STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1, Open-label, Multicohort Study to Evaluate the Impact of Inhibitors and Inducers of Cytochrome P450 Enzyme (CYP)3A and/or P-glycoprotein (P-gp) on the Pharmacokinetics (PK) of Vesatolimod (VES) in Virologically Suppressed Adults With HIV-1 on Antiretroviral Therapy (ART)
Study Phase:	1
Name of Test Drug:	Vesatolimod
Study Number:	GS-US-382-1587
Protocol Version (Date):	Amendment 3 (12 December 2022)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	19 January 2024
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
TABLE OF CONTENTS 2
LIS OF IN-TEXT TABLES 3
LIST OF IN-TEXT FIGURES 3
LIST OF ABBREVIATIONS 4
PHARMACOKINETIC ABBREVIATIONS 5
1. INTRODUCTION 6
1.1. Study Objectives and Endpoints 6
1.2. Study Design 6
1.3. Sample Size and Power 11
2. TYPE OF PLANNED ANALYSIS 12
2.1. Interim Analysis 12
2.2. Final Analysis 12
2.3. Changes from Protocol-Specified Analysis 12
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 13
3.1. Analysis Sets 13
3.1.1. All Enrolled Analysis Set 13
3.1.2. Safety Analysis Set 13
3.1.3. Pharmacokinetic Analysis Sets 13
3.2. Strata and Covariates 13
3.3. Examination of Participant Subgroups 13
3.4. Multiple Comparisons 13
3.5. Missing Data and Outliers 14
3.5.1. Missing Data 14
3.5.2. Outliers 14
3.6. Data Handling Conventions and Transformations 14
3.7. Visit Definitions 16
3.7.1. Definition of Predose, Postdose, and Study Day 16
3.7.2. Analysis Visits 16
3.7.3. Selection of Data in the Event of Multiple Records on the Same Day 17
4. PARTICIPANT DISPOSITION 18
4.1. Participant Enrollment and Disposition 18
4.2. Extent of Exposure 18
4.3. Protocol Deviations 19
4.4. Assessment of COVID-19 Impact 19
4.4.1. Study Drug or Study Discontinuation Due to COVID-19 19
4.4.2. Protocol Deviations Due to COVID-19 19
4.4.3. Missed and Virtual Visits due to COVID-19 19
4.4.4. Adverse Events Due to COVID-19 19
5. BASELINE CHARACTERISTICS 20
5.1. Demographics and Baseline Characteristics 20
5.2. Other Baseline Characteristics 20
5.3. Medical History 20
6. EFFICACY ANALYSES 21

7. SAFETY ANALYSES 22
7.1. Adverse Events and Deaths 22
7.1.1. Adverse Event Dictionary 22
7.1.2. Adverse Event Severity 22
7.1.3. Relationship of Adverse Events to Study Drug 22
7.1.4. Relationship of Adverse Events to Study Procedure 22
7.1.5. Serious Adverse Events 22
7.1.6. Treatment-Emergent Adverse Events 22
7.1.6.1. Definition of Treatment Emergent Adverse Events 22
7.1.6.2. Incomplete Dates 23
7.1.7. Summaries of Adverse Events and Deaths 23
7.1.8. Additional Analysis of Adverse Events 24
7.2. Laboratory Evaluations 24
7.2.1. Summaries of Numeric Laboratory Results 25
7.2.2. Graded Laboratory Values 25
7.2.2.1. Treatment-Emergent Laboratory Abnormalities 25
7.2.2.2. Summaries of Laboratory Abnormalities 25
7.3. Body Weight, Height, BMI, and Vital Signs 26
7.4. Prior and Concomitant Medications 26
7.5. Electrocardiogram Results 26
7.5.1. Investigator Electrocardiogram Assessment 27
7.6. Other Safety Measures 27
8. PHARMACOKINETIC EVALUATION/ANALYSIS 28
8.1. Estimation of Pharmacokinetic Parameters 28
8.2. Pharmacokinetic Parameters 28
8.3. Statistical Analysis Methods 29
8.3.1. General Considerations 29
8.3.2. Statistical Methodology 31
8.3.2.1. Analysis of Drug-Drug Interaction 31
8.4. Sensitivity Analysis 32
9. REFERENCES 33
10. SOFTWARE 34
11. SAP REVISION 35
12. APPENDICES 36

LIS OF IN-TEXT TABLES

Table 8-1. Study Treatments and Associated Analytes 28
Table 8-2. Pharmacokinetic Parameters for Each Analyte in Plasma 29
Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses 31
Table 12-1. Study Procedures Table for Cohort 1, Period 1 and 2 37
Table 12-2. Study Procedures Table for Cohort 1, Period 3 40
Table 12-3. Study Procedures Table for Cohort 2, Periods 1 and 2 42
Table 12-4. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits 46

