The GLS means of PK parameters on first administration (e.g. Day 1) and last administration (e.g. Day 6), 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 in Section 4.6.2.1 and Section 4.6.2.2 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.

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4.7. Interim Analyses

An informal planned interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1a have completed their Day 11 visit. A second informal planned interim analysis will be conducted after 9 participants (i.e., 4 participants per active arm and 1 placebo participant) from Part 1b have completed their Day 11 visit.

The planned interim analyses will evaluate the PK and pharmacodynamics (antiviral activity) of each respective capsid inhibitor and inform whether a third pre-specified optional dosing arm for each capsid inhibitor will be evaluated in Part 2. Depending on Part 1 results, a higher dose, lower dose, or a dose between the two doses evaluated in Part 1 will be evaluated in Part 2. It is also possible that Part 2 will not be conducted for one or both capsid inhibitors if the doses evaluated in Part 1 adequately describe the exposure-response of each capsid inhibitor. The interim results will also inform future clinical development of both compounds.

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Outputs created in the first interim analysis will include only participants from Part 1a who have completed their Day 11 visit. Other participants from Part 1a who have potentially been randomized at the time of data cut for the first interim but have not yet completed the Day 11 visit will not be included in any of the first interim analysis outputs.

Outputs created in the second interim analysis will include only participants from Part 1b who have completed their Day 11 visit. Other participants from Part 1b who have potentially been randomized at the time of data cut for the second interim but have not yet completed the Day 11 visit will not be included in any of the second interim analysis outputs. Participants from part 1a who have completed their Day 11 visit and were not included in the first interim analysis outputs, will be included in the second interim analysis outputs (in other words, the first interim analysis outputs will be updated to include data from all participants in Part 1a at the time of second interim).

Safety outputs provided at an interim analysis will summarise data across all treatment arms within a study part (e.g. at first Interim, Safety outputs will summarise data from CCI [redacted] and placebo collectively). In other words, Safety data summaries will be blinded. Any 'by visit' outputs could include data from the Follow-Up period, if available.

The Tables, Figures and Listings that will be provided at each planned interim analysis are described in the OPS.

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CCI [redacted]

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 on Day 39 visit) and final datasets authorization. At the EoS analysis all primary, secondary and exploratory 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 analyses specified in the protocol (Dated: 08 May 2023).

The term “partial” dose used in protocol Section 9 was updated with “incorrect” dose in the definition of Estimands and Analysis Sets as it became apparent that it is possible a participant to receive lower (i.e. partial) or higher dose at an administration visit. This does not affect the planned analyses specified in the protocol but provides further clarity for programming work.

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 6.1.

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 Monotherapy period if has completed Day 11 visit and has not started SoC prior to Day 11. If a participant has started SoC treatment prior to Day 11 visit and has performed Day 11 visit, he/she will be classified as '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.

For treatment arms where more than one study treatment administration is used during the monotherapy period (e.g. in Part 1b), 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 treatment discontinuation and a listing of reasons for study withdrawal will be provided.

Subject-level disposition information will be available via CCI [redacted].

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 CCI Participant-level HIV-1 associated conditions and pregnancy data will also be available via CCI

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 CCI

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 CCI .

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 Section 10.7 of the protocol.

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

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6.2.2. 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.

Monotherapy is defined as time from first study intervention dose (typically Day 1) to start of SoC treatment (typically Day 11).

- 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.

Follow-Up is defined as time from first dose of SoC treatment until study completion or withdrawal

- If time of assessment or time of SoC initiation is not collected, Day 11 assessments other than AEs are considered to have occurred prior to SoC initiation and therefore considered on Monotherapy period, whereas AEs with Day 11 onset are considered to have occurred after SoC 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	Monotherapy	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 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

6.2.4. 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		Baseline
		Study Day 2	Study Day 2	Study Day 2	Day 2
		Study Day 4	Study Day 3	Study Day 5	Day 4
		Study Day 6	Study Day 6	Study Day 6	Day 6
		Study Day 7	Study Day 7	Study Day 7	Day 7
		Study Day 9	Study Day 8	Study Day 10	Day 9
		Study Day 11	Study Day 11	Study Day 11	Day 11
		Study Day 18	Study Day 15	Study Day 21	Day 18
		Study Day 25	Study Day 22	Study Day 28	Day 25
		Study Day 32	Study Day 29	Study Day 35	Day 32
		Study Day 39	Study Day 36	Study Day 42	Day 39

Assessments performed on Study Days 12, 13, 14 or after Study Day 42 will not be included in 'by visit' data summaries.

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6.2.5. Multiple measurements at One Analysis Time Point

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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

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

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).

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>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.</td></tr>
<tr><td>Missing start day and month</td><td>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.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>

Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:

<table>
<tr><td>Missing start day</td><td>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:</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
		• 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	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	Trademarks not owned by the GlaxoSmithKline / ViiV Healthcare Group of Companies
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6.2.8. Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ART	Antiretroviral Treatment
BLQ	Below the limit of quantification

CAI	Capsid Inhibitors
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
SoC	Standard of Care
TN	Treatment Naive
ULN	Upper Limit Normal
VLD	Viral Load Decline
VH	ViiV Healthcare group of companies

7. REFERENCES

GlaxoSmithKline Document Number TMF- 16106355 Study 218307. A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled, Phase 2a Trial to Investigate the Antiviral Effect, Safety, Tolerability and Pharmacokinetics of Orally Administered Investigational Capsid Inhibitor Monotherapy in HIV-1 Infected Treatment-Naïve Adults. 08 MAY 2023.

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.

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed 16 June 2023).

ViiV Healthcare Protocol for Study 218307, Proof of concept treatment study of orally administered VH4004280 or VH4011499 in HIV-1 infected adults, VH Document No. TMF-16106355, Original, May 2023.