Statistical Analysis Plan Amendment 3

Study ID: 217058

Official Title of the Study: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Orally Administered VH4004280 in Healthy Participants.

NCT Number: NCT05163522

Date of Document: 9 December 2022

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A Randomized, Double-Blind (Sponsor Unblinded), Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Orally Administered VH4004280 in Healthy Participants.

Study Number: 217058

Compound Number: GSK4004280 (Also known as VH4004280)

Abbreviated Title: VH4004280 First-Time-in-Human-Study

Sponsor Name: ViiV Healthcare UK Limited

Regulatory Agency Identifier Number(s)

Registry	ID
IND	156318

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	10 Dec 2021	Version 1 (18 Oct 2021)	Not Applicable	Original version
2	09 Dec 2022	Amendment 02 (17 NOV 2022)	Protocol amendment	Describe the data analyses of additional dosing groups in MAD/DDI (in part 2) and study part 3. Add Urinalysis data outputs

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 217058. Details of the planned final analyses are provided.

Descriptive study population analyses, such as summary of demographic and baseline characteristics, and additional details with regards to data handling conventions and the list of tables, figures and listings and specification of data displays are provided in the Output and Programming Specification (OPS) document.

1.1. Changes to the Protocol Defined Statistical Analysis Plan

There are no changes from the originally planned statistical analysis specified in the protocol amendment 02 (Dated: 17-NOV-2022).

1.2. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single (Part 1 and 3) and multiple (Part 2) doses of VH4004280 in healthy participants.	• Incidence of adverse events (AEs), severity of AEs and proportion of participants who discontinue treatment due to AEs • Absolute values, change from baseline and maximum toxicity grade increase from baseline for liver panel laboratory parameters [consists of total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)]
To describe the plasma PK characteristics of VH4004280 in healthy participants following single (Part 1) and multiple (Part 2) doses.	• Area under the plasma-concentration time curve (AUC): $AUC_{(0-\infty)}$ for single dose and $AUC_{(0-\tau)}$ for repeat dose. • Maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and apparent terminal half-life ($T_{1/2}$) will be calculated for each part (Part 1 SAD and Part 2 MAD) as data in each part permits.

Objectives	Endpoints
Safety	
To further assess the safety and tolerability of single (Parts 1 and 3) and multiple (Part 2) doses of VH4004280 in healthy participants.	• Post baseline values and changes over time of vital signs and ECG parameters • Absolute values, change from baseline and maximum toxicity grade increase from baseline for hematology, coagulation and remaining chemistry panels
CCI [redacted]	

Objectives	Endpoints
CCI	

1.2.1. Estimands

Table 1 Estimands

Objective	Estimand		
	Variable/Endpoint	**Population & Summary Measure**	**Intercurrent event (IE) strategy & rationale**
Primary Objective 1: To assess the safety and tolerability of single (Part 1 and 3) and multiple (Part 2) doses of VH4004280 in healthy participants.	• Incidence of AEs overall and by severity grade • Incidence of AEs leading to discontinuation of study treatment[1] ○ Absolute values and change from Baseline in liver panel laboratory parameters ○ Liver panel laboratory parameters maximum grade increase post-Baseline relative to Baseline for gradable parameters or worst-case post-baseline changes from baseline with respect to normal range for any non-gradable lab parameters	Safety analysis set • Number and percentage in each treatment arm[2] ○ Summaries (e.g. mean, median, std etc.) of absolute values and change from Baseline values by visit and treatment arm[1] in liver panel laboratory parameters. ○ Number and percentage of participants with maximum grade increase relative to Baseline in gradable liver panel laboratory parameters by treatment arm[1], or number and percentage of participants with worst-case post-baseline changes from baseline with respect to normal range for any non-gradable lab parameters	IE Strategy: Discontinuation of study treatment: **treatment policy** strategy for part 2 (discontinuation of study treatment can't occur in parts 1 and 3 as participants receive only 1 dose). All available AE, liver panel data will be used. No imputation will be done for missing data. For parts 1 and 3 no relevant intercurrent events are anticipated. Rationale: Interest lies to estimate safety effects likely to be attributable to VH4004280 irrespective of whether the participant completed the treatment.
Primary Objective 2:	○ Part 1: ▪ VH4004280 PK Concentrations,	VH280 Pharmacokinetic analysis set	IE Strategy:

Objective	Estimand		
	Variable/Endpoint	**Population & Summary Measure**	**Intercurrent event (IE) strategy & rationale**
To describe the plasma pharmacokinetic (PK) characteristics of VH4004280 (PiB) in healthy participants following single (Part 1) and multiple (Part 2) doses.	▪ VH4004280 PK parameters: $AUC_{(0-24)}$, $AUC_{(0-tlast)}$, $AUC_{(0-\infty)}$, C_{max}, C_{24}, T_{max}, $T_{1/2}$, C_{last}, T_{last}, and $\%AUC_{ex}$ ○ Part 2: ▪ VH4004280 PK Concentrations, ▪ VH4004280 PK parameters: – First Dose (Day 1 or 2): C_{max}, t_{max} and any other PK parameters included in SDTM.PP – Last dose (Day 14 or 15): $AUC_{(0-\tau)}$, C_{max}, T_{max}, $T_{1/2}$and any other PK parameters included in SDTM.PP	○ Part 1: PK Concentrations & parameters: Summary statistics (e.g. geometric mean, median, mean, std, %CV, min, max etc.) by visit (only for concentrations) and dosing group. ○ Part 2: PK Concentrations & parameters: Summary statistics (e.g. geometric mean, median, mean, std, %CV, min, max etc.) by visit (only for concentrations) and dosing group.	Discontinuation of VH4004280 administration in part 2 will be addressed with **while on-treatment** strategy. No imputation will be done for missing data. For part 1 no relevant intercurrent events are anticipated. <u>Rationale:</u> Discontinuation of VH4004280 may bias the evaluation of Pharmacokinetic behavior of VH4004280 (PiB).
<u>Safety Objective:</u> To further assess the safety and tolerability of single (Part 1) and multiple (Part 2) doses of VH4004280 in healthy participants.	• Absolute values and change from Baseline in vital signs and ECG parameters ○ Absolute values and change from Baseline and maximum grade increase post-Baseline relative to Baseline for gradable lab	Safety analysis set • Summaries (e.g. mean, median, std etc.) of absolute values and change from Baseline values by visit and treatment arm[2] ○ Summaries (e.g. mean, median, std etc.) of absolute values and	<u>IE Strategy:</u> Discontinuation of study treatment: **treatment policy** strategy for part 2 (discontinuation of study treatment can't occur in parts 1 and 3 as participants receive only 1 dose). All available data will be used. No imputation will be done for missing data.