LIST OF IN-TEXT FIGURES

Figure 1. Study Schema 7

LIST OF ABBREVIATIONS

AE	adverse event
ART	antiretroviral therapy
BCRP	breast cancer resistance protein
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
COBI	Cobicistat
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
d-RFB	25-O-desacetylrifabutin
DAIDS	Division of Aids
DMC	data monitoring committee
ECG	Electrocardiogram
ET	early termination
FBX	Febuxostat
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	preferred term
Q1, Q3	first quartile, third quartile
RFB	Rifabutin
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units (Systeme International d'Unites)
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TOST	two one-sided tests
ULN	upper limit of normal
VES	Vesatolimod
VOR	Voriconazole
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable plasma concentration of the drug
C_{max}	maximum observed plasma concentration of drug
C_{trough}	observed plasma concentration of drug at the end of the dosing interval
$t_{½}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z/F	apparent volume of distribution of the drug $V_z/F = Dose/(\lambda_z * AUC_{inf})$, where "Dose" is the dose of the drug

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-382-1587. This SAP is based on the study protocol Amendment 3 dated 12 December 2022 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

1.1. Study Objectives and Endpoints

Primary Objective(s)	Primary Endpoint(s)
To evaluate the impact of the following drugs on VES PK • Cobicistat (P-gp, BCRP, and strong CYP3A inhibitor) • Voriconazole (strong CYP3A inhibitor) • Rifabutin (moderate CYP3A inducer) To evaluate the safety of VES administered alone and in combination with inhibitors and inducers of metabolizing enzymes and transporters involved in VES disposition	Primary PK parameters throughout the study • VES AUC_{last}, AUC_{inf}, C_{max} Secondary PK parameters throughout the study • VES $\%AUC_{exp}$, T_{max}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, V_z/F Safety parameters • Incidence of TEAEs and laboratory abnormalities throughout the study
CCI [redacted]	[redacted]
[redacted]	[redacted]

1.2. Study Design

This is an open-label, multicohort Phase 1 study to evaluate the impact of inhibitors and inducers of CYP3A and/or P-gp on the PK and PD of VES in virologically suppressed adults with HIV-1 on antiretroviral therapy (ART).

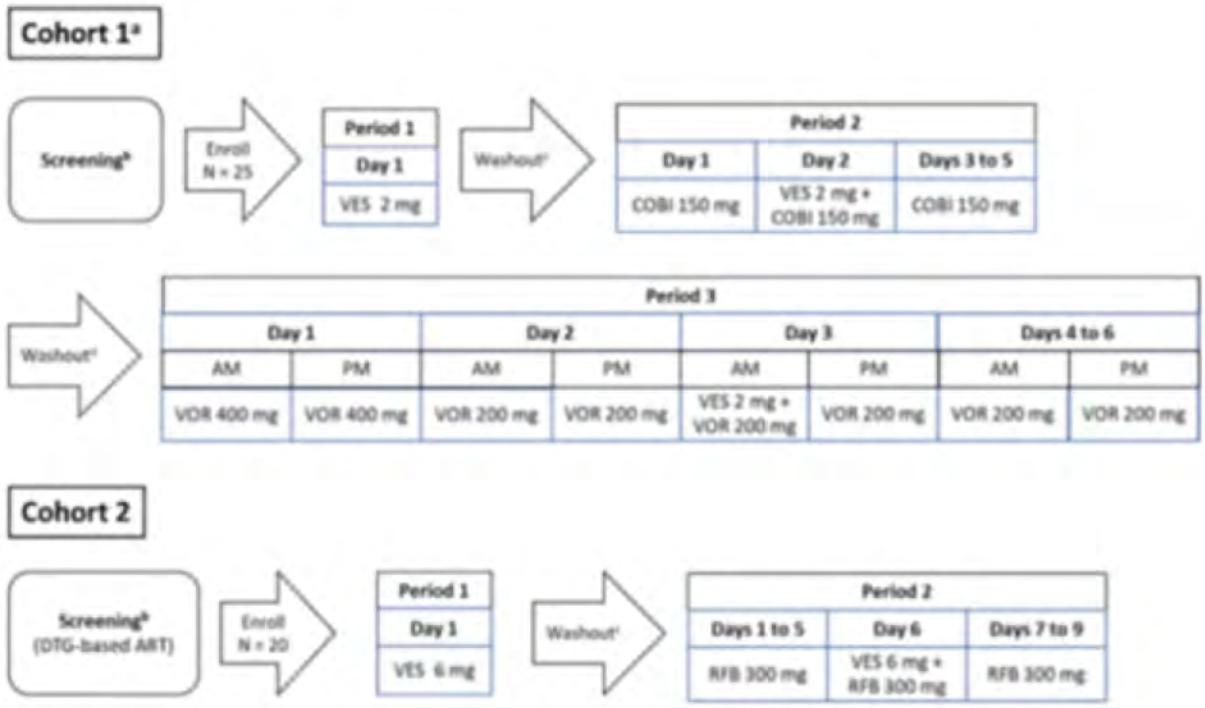
The study will be conducted in 2 cohorts:

- Cohort 1: An open-label, single sequence cohort to evaluate the impact of cobicistat (COBI; P-gp, BCRP, and strong CYP3A inhibitor) and voriconazole (VOR; strong CYP3A inhibitor) on VES PK and PD
- Cohort 2: An open-label, single sequence cohort to evaluate the impact of rifabutin (RFB; moderate CYP3A inducer) on VES PK and PD

A safety review team will assess relevant and available safety data for the first 3 participants in Cohort 1 who are dosed with COBI (up to and including Period 2 Day 3) before initiation of any additional participants in Cohort 1.

The study schema for each cohort is shown below in Figure 1.

Figure 1. Study Schema



ART = antiretroviral therapy; COBI = cobicistat; DTG = dolutegravir; RFB = rifabutin; SRT = safety review team; VES = vesatolimod; VOR = voriconazole

a An SRT review of the available safety data after the first 3 participants who are dosed with COBI in Cohort 1 up to and including Period 2 Day 3 should occur before initiation of the rest of the cohort.
b Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.
c Washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1.
d Washout of period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1

Pharmacokinetic Assessments

Plasma PK:

Plasma samples for quantification of VES concentrations will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose

Plasma concentrations of COBI, VOR, and RFB may be determined and PK parameters may be estimated.

Time windows allowed for PK samples to be collected are provided in Table 8 of the study protocol.

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the electronic data capture (EDC) system.

Biomarker Testing

Biomarker samples will be collected to assess the PD and safety following VES administration.

Serum samples for biomarker assessments will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours postdose

The serum biomarkers to be evaluated may include (but not limited to): interferon-alpha (IFN-α), interleukin (IL)-1 receptor antagonist, interferon-gamma inducible protein-10, interferon-inducible T cell alpha chemoattractant, interferon-gamma, IL-1 beta, IL-6, tumor necrosis factor alpha, and C-reactive protein.

Whole blood samples for ISG mRNA expression (including, but not limited to, MX1, ISG15, OAS1) will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose

Whole blood for immune cell phenotyping will be collected at the following time points relative to VES dosing in each period

- Predose (within 0.5 hours before dosing) and 24, 72, and 96 hours postdose

Whole blood to evaluate VES TruCulture cytokine response will be collected for Cohort 2 at the following visit in Period 1

- On Day 1 (predose)

A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the EDC system.

Pharmacogenetic Assessments

A pharmacogenetics (PGx) sample will be collected on Day 1 Period 1 if applicable (preferably) or at any other time during the study for toll-like receptor 7 (TLR7) and BCRP (also known as the adenosine triphosphate-binding cassette transporter G2; gene symbol *ABCG2*) genotyping.

Cohort 1 (only): A PGx sample for CYP2C19 genotyping will be collected at screening as part of the inclusion/exclusion criteria.

Safety Assessments

Safety assessments will include a complete and symptom-driven physical examination, vital signs, height, weight, clinical laboratory tests, urine drug and alcohol assessments, 12-lead electrocardiogram (ECG), pregnancy testing, HBV and HCV testing, HIV-1 viral load test, CD4 cell count test, SARS-CoV-2 test, and assessment of AEs.

All safety assessments will be completed predose unless otherwise specified.

- *Complete physical examination:* Screening, follow-up, and early termination (ET) visits, if applicable
- *Symptom-driven physical examination:* every day during confinement, as needed, based on reported signs and symptoms
- *Vital signs (blood pressure, heart rate, oxygen saturation, and body temperature):*
  - Cohort 1: Screening, Period 1 Day 1 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 2 Day 2 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 3 Day 3 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Period 1 Day 1 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 2 Day 6 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; at the follow-up visit, and at the ET visit, if applicable
- *Height:* Screening
- *Weight:*
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 6, Period 3 Day 7, at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 10, at the follow-up visit, and at the ET visit, if applicable

- Coagulation panel: Screening
- Clinical laboratory tests (hematology, chemistry, calculated creatinine clearance, and urinalysis):
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 6, Period 3 Day 7, at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 10, at the follow-up visit, and at the ET visit, if applicable
- Urine drug and alcohol assessments:
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 3, Period 2 Day 4, and Period 3 Day 5
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 3, and Period 2 Day 8

  Note: On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1.

  If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
- 12-lead ECG:
  - Cohort 1: Screening; Period 1 Days 1, 2, and 5; Period 2 Days 2, 3, and 6; Period 3 Days 3, 4, and 7
  - Cohort 2: Screening, Period 1 Days 1, 2, and 5; and Period 2 Days 6, 7, and 10
- *Serum or urine pregnancy test (participants assigned female at birth of childbearing potential only):* Screening (serum), Day −1 of each period (serum or urine), at the follow-up visit (urine), and at the ET visit (urine), if applicable. For Cohort 2 only, an at-home urine pregnancy test will be completed 10 days after the last dose of RFB. Participants will be contacted by telephone to report at-home pregnancy test results.

  Note: Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required.
- Follicle-stimulating hormone (participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12months but do not have documentation of ovarian hormonal failure): Screening
- Hepatitis B virus, hepatitis C virus: Screening

- HIV-1 viral load testing:
  - Cohort 1: Screening, and Day −1 of Period 2 and Period 3
  - Cohort 2: Screening and Day −1 of Period 2
- CD4 cell count: Screening
- SARS-CoV-2: Day −1 of each period
- Assessment of AEs and concomitant medications will continue throughout the study. All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Additional details regarding study assessments can be found in Appendix 1.

1.3. Sample Size and Power

With 18 evaluable participants per cohort, the estimated 2-sided 90% CI of the GLSM ratio of test versus reference treatments with regards to AUC_{inf} and C_{max} will be within (0.50, 2.00) with at least 90% probability if the true GLSM ratio was 1.0. This is assuming a root mean square error of no more than 0.6 on a natural logarithm scale, which is supported by the previous Study GS-US-234-0101. With 35% and 10% overage for Cohorts 1 and 2, a total sample size of 25 participants and 20 participants will be required for Cohorts 1 and 2; respectively.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program.

A safety review team (SRT) will be established to assess relevant and available safety data for the first 3 participants in Cohort 1 who are dosed with COBI (up to and including Period 2 Day 3) to decide to continue or halt enrollment of additional participants in Cohort 1.

2.2. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint will be conducted at the time of the final analysis.

2.3. Changes from Protocol-Specified Analysis

25 participants were planned for Cohort 1. Due to slow enrollment, Cohort 1 was closed after 15 participants enrolled in the cohort.

Rifabutin is a moderate CYP3A inducer, and plasma VES exposures were expected to decrease when co-administered with RFB. However, based on interim PK results from 2 participants, VES exposure was increased when co-administered with RFB. Given this finding, Cohort 2 was closed to further enrollment.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-participant listings will be presented for all participants in the All Enrolled Analysis Set, and sorted by participant identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within participant. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be provided in the disposition table as detailed in Section 4. A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants who received a study participant identification number in the study after screening. This is the primary analysis set for safety listings.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.3. Pharmacokinetic Analysis Sets

The PK Analysis Sets will include all enrolled participants who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory for the corresponding analytes. These are the primary analysis sets for all PK analyses.

3.2. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling participants.
No covariates will be included in the analyses.

3.3. Examination of Participant Subgroups

There are no prespecified participant subgroupings for analyses.

3.4. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document. Missing PK sampling dates may be imputed based on other visit information. Missing PK sampling times may be imputed to nominal times. Missing drug concentrations will not be imputed.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2.

3.5.2. Outliers

Outliers of non-PK data will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

Individual study drug concentration values may be identified as outliers by the clinical pharmacokineticist and excluded from concentration summary tables and figures and from the noncompartmental PK analysis. Outlier drug concentrations will be identified in the concentration listing along with the justification for exclusion.

3.6. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled participant was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For participants without an enrollment date, the date when the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK Data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ at the same precision level of the originally reported value will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or <0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as the bullet point above.
- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ).

Data Handling for PK Summaries

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithmic transformation will be used for analyzing non-BLQ concentrations and PK parameters. Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes. The number of samples will be summarized to reflect the actual number of samples assessed at that time point.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of summary and order statistics for postdose time points:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

Concentration related PK parameters (eg, C_{max}) that are BLQ will be excluded before log transformation or statistical model fitting and displayed as described above.

3.7. Visit Definitions

3.7.1. Definition of Predose, Postdose, and Study Day

Predose value is defined as the last available off-treatment value collected prior to the first dose of study drug. This definition will be used when only one predose is available for a given parameter. When a predose value is available for each period, each predose value will be used for change from predose calculations.

Postdose value is defined as any value collected after the first dose of study drug, or after the dose in each period, as applicable.

Study Day will be calculated from date of first dose of study drug administration in the first period and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date in the first period + 1
- For days prior to the first dose: Assessment Date – First Dosing Date in the first period

Therefore, study day 1 is the day of first dose of study drug administration in the first period

Treatment Day is the day relative to the first dose of study drug administration in each period. Treatment Day 1 will be defined as the first dosing date of study drug in each period.