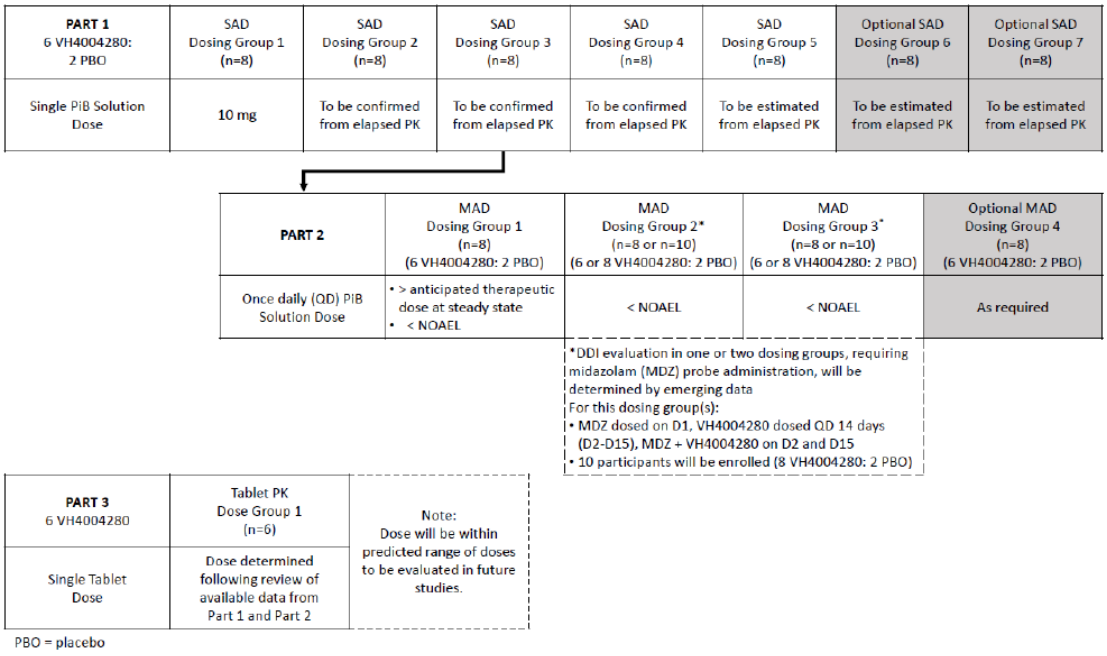
Objective	Estimand		
	Variable/Endpoint	**Population & Summary Measure**	**Intercurrent event (IE) strategy & rationale**
	hematology, coagulation and remaining chemistry parameters, or worst-case post-baseline changes from baseline with respect to normal range for non-gradable lab parameters including urinalysis	change from Baseline by visit and treatment arm, and number and percentage of participants with maximum grade increase relative to Baseline by treatment arm[2] for gradable lab parameters, or number and percentage of participants with worst-case post-baseline changes from baseline with respect to normal range for non-gradable lab parameters	For parts 1 and 3 no relevant intercurrent events are anticipated. <u>Rationale:</u> Interest lies to estimate safety effects likely to be attributable to VH4004280 irrespective of whether the participant completed the treatment.
CCI [redacted]			

Objective	Estimand		
	Variable/Endpoint	Population & Summary Measure	Intercurrent event (IE) strategy & rationale
CCI	[redacted]		

[1]In part 1 study treatment is VH4004280 or placebo, in part 2 is VH4004280 with or without midazolam or placebo and in part 3 is VH4004280
[2]Data summaries will be presented for each dosing group for VH4004280 and collectively from all dosing groups for placebo, within each part of the study

1.3. Study Design

Overview of Study Design and Key Features



Design Features	• Phase 1, First Time in Human study in healthy participants • Randomized, Placebo-Controlled (for parts 1 and 2), dose-escalation study • Double-Blind (Sponsor Unblinded) • A screening visit within 30 days prior to their first dose • Follow-up period will be approximately 11 weeks (inpatient Days -1 to 7) for participants in Part 1 (SAD) and Part 3 and approximately 13 weeks (inpatient Days -1 to 21) for participants in Part 2 (MAD) • Participants within each dosing group in Part 1 (SAD) will receive a single dose of VH4004280 (PiB) or placebo on Day 1, participants within each dosing group in part 2 will receive one dose daily of VH4224280 (PiB) or placebo for 14 days (Days 1-14) and participants in Part 3 will receive a single dose of VH4004280 (tablet) • Estimated last follow-up visit is on Day 49 for part 1 (SAD) and part 3 and Day 63 for part 2 (MAD) • Primary analysis will be at the End of Study (EoS)
Study intervention Assignment	Part 1 (SAD): It will be conducted in up to 7 ascending separate dosing groups. Within each dosing group, 8 participants will be randomized to receive a single dose of blinded VH4004280 (PiB) or blinded PBO (in a 6:2, active:PBO ratio) administered orally. At the start of each SAD dosing group, 2 of the total number of participants will serve as sentinel participants, with one receiving blinded VH4004280 and the other receiving blinded PBO. The proposed dosing schedule is designed to investigate single doses of