Treatment Day will be calculated from the date of first dose of study drug administration in each period and derived as follows:

- For postdose study days: assessment date – first dosing date in each period + 1
- For days prior to the first dose: assessment date – first dosing date in each period.

3.7.2. Analysis Visits

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in summaries. However, the following exceptions will be made:

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of predose value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postdose toxicity grade.
- For participants who discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination Visit".

3.7.3. Selection of Data in the Event of Multiple Records on the Same Day

Depending on the statistical analysis method, single values may be required for each day. For example, change from predose by visit usually requires a single value.

If multiple valid, nonmissing observations exist on a day, records will be chosen based on the following rules if a single value is needed:

- For predose, the last available non-missing record on or prior to the date and time of the first dose of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the predose value will be the average (arithmetic or geometric mean, as appropriate) of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.
- For postdose values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates first participant enrolled, last participant enrolled, last participant last visit for PK assessment, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment and disposition will be provided by cohort and overall. This summary will present the number of participants enrolled, and the number and percentage of participants in each of the categories listed below. For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of participants enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set for each column.

- Safety Analysis Set
- PK Analysis Set for each analyte
- Completed study drug
- Did not complete study drug with reason for premature discontinuation of study drug
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

In addition, the total number of participants who were enrolled, and the number of participants in each of the disposition categories listed above will be displayed in a flowchart.

The following by-participant listings will be provided by participant identification (ID) number in ascending order to support the above summary tables:

- Participants who discontinued study drug

A by-participant listing of participant disposition including cohort, date of the last dose of study drug(s) (study day), last period/day, study drug completion status, reason for study drug discontinuation, study completion status, reason for study discontinuation, and PK set status (indicating whether or not a participant is included in a PK analysis set) will be provided by Participant ID number in ascending order.

4.2. Extent of Exposure

A participant's extent of exposure to study drug data and fasting status data will be generated from the study drug administration page in the eCRF. Exposure, fasting status, and meal administration (if applicable) data will be listed.

4.3. Protocol Deviations

A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 violation) that participants did not meet and related comments, if collected.

Important protocol deviations occurring after participants entered the study are documented during routine monitoring. Any important deviations identified will be included in a by-participant listing, and evaluated to determine if it justifies excluding the participant from any analysis sets.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants might have been unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Section 12.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], and body mass index [BMI; in kg/m^2]) will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. For baseline body weight, height, and BMI, descriptive statistics will also be presented by sex in the same table. The summary of demographic data will be provided for the All Enrolled Analysis Set.

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

A by-participant listing of CP2C19 genotype and BCRP genotype data will be provided.

5.3. Medical History

Medical history data will be collected at screening and listed only. General medical history data will not be coded.

A by-participant listing of general medical history will be provided by participant ID number in ascending order. The listing will include relevant medical condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

6. EFFICACY ANALYSES

Efficacy will not be evaluated in the study.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be presented last in the summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE case report form (CRF) to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure related AEs are those for which the investigator selected "Yes" on the AE case report form (CRF) to the question of "Related to Study Procedures." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be considered related to study procedure for summary purposes. However, by-participant data listings will show the relationship as missing from that captured on the CRF.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE listings from the Gilead Patient Safety database before database finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.

If the AE onset date is the same as the date of study drug start date then the AE onset time must be on or after the study drug start time. If the AE onset time is missing when the start dates are the same the AE will be considered treatment emergent.

- Any AEs leading to discontinuation of study drug.

7.1.6.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset will determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the date of first dose of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the date of the first dose of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary. The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group as follows:

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs by grade
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All TEAEs with severity of Grade 3 or higher
- All TEAEs leading to discontinuation of study drug
- All SAEs
- All Deaths

7.1.8. Additional Analysis of Adverse Events

A table of treatment-emergent adverse events of flu-like symptoms based on the MST list provide in Appendix 3 will be provided by treatment group, SOC, and PT using participants in the Safety Analysis Set.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for participants who have permanently discontinued study drug or all available data at the time of the database snapshot for participants who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are BLQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by cohort for each laboratory test specified in the study protocol as follows:

- Predose values
- Values at each postdose time point [visit]
- Change from predose at each postdose time point [visit]

Predose and postdose values will be defined as described in Section 3.7.1. Change from predose to a postdose visit will be defined as the visit value minus the predose value. Laboratory test results collected at unscheduled visits will be included for the predose and postdose maximum and minimum value selection. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.2.2. Graded Laboratory Values

The severity of laboratory abnormalities will be graded (1 to 4) using the Gilead Grading Scale for Severity of Adverse Events Antiviral Toxicity Grading Scale, V01. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from predose at any postdose time point, up to and including the date of last dose of study drug plus 30 days for participants who permanently discontinued study drug, or the last available date in the database snapshot for participants who were still on treatment at the time of an interim analysis. If the relevant predose laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at predose and each scheduled postdose visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; participants will be categorized according to the most severe postdose abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 graded laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postdose values up to 30 days after last dosing date.