Overview of Study Design and Key Features	
	VH4004280 PiB in Part 1 and then, at a suitable cross-over point, begin repeated once-daily dosing of VH4004280 PiB in Part 2. Part 2 (MAD): It will be conducted in up to 4 ascending separate dosing groups. The starting dose in Part 2 (MAD) will be identified after preliminary PK data are evaluated in Part 1 (SAD). Within each dosing group each participant will be randomized to receive a once-daily (QD) dose of blinded VH4004280 (PiB) or blinded PBO (6:2) administered orally for 14 days. In up to two dosing groups (MAD/DDI dosing groups), participants will receive a single dose of midazolam on Days 1, 2 and 15 and daily doses of VH4004280 (PiB) or placebo (8:2) on Day 2 through to Day 15. A single dose of midazolam will be co-administered with a dose of VH4004280 (PiB) or PBO on Days 2 and 15. The MAD/DDI dosing group(s) will also include the collection of endogenous biomarker (coproporphyrin I) samples before and following repeat dose administration of VH4004280 (PiB) or PBO to investigate the potential of VH4004280 to inhibit OATP1B1/1B3. Part 3 (Tablet PK): It will be conducted in 1 dosing group. Participants will receive a single dose of VH4004280 tablet on Day 1 and will remain in the clinic until completion of the Day 7 procedures. They will return to the clinic on Days 14, 21, 28, 35, and 42 for follow up procedures and a final follow up visit on Day 49. The dose to be administered in Part 3 will be determined based on review of available data from previous dosing groups in Parts 1 (SAD) and 2 (MAD) and predicted clinical doses.
Interim Analysis	There will be no formal interim analysis. However, all preliminary safety, tolerability, and available pharmacokinetic data (including data from the dosing group in part 3) will be reviewed internally by the Safety and Dose Escalation Committee prior to each dose escalation and according to the dose escalation charter. Dose escalation can only occur after SDEC has found that the safety and PK profiles are supportive to proceed with the evaluation of the next dose level (see protocol Section 4.4 Safety and Dose Escalation Committee).

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses are to be tested. Study objective will be evaluated through descriptive summaries.

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be made.

3. ANALYSIS SETS

Table 2 Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	• All participants who signed the Informed Consent Form (ICF), passed screening and randomized in the study • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Safety	• All enrolled participants who take at least one full or partial dose of study treatment (i.e. VH4004280 or midazolam or placebo) • For VH4004280 PiB, participants who have taken either a full or part (i.e. CCI [redacted] of solution) dose will be included in the Safety analysis set • Participants will be analysed according to the treatment they actually received.	• Study Population • Safety
VH280 Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least one dose of VH4004280 tablet or have ingested at least one full dose (i.e. CCI [redacted]) of VH4004280 PiB and who had at least one non-missing VH4004280 PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	PK
MDZ Pharmacokinetic	• All participants in the Enrolled analysis set who received at least one dose of midazolam and have at least 1 non-missing midazolam or 1-hydroxymidazolam PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	PK

Analysis Set	Definition / Criteria	Analyses Evaluated
CP-1 Pharmacokinetic	• All participants in the Enrolled analysis set who have at least 1 non-missing Coproporphyrin I PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

If participants prematurely discontinue the study for non-safety reasons or intolerance to ingestion of the study drug (i.e., vomiting the solution shortly after ingestion), 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.

Confidence intervals for PK analyses will use 90% confidence levels, unless otherwise specified.

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.
- Categorical data: number and percentage of participants in each category.

PK values collected outside analysis visit windows (see OPS) will be excluded from the 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 visit windows). Lab values from any laboratory will be included in data summaries.

Within each part of the study, data will be summarised by dosing group for VH4004280 and collectively from all dosing groups for placebo, unless otherwise specified.

CCI [redacted]. Only selected listings required by regulatory agencies will be created in static fashion. See OPS for the list of selected listings.

4.1.2. Baseline Definition

For all endpoints, except for ECG, the baseline value will be the latest assessment with a non-missing value, including those from unscheduled visits, prior to either VH4004280 or midazolam administration. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose (of either VH4004280 or midazolam) and used as baseline.

Day 1 pre-dose ECGs for each dosing group will be performed in triplicate. In such case of triplicate measurement for pre-dose, the average will be used as baseline. In case one of the three assessments is missing, the average of the two available assessments will be used as baseline. In all other cases (e.g. when a single Day 1 pre-dose assessment is available, or Day 1 assessment is completely missing) the last pre-dose ECG assessment will be used as baseline.

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

4.2. Primary Endpoint(s) Analyses

Adverse Events (AEs)	The number and proportion of participants reporting AEs will be tabulated by dosing group for VH4004280 and collectively for Placebo. AEs will also be tabulated by severity grade and relationship to study drug. AEs will be tabulated using MedDRA preferred terms. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or relationship to study product. For part 2, AEs leading to study treatment (i.e. VH4004280 or midazolam or placebo) withdrawal will also be summarized by dosing group for VH4004280 and collectively for Placebo). In parts 1 and 3, discontinuation of study treatment can't occur as participants receive only 1 dose of study treatment. The analyses will be repeated for each part of the study.
Liver panel laboratory parameters	Liver panel data will be summarised by dosing group for VH4004280 and collectively for Placebo and by visit. Summary statistics (e.g. mean, median, std) for absolute values and change from baseline. Summaries of maximum grade increase relative to Baseline for graded lab parameters or summaries of worst-case post-baseline changes from baseline with respect to normal range for any non-gradable lab parameters will be presented. The analyses will be repeated for each part of the study.
PK for VH4004280 PiB	Summary statistics (e.g. geometric mean, median, %CV etc.) will be provided for the VH4004280 Pharmacokinetic concentrations and parameters per dosing group for VH4004280 in each part of the study. The analyses will be repeated for each part of the study.

4.2.1. Definition of endpoint(s)/estimands

- Adverse Events:
  - Number and percentage of participants with AEs
- Liver panel laboratory parameters (i.e. ALP, ALT, AST, total and direct bilirubin):
  - Absolute values
  - change from Baseline
  - Number and percentage of participants with maximum grade increase relative to Baseline (for DAIDS-graded lab parameters)
  - Number and percentage of participants with worst-case post-baseline changes from baseline with respect to normal range (for any non-gradable lab parameters)
- PK:
  - Part 1: $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}\infty)}$, C_{max}, C_{24}, T_{max}, $T_{1/2}$, C_{last}, T_{last}, $\%AUC_{ex}$ and CL/F
  - Part 2 dosing groups without midazolam administration:
    - Day 1 (first dose): C_{max}, t_{max} and any other PK parameters included in SDTM.PP
    - Day 14 (last dose): $AUC_{(0\text{-}\tau)}$, C_{max}, T_{max}, $T_{1/2}$ and any other PK parameters included in SDTM.PP
    -
  - Part 2 dosing groups with midazolam administration:
    - Day 2 (first dose): C_{max}, t_{max} and any other PK parameters included in SDTM.PP
    - Day 15 (last dose): $AUC_{(0\text{-}\tau)}$, C_{max}, T_{max}, $T_{1/2}$ and any other PK parameters included in SDTM.PP

For definition of estimands see Table 1.

4.2.2. Main analytical approach of primary Safety analyses

All primary safety analyses (i.e. AEs and liver panel lab parameter analyses) will be based on the Safety analysis set.

4.2.2.1. 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.

Analyses of adverse events (AEs), Serious AEs (SAEs), AEs leading to study treatment withdrawal and other significant AEs will be based on GSK Core Data Standards.

Summaries will be produced using all follow-up data from Day 1 (inclusive) available at the time of analysis. AEs occurring while participants received any study intervention

(i.e.VH400280 or Midazolam or placebo) and post study intervention (e.g. after participants stopped VH400280 or/and midazolam) will be summarised collectively. The following categories and subcategories of AEs will be summarised for each dosing group of VH4004280 and Placebo (collectively from all dosing groups) for each part of the study:

- AEs
  - Overall
  - By Maximum Grade
- AEs leading to withdrawal from study in part 1
- AEs leading to permanent discontinuation of study treatment (VH4004280 or midazolam or placebo) in part 2 or withdrawal from study
- Drug-related AEs
  - Overall
  - By Maximum Grade
- Drug-related Non-serious AEs
- Common (≥5%) non-Serious AEs
- SAEs
- Drug-related SAEs

Each summary display will contain the number and percentage of participants with the AE.

The Common (≥5%) non-Serious AEs display will include also the number of events of the AE.

AEs will be displayed by
- Column: Treatment arm or intensity.
- Row: in descending order by SOC and PT, or PT only, as applicable

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

For MAD/DDI dosing groups in part 2, summaries of AE tables will include AEs from Day 1 (when participants are on midazolam only) and from all subsequent days (when participants are on VH4004280 + midazolam, or VH4004280 only or receiving no treatment after the completion of VH4004280 and midazolam administration). No distinction between summaries of AEs recorded on Day 1 (midazolam only) and summaries of AEs from subsequent days will be provided. AEs with onset on Day 1 will be available through subject-level data CCI [redacted] (SAEs will also be available in the SAE listing; see OPS).

Tables of drug related AEs occurring in the part 2 MAD/DDI dosing groups will include AEs related to either VH4004280 or midazolam, as recorded in eCRF (there will be no distinction between AEs related to VH4004280 or related to midazolam).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the DAIDS (Version 2.1) grading table.

All planned AE displays are provided in the OPS document.

4.2.2.2. Liver panel laboratory analyses

The ADLB dataset will be used, which contains the data that is available at a particular timepoint, with no imputation for missing values. For each part of the study the following analyses on the liver panel laboratory parameters (i.e. ALP, ALT, AST, total and direct bilirubin) will be performed.

Absolute and change from baseline values for liver panel laboratory parameters will be summarised by dosing group of VH4004280 and Placebo (collectively from all dosing groups) at every assessed time point.

Laboratory toxicities will be graded according to the Division of AIDS (DAIDS) Criteria Version 2.1.

For liver panel lab tests that are gradable by DAIDS (e.g. ALT, AST), summaries of worst-case grade increase from baseline grade will be provided. These summaries 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.

For any liver panel lab tests that are not gradable by DAIDS (e.g. total protein), summaries of worst-case post-baseline changes from baseline with respect to normal range will be generated by treatment. The change categories are: to low, to normal or no change, and 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. If a subject has both a decrease 'To Low' and an increase 'To High', then the subject is counted in both the 'To Low' and 'To High' categories. If a subject was High at baseline and decreases to Low during the time interval, then the subject is counted in the 'To Low' category. If the low or high category (compared to normal) is not applicable for a liver lab parameter, then it will be excluded from the display.

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.

4.2.3. Main analytical approach of primary PK (VH4004280) analyses

Pharmacokinetic parameters for VH4004280 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 final 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 Table 1, in case of discontinuation of VH4004280 administration in part 2 of the study, only serum VH4004280 concentration data up to the time of discontinuation of VH4004280 will be used in derivation of VH4004280 PK parameters.

Table 3 Definition of primary PK parameters

Study Part	PK parameter	Definition
Part 1	$AUC_{(0-\infty)}$	Area under the plasma concentration time curve from time zero to infinity calculated as $AUC_{(0-\infty)} = AUC_{(0-t)} + C_{last}/\lambda z$
Part 2	$AUC_{(0-\tau)}$	Area under the plasma concentration vs time curve over a dosing interval from time of dosing to the time of the subsequent dose
Part 1 & 2	$\%AUC_{ex}$	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation calculated as $\%AUC_{ex} = [AUC_{(0-\infty)} - AUC_{(0-t)}]/AUC_{(0-\infty)} \times 100$
Part 1 & 2	C_{max}	Maximum observed plasma concentration
Part 1 & 2	T_{max}	Time to first occurrence of C_{max}
Part 1 & 2	$T_{1/2}$	Apparent terminal elimination phase half-life calculated as $\log_e 2/\lambda z$ where λz terminal phase rate-constant estimated by linear regression of logarithmically transformed concentration versus time data.
Part 1 & 2	$AUC_{(0-24)}$	Area under the plasma concentration vs time curve from time = 0 hours to time = 24 hours

Study Part	PK parameter	Definition
Part 1 & 2	$AUC_{(0\text{-}tlast)}$	Area under the plasma concentration vs time curve from time = 0 hours to the last observed quantifiable concentration
Part 1 & 2	C_{24}	Concentration at 24h Post-Dose
Part 1 & 2	C_{last}	Last observed quantifiable concentration in a concentration time course
Part 2	C_{τ}	Concentration at the end of the dosing interval at steady state
Part 1 & 2	T_{last}	Time of the last observed quantifiable concentration in a concentration time course
Part 1 & 2	CL/F	Apparent Clearance following oral administration

Note: Additional Parameters may be included as required

All primary pharmacokinetic analyses will be performed on the VH280 Pharmacokinetic analysis set.