A by-participant listing of treatment-emergent laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.3. Body Weight, Height, BMI, and Vital Signs

Descriptive statistics will be provided by cohort for body weight, height, BMI, and vital signs as follows:

- Predose value
- Values at each postdose visit
- Change from predose at each postdose visit

Predose and postdose values will be defined as described in Section 3.7.1. Change from predose to a postdose visit will be defined as the postdose value minus the predose value. Body weight and vital signs measured at unscheduled visits will be included for the predose value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits, otherwise they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

A summary of prior and concomitant medications will not be provided.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Electrocardiogram Results

Summaries of investigator assessment of ECG readings will be provided for the Safety Analysis Set as described below. No inferential statistics will be generated.

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each time point compared with predose values will be presented by cohort using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at predose or postdose will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-participant listing for safety ECG assessment results will be provided by participant ID number and time point in chronological order.

7.6. Other Safety Measures

A by-participant listing of participant pregnancies during the study will be provided by participant ID number. No additional safety measures are specified in the protocol.

Although not necessarily related to safety, a by-participant listing of all comments received during the study on the comments form will be provided by participant ID number, and form for which the comment applies.

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up/log down trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to zero for the calculation of PK parameters.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{inf}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of the drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all participants for whom parameters can be derived. The analyte(s) presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

Cohort	Treatment	Analyte(s)
1	VES, VES + COBI, VES + VOR	VES, COBI, and VOR
2	VES, VES + RFB	VES, RFB, and d-RFB

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{last}, AUC_{inf}, and C_{max} of VES. The PK parameters that may be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte in Plasma

Analyte	Cohort		Period	Visit	Parameters
VES	Cohorts 1 and 2		All periods	Various	AUC_{last}, AUC_{inf}*, C_{max}*, $\%AUC_{exp}$, T_{max}, C_{last}, T_{last}, λz, $t_{1/2}$, CL/F, V_z/F
COBI	Cohort 1	Period 2	Day 2		AUC_{tau}, C_{max}, T_{max}
			Days 2, 3, 4, 5		C_{trough}
VOR	Cohort 1	Period 3	Day 3		AUC_{tau}, C_{max}, T_{max}
			Days 3, 4, 5, 6		C_{trough}
RFB	Cohort 2	Period 2	Day 6		AUC_{tau}, C_{max}, T_{max}
			Days 3, 4, 5, 6		C_{trough}

* Parameter used in sample size and power calculations.

8.3. Statistical Analysis Methods

8.3.1. General Considerations

Individual participant concentration data and individual participant PK parameters for COBI, RFB, VES, and VOR will be listed and summarized using descriptive statistics by cohort and treatment. Summary statistics (numbers of participants, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual participant concentration data by time point and individual participant PK parameters by cohort and treatment. Moreover, the geometric mean, 95% confidence interval (CI), %Geometric CV [%GCV], and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Individual concentration data listings and summaries will include all participants with concentration data. Outlier drug concentrations will be identified in the concentration listing. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number and percentage of participants with concentration BLQ, as well as an indicator if more than one-third of the participants are BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and postdose time points. If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point. Concentration values will be presented as received from the bioanalytical lab and summary statistics will be presented to three significant digits.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. PK parameters marked for exclusion from the PK summary will be identified. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter. Data and summary statistics will be presented to three significant digits.

The following tables will be provided for each analyte:

- Individual participant concentration data and summary statistics by cohort and treatment
- Individual participant plasma PK parameters and summary statistics by 1) cohort and treatment, 2) by treatment and BCRP genotype (for VES Period 1).
- Results of statistical comparisons for drug interaction assessment.

The following figures will be provided by cohort:

- Individual participant concentration data versus time (on linear and semilogarithmic scales) will be displayed 1) by treatment (participants overlaid; for all analytes) and 2) by participant (treatments overlaid; for VES). Values of BLQ will be displayed as 0 on the linear scale and missing on the semi-logarithmic scale.
- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales) will be displayed by treatment (for all analytes). If more than one-third of the values at a postdose time point are BLQ then the mean and SD will not be presented at that time point and remaining points connected. If lower error bar (mean-SD) is < 0 at a timepoint then it will not be presented at that timepoint.
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales) will be displayed by treatment (for all analytes). If more than one-half of the values at a timepoint are BLQ then the median and quartile values will not be presented at that timepoint, and remaining points connected. If lower error bar (Q1) is BLQ at a timepoint then it will be presented as LLOQ at that timepoint.
- Individual participant C_{trough} versus study day (on linear and semilogarithmic scales) (participants overlaid; for COBI, VOR, RFB, and d-RFB)
- Boxplots of VES AUC_{last}, AUC_{inf}, C_{max}, and $t_{1/2}$ by 1) cohort and treatment and 2) by cohort and BCRP genotype (for VES Period 1) (include individual points on the box plots)

The following listings will be provided:

- PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age
- Individual data on determination of plasma half-life and corresponding regression correlation coefficient

8.3.2. Statistical Methodology

8.3.2.1. Analysis of Drug-Drug Interaction

The statistical comparisons of the natural log-transformed PK parameters for each analyte and treatment comparison of interest will be performed. The statistical modeling will be based on the PK analysis set for the analyte under evaluation. For each analyte, all participants with available data for the PK parameter under evaluation will be included in the modeling.

Treatment comparisons of interest are shown in Table 8-3.

Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses

Analyte(s)	Parameter	Comparison		
		Test	Reference	Boundary
VES	AUC_{inf}	Cohort 1 (VES + COBI) Fasted	Cohort 1 (VES alone) Fasted	Not Prespecified
	AUC_{last}			
	C_{max}			
	$t_{1/2}$			
	T_{max}			
VES	AUC_{inf}	Cohort 1 (VES + VOR) Fasted	Cohort 1 (VES alone) Fasted	Not Prespecified
	AUC_{last}			
	C_{max}			
	$t_{1/2}$			
	T_{max}			

For each analyte, and each PK parameter, a parametric (normal theory) mixed-effects ANOVA model will be fitted to the natural log-transformed values of the PK parameter under evaluation using SAS® PROC MIXED.

The statistical model will include treatment as a fixed effect and subject as a random effect. The following SAS PROC MIXED code will provide the cohort comparison analysis and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
  where analyte='VES and param='AUCinf';
  class treatment;
  model lnest = treatment / ddfm=kr;
  random subjid;
  lsmeans treatment / diff cl alpha = 0.1;
  estimate 'Test versus Reference' treatment -1 1 / cl alpha = 0.10;
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}.

Nonparametric analyses for certain PK parameters (eg. t_{max}) may be performed. If needed, these analyses will be performed using the Wilcoxon signed-rank for fixed-sequence between the test and reference groups for VES.

8.4. Sensitivity Analysis

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

9. REFERENCES

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

Phoenix WinNonlin® 7.0. Pharsight Corporation, Princeton, NJ, USA.

nQuery Advisor(R) Version 9.2.1.0 Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of ASsessments
Appendix 2. Data Collection of COVID-19 Data
Appendix 3. MST List for cytokine release syndrome

Appendix 1. Schedule of ASsessments

Table 12-1. Study Procedures Table for Cohort 1, Period 1 and 2

Study Procedure	Screening[a]	Study Day														
		Period 1 (VES)							Period 2 (VES + COBI)							
		−1[b]	1	2[c]	3	4	5	Wash out[d]	−1[b]	1	2	3[c]	4	5	6	Wash out[e]
Written informed consent	X															
Eligibility criteria	X															
Complete medical history	X	X							X							
ART history[f]	X															
Complete physical examination	X															
Symptom-driven physical examination[g]		X	X	X					X	X	X	X				
Demographics	X															
Height	X															
Weight	X	X					X		X						X	
Vital signs[h]	X		X	X							X	X				
12-lead ECG[i]	X		X	X			X				X	X			X	
HIV-1 viral load	X								X							
CD4 cell count	X															
HBV and HCV testing[j]	X															
SARS-CoV-2[k]		X							X							
Urine drug and alcohol screen[n]	X	X			X				X				X			
Pregnancy test (women of childbearing potential)[l]	X	X							X							
FSH (postmenopausal women)[m]	X															

		Study Day														
		Period 1 (VES)							Period 2 (VES + COBI)							
Study Procedure	Screening[a]	−1[b]	1	2[c]	3	4	5	Wash out[d]	−1[b]	1	2	3[c]	4	5	6	Wash out[e]
Blood chemistry[a]	X	X					X		X						X	
Calculated CL_{cr}[a]	X	X					X		X						X	
Coagulation panel	X															
Hematology[a]	X	X					X		X						X	
Urinalysis[a]	X	X					X		X						X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Enrollment			X													
Confinement[a]		X	X	X					X	X	X	X				
VES dosing			X								X					
COBI dosing										X	X	X	X	X		
Plasma VES and perpetrator PK[a]			X	X	X	X	X				X	X	X	X	X	
Serum biomarkers[a]			X	X	X		X				X	X	X		X	
Whole blood ISG mRNA[a]			X	X	X	X	X				X	X	X	X	X	
PGx (TLR7 and BCRP)[f]			X													
PGx CYP2C19[a]	X															
Immune cell phenotyping[g]			X	X		X	X				X	X		X	X	