4.2.3.1. Summaries of PK concentration values and PK parameters

In each part of the study, each pharmacokinetic concentration for VH4004280 at every scheduled time point will be summarized, as long as it's been collected within the PK sampling windows. PK concentrations sampled outside the PK sampling windows will be included in listings and in subject level figures but will not be included in summaries. The PK sampling windows are included in the OPS. The 95% confidence interval for the mean will be displayed.

All derived VH4004280 PK parameters will be summarised for each dosing group using descriptive statistics. The following summary measures will be used: geometric mean, 95% CI of geometric mean, standard deviation of the $\log_e$-transformed data (SD logs), between subject geometric coefficient of variation (%CV_b), arithmetic mean, 95% CI of arithmetic mean, sd, median, minimum, maximum.

In Part 2 of the study, PK concentrations or PK parameters derived after discontinuation of study treatment will be excluded from data summaries in accordance with the "while on-treatment" strategy for IE as described in Section 1.2.1.

In Part 2 of the study, if a participant does not take the full dose (i.e. CCI) of study treatment or miss a dose, any PK concentrations and PK parameters inferred within 24h from the partial or missed dose may be excluded from data summaries and statistical analyses, as appropriate.

The following figures will be produced:

- A by-subject graph of the concentration data over time, on linear and semi-logarithmic scales.
- Separate graphs of the mean and median concentration data over time, on linear and semi-logarithmic scales by dosing-group.

- Individual and box plot of PK parameters by dosing group

A by-subject listing of pharmacokinetic concentration values at each time point will be produced. All PK parameters will also be listed.

4.3. Safety Analyses

4.3.1. Safety endpoint(s)

Vital Signs	Post Baseline values and change from Baseline for vital signs (e.g. blood pressure) will be summarised by treatment (i.e. for each dosing group for VH4004280 and collectively for Placebo) and visit for each part of the study. Proportion of participants with worst case post-Baseline vital signs relative to Baseline will be presented.
ECG	Post Baseline values and change from Baseline for ECG parameters (e.g. QTc, PR, QRS) will be summarised by treatment (i.e. for each dosing group for VH4004280 and collectively for Placebo) and visit for each part of the study. Proportion of participants with increase in QTc relative to Baseline will be presented.
Hematology, coagulation, urinalysis and remaining chemistry panel laboratory parameters	Post Baseline values and change from Baseline for hematology, coagulation (e.g. PT, PTT, INR), urinalysis and remaining chemistry laboratory parameters will be summarised by treatment (i.e. for each dosing group for VH4004280 and collectively for Placebo) and visit for each part of the study. Summaries of maximum grade increase relative to Baseline for graded lab parameters or summaries of worst-case post-baseline changes from baseline with respect to normal range for non-gradable lab parameters will be presented.

4.3.1.1. Definition of endpoint(s)/estimands

Refer to Table 1 in Safety Objective section.

4.3.1.2. Main analytical approach

All safety analyses will be performed on the Safety analysis set. The following analyses will be performed for each part of the study.

Vital Signs

Values of vital signs (temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and pulse oximetry) and change from baseline will be summarized by scheduled visit and treatment.

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 by treatment. 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 within range baseline value.

All vital signs data for participants with at least one value of potential clinical importance will be included in a listing.

PCI values for vital signs and all vital signs displays are included in the OPS.

ECG

Values of ECG parameters (heart rate, PR, QRS, QT, and QTc intervals) and change from baseline will be summarized by scheduled visit and treatment.

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

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

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

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced. The figure will have reference lines at 480 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45-degree line), at equality plus 30 msec, and at equality plus 60 msec.

All ECG data for participants with a value of potential clinical importance will be included in a listing.

PCI values for ECG and all ECG displays are included in the OPS.

Hematology, coagulation, urinalysis and remaining chemistry lab parameters

The ADLB dataset will be used, which contains the data that is available at a particular timepoint, with no imputation for missing values.

Absolute and change from baseline values for hematology, coagulation, urinalysis (e.g. specific gravity) and remaining (non-primary) chemistry laboratory parameters will be summarised by treatment at every assessed time point. For urinalysis parameters assessed with the dipstick method (categorical parameters), number and percentage of participants in each outcome category will be summarised at every assessed time point.

For graded lab parameters by DAIDS, the number of participants with laboratory results will be summarized by laboratory test, treatment and maximum grade increase. The maximum grade increase categories and maximum increase subtotals will be included in the display (same as for liver lab parameters in Section 4.2.2.2). 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. Check Section 4.2.2.2 for more details (analysis is the same as for graded liver panel lab parameters).

For lab parameters which are not graded by DAIDS, the number of participants with worst case laboratory results relative to normal range criteria which are post-baseline relative to baseline will be summarized by laboratory test and category. Check Section 4.2.2.2 for more details (analysis is the same as for non-graded liver panel lab parameters).

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

Listings of hematology, coagulation, urinalysis and chemistry laboratory data will be created. The hematology, coagulation and chemistry listings will include only participants with at least one abnormal lab value (i.e. DAIDS grade ≥1 or outside normal range) in any lab parameter within each lab data category. 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. All lab parameters at all visits will be listed for the participants included in the listing.

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

4.3.2. Other Safety Analyses

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

4.3.2.1. Extent of Exposure

For parts 1 and 3 of the study each participant receives a single dose. Therefore, no summaries of extent of exposure or cumulative dose will be generated for parts 1 and 3.

Extend of exposure to VH4004280 or placebo will be summarised for part 2. Number of days of exposure will be calculated based on the formula:
Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1

For MAD/DDI dosing groups in part 2, treatment start and stop dates refer to VH4004280 or placebo; administration of midazolam is not considered in calculation of exposure.

Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

The cumulative dose will be based on the formula:
Cumulative Dose = Sum of (Number of Days x Total Daily Dose)

If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

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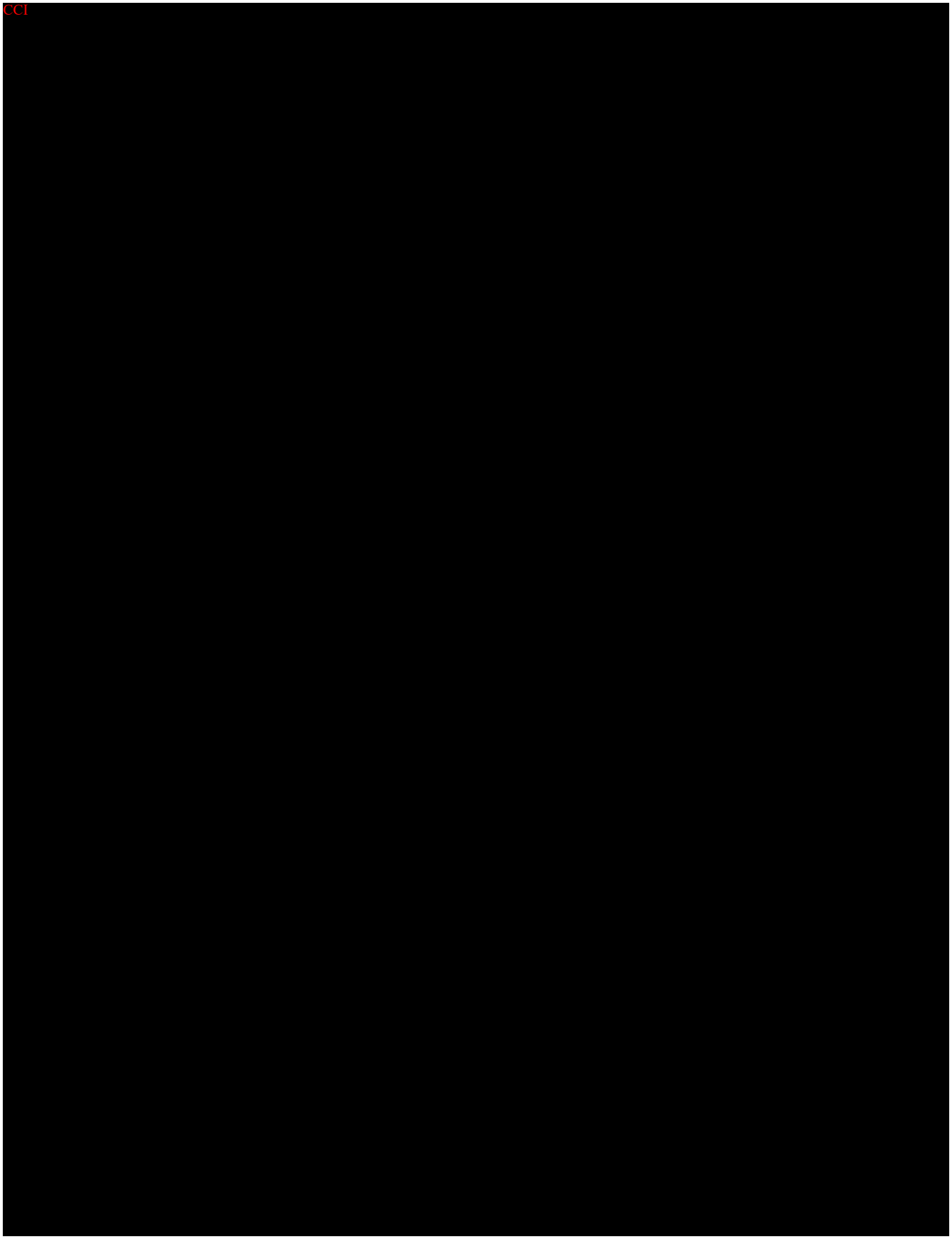

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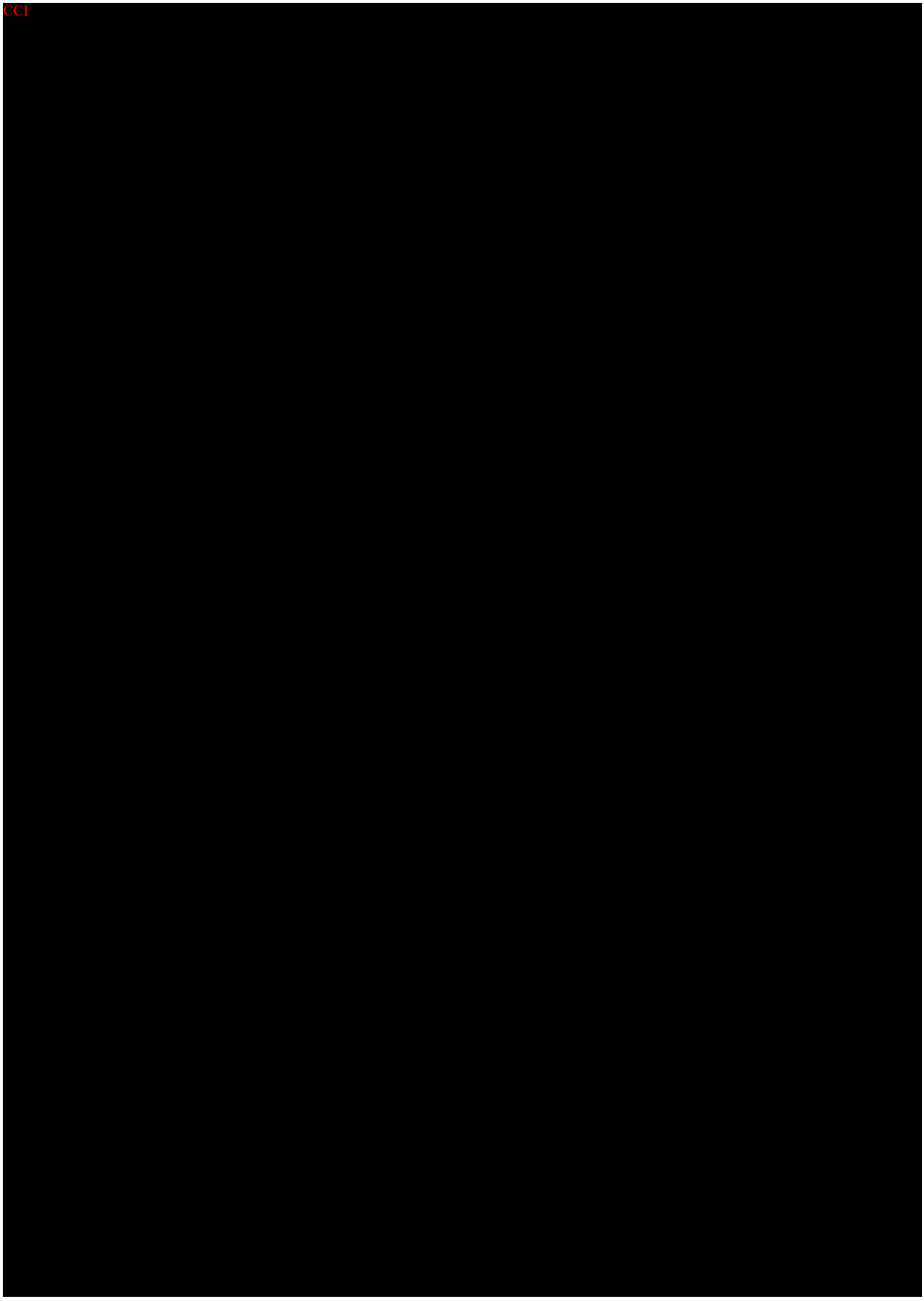

4.5. Other Analyses

4.5.1. Subgroup Analyses

No subgroup analyses are planned.

4.5.2. Other Pharmacokinetic Analyses

All other pharmacokinetic analyses will be performed on the VH280 Pharmacokinetic analysis set.

For other pharmacokinetic statistical analyses on part 2:

- PK parameters derived after discontinuation of study treatment will be excluded from statistical analyses in accordance with the "while on-treatment" strategy for IE as described in Section 1.2.1.
- If a participant does not take the full dose (i.e. [redacted]) of VH4004280 or miss a dose, any PK concentrations and PK parameters inferred within 24h from the partial or missed dose may be excluded from the statistical analyses, as appropriate.

4.5.2.1. Dose Proportionality Assessment

Dose proportionality will be assessed in Part 1 of the study. If required, dose proportionality may be assessed in Part 2 of the study.

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 SAD part: $AUC_{(0-\infty)}$ (AUC_{0-t} may be used if required), C_{max}
• For MAD part:
  ○ First dose (Day 1 or 2): C_{max}, AUC_{0-24}
  ○ Last dose (Day 14 or 15): C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$

Model Specification
• Dose proportionality of VH4004280 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 below: $$log_e y = log_e \alpha + \beta log_e dose$$ • Data from all available doses in each part of the study will be considered.
Model Results Presentation
Table: Estimates of slope β will be reported in a Table along with corresponding 90% confidence intervals. Figure: Comparative plots will be provided showing individual subject values by treatment (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.

The PK parameter (e.g. $AUC_{(0-\infty)}$, C_{max}) will be dose-normalised prior to $\log_e$-transformation 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 dose and will also include the geometric mean and 95% CI for each dose.

Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment (dose) for PK parameters together with 90% confidence interval.

4.5.2.2. Estimation of Accumulation Ratios in MAD

Accumulation ratios will be estimated in Part 2. These are defined as the ratio of last dose (Day 14 or 15) to first dose (Day 1 or 2) PK parameters as follows:

$$R\left(AUC_{(0-\tau)}\right) = \frac{AUC_{(0-\tau)} \text{ on Day } 14}{AUC_{(0-\tau)} \text{ on Day } 1},$$

$$R(C_{max}) = \frac{C_{max} \text{ on Day } 14}{C_{max} \text{ on Day } 1},$$

$$R(C_{\tau}) = \frac{C_{\tau} \text{ on Day } 14}{C_{\tau} \text{ on Day } 1},$$

The analysis will be based on the available $AUC_{(0-\tau)}$, C_{max} and C_{τ} PK parameters. No imputation will be done for such missing PK parameters for any participant.

To estimate the accumulation ratios for each dose in part 2, a mixed-effects ANOVA model will be used on the loge-transformed PK parameters ($AUC_{(0-\tau)}$, C_{max} and C_{τ}), 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 of VH4004280 will be estimated by calculating the ratio of the geometric least squares (GLS) means of PK parameters between last dose (Day 14 or 15) and first dose (Day 1 or 2) and the corresponding 90% CI. The GLS means of $AUC_{(0-\tau)}$, C_{max} and C_{τ} on first dose (Day 1 or 2) and last dose (Day 14 or 15), along with the estimated accumulation ratio and its 90% CI will be displayed.

4.5.2.3. Assessment of attainment of steady state in MAD

To estimate the attainment of steady state for each dose in part 2, a mixed-effects ANCOVA model will be used on the $\log_e$-transformed C0 and C_{τ}, with a random intercept (for each participant) and fixed effect for the day. Day will be treated as a continuous variable in the model. The Kenward & Roger (KR2) degrees of freedom approach will be used [Kenward & Roger, 2009]. Achievement of plasma VH4004280 steady state will be assessed by visual inspection of plots of C0 (from days 2 through 14 or from days 3 through 15) and Cτ (from day 15 or 16) by day and by calculating the point estimate and 90% CI of the slope of the linear regression of C0 and Cτ versus day for Days 2-15 or for 3-16. To claim that steady state is reached, the pre-dose concentration slope estimate should be close to zero or the 90% CI for the slope estimate should include zero.

The same analysis will be repeated by dropping one earlier day at time until at least the last 3 pre-dose concentrations remain. The results will be presented in the same table.

In addition, as mentioned above, C0 on Day 2 through 14 or Day 3 through 15 for the part 2 MAD/DDI dosing groups and Cτ on day 15 or 16 (for MAD/DDI) will be plotted versus day by dose.

For each of the statistical models in Section 4.5.2.1 –Section 4.5.2.3, distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

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

4.6. Interim Analyses

There will be no formal interim analysis. However, all preliminary safety, tolerability, and available pharmacokinetic data (including data from the dosing group in part 3) will be reviewed internally by the Safety and Dose Escalation Committee (see protocol Section 4.4) prior to each dose escalation and according to the dose escalation charter. Safety (AEs, vital signs, clinical laboratory findings, ECG) and PK data will be reviewed by the PI and ViiV/GSK study team after completion of each dose level. Dose escalation can only occur after PI and ViiV/GSK study team has found that the safety and PK profiles are supportive to proceed with the evaluation of the next dose level.

Additional data cuts and analyses may be conducted to support regulatory needs, publications or for other purposes, if needed. Criteria for data quality for data released for these purposes will be described in the study data management plan.

At each dose, the Bayesian probability of any individual exceeding the Cmax threshold in Part 1 and the Bayesian probability of any individual exceeding either the Cmax or $AUC_{(0\text{-}24)}$ (on day 14) threshold in Part 2, among the individuals planned to receive the next dose will be calculated. This probability, together with safety, tolerability and other PK data will be used by SDEC for dose escalation. The Bayesian probability will be based on Whitehead's model shown below [Whitehead, 2001] using non-informative prior for model parameters.

$$y_i = \theta_1 + \theta_2 \, d_i + \epsilon_i$$

Where y_i is log-PK of i-th participant, d_i is the log-dose administered to the i-th participant. θ_1 and θ_2 are population intercept and slope, respectively, and ϵ_i is the random error of the i -th participant.

For the prediction of the second dose in Part 1 and Part 2, θ_2 will be assumed to equal 1 (representing a dose proportionality assumption). This will allow for the estimation of the remaining parameters of the model using data from only one dose level. After the second dose, θ_2 will be estimated by the data.

5. SAMPLE SIZE DETERMINATION

Sample size for all parts of the study is based on feasibility and no formal calculation of power or sample size has been performed. A sample size of approximately 6-8 active and 2 placebo participants per dosing group should be sufficient to provide useful estimates of both inter- and intra- participant variability for VH4004280 PK parameters and initial safety assessment.

Although the sample size is not based on statistical criteria, general probabilities can be determined for the likelihood of observing AEs. With 6 or 8 active participants per dosing group, if the true rate of an adverse event is 5%, the chance of seeing at least 1 participant with the adverse event for a given dosing group is 26% or 34%, respectively. Similarly, if the true adverse event rate is 20%, the chance of seeing at least 1 participant with the adverse event for a given dosing group is 74% or 83%, respectively.

For further details on sample size and sample size sensitivity see Section 9.6 in the protocol.

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, and exposure and treatment compliance 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 of participants who enrolled or failed screening will be provided. A summary of the number and percentage of participants who failed screening overall and by screen failure reason will be provided.

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

For part 2, 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. In parts 1 and 3, study treatment discontinuation is not possible as participants receive only 1 dose of study treatment.

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

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6.1.2. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance to 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 for each part of the study 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 and listings of important protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

6.1.3. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, race, height and weight 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.

All Demographic characteristics listings are described in the OPS.

6.1.4. Concomitant Medications and Current Medical Conditions

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.

Medical occurrences beginning after obtaining informed consent but before the start of study drug will be recorded as current medical conditions, not as AEs, CCI [redacted]

6.1.5. Subject Disposition & Study Treatment Discontinuation

Tables “Summary of Subject Status and Subject Disposition for the Study Conclusion Record” and “Summary of Treatment Status and Reasons for Discontinuation of Study Treatment” will be repeated, with the reason for study withdrawal and study treatment discontinuation, respectively, categorized as due to the COVID-19 pandemic, or non-due to the COVID-19 pandemic based on information collected on the COVID-19 Pandemic Study Impact eCRF page. The summaries will be based on GSK Core Data Standards and details are provided in the OPS.

6.1.6. Protocol Deviations

In addition to the overall summary of important protocol deviations, separate summaries will be produced of important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19. PDs related to COVID-19 pandemic will have the standard text “COVID-19: ” as prefix. Important protocol deviations related to COVID-19 will be included in the Listing of Important protocol deviations.

The listing of important protocol deviations will be based on GSK Core Data Standards and details are provided in the OPS.

6.1.7. Additional COVID-19 Assessments

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable or confirmed COVID-19 infection

among participants with a COVID-19 reported Adverse Event, and of COVID-19 test results will be summarized.

COVID-19 tables will be based on GSK Core Data Standards.

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6.2. Appendix 2 Abbreviations and Trademarks

6.2.1. Abbreviations

AE	Adverse Event
CP-1	Coproporphyrin I
DAIDS	Division of AIDS
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
MAD	Multiple Ascending Dose
MDZ	Midazolam
PCI	Potential Clinical Importance
PK	Pharmacokinetic(s)
QD	Once daily
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
SAD	Single Ascending Dose
SAE	Serious Adverse Event
VH	ViiV Healthcare group of companies

Trademarks

Trademarks of ViiV Healthcare
None

Trademarks not owned by ViiV Healthcare
WinNonlin

7. REFERENCES

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