AE = adverse event; ART = antiretroviral therapy; BCRP = breast cancer resistance protein; CD4 = clusters of differentiation 4; CL_{cr} = creatinine clearance; COBI = cobicistat; CYP = cytochrome P450 enzyme; CRS = cytokine release syndrome; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = interferon-stimulated genes; mRNA = messenger RNA; PGx = pharmacogenetics; PK = pharmacokinetics; TLR7 = toll-like receptor 7; VES = vesatolimod

a Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.
b Admission to clinic.
c Discharge from clinic.
d There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1. Participants should inform the site of any AE during the washout period.

e There will be a washout period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1 . Participants should inform the site of any AE during the washout period.
f Collect ART history for at least the past 12 months.
g Every day during confinement, as needed, based on reported signs and symptoms.
h Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after each dose of VES.
i 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after each dose of VES.
j HBV core antibody, HBsAg, and HCV antibody at screening.
k COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed prior to the next scheduled test based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
l For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required.
m For participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
n In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day -1 until completion of assessments on Day 3. Participants may remain confined for a longer duration within each treatment period if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.
o VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after each dose of VES. Time windows allowed for PK samples to be collected are provided inTable 8 of the study protocol.
p Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after each dose of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30 minute window.
q Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30-minute window.
r A PGx sample will be collected on Day 1 (preferably) or at any other time during the study.
s Results must be reviewed prior to enrollment.
t Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30-minute window.
u On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Table 12-2. Study Procedures Table for Cohort 1, Period 3

	Study Day								
	Period 3 (VES + VOR)								
Study Procedure	−1[a]	1	2	3	4[b]	5	6	7	Follow-up[c]/ET[d]
Complete physical examination									X
Symptom-driven physical examination[e]	X	X	X	X	X				
Weight	X							X	X
Vital signs[f]				X	X				X
12-lead ECG[g]				X	X			X	
HIV-1 viral load	X								
SARS-CoV-2[h]	X								
Urine drug and alcohol screen[i]	X					X			
Pregnancy test (women of childbearing potential)[j]	X								X
Blood chemistry[k]	X							X	X
Calculated CL_{cr}[k]	X							X	X
Hematology[k]	X							X	X
Urinalysis[k]	X							X	X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Confinement[l]	X	X	X	X	X				
VES dosing[k]				X					
VOR dosing[l]		X	X	X	X	X	X		
Plasma VES and perpetrator PK[m]				X	X	X	X	X	
Serum biomarkers[n]				X	X	X		X	
Whole blood ISG mRNA[o]				X	X	X	X	X	
Immune cell phenotyping[p]				X	X		X	X	

CL_{cr} = creatinine clearance; CRS = cytokine release syndrome; ECG = electrocardiogram; ET = early termination; ISG = interferon-stimulated genes; mRNA = messenger RNA; PK = pharmacokinetics; VES = vesatolimod; VOR = voriconazole

a Admission to clinic.
b Discharge from clinic.

c Participants will return for an in-clinic follow-up visit 10 (± 3) days after the last dose of VES.
d Assessments will be performed within 72 hours of ET from the study, if possible.
e Every day during confinement, as needed, based on reported signs and symptoms.
f Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after the VES dose in Period 3.
g 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after the VES dose in Period 3.
h COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
i For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required. Urine pregnancy testing is repeated at the follow-up visit and ET visit, if applicable.
j In Period 3, participants will be confined beginning on Day −1 until completion of assessments on Day 4. Participants may remain confined for a longer duration if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.
k VES will be dosed in the morning.
l VOR will be dosed twice daily.
m VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after administration of VES. Time windows allowed for PK samples to be collected are provided in Table 8 of the study protocol.
n Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after administration of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.
o Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30 minute window.
p Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30-minute window.
q On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Table 12-3. Study Procedures Table for Cohort 2, Periods 1 and 2

Study Procedure	Screening[a]	Study Day																	Follow-up[e]/ET[f]	Telephone contact[g]
		Period 1 (VES)						Wash out[d]	Period 2 (VES + RFB)											
		−1[b]	1	2[c]	3	4	5		−1[b]	1	2	3	4	5	6	7[c]	8	9	10	
Written informed consent	X																			
Eligibility criteria	X																			
Complete medical history	X	X							X											
ART history[h]	X																			
Complete physical examination	X																		X	
Symptom-driven physical examination[i]		X	X	X					X	X	X	X	X	X	X	X				
Demographics	X																			
Height	X																			
Weight	X	X					X		X										X	X	
Vital signs[j]	X		X	X											X	X				X	
12-lead ECG[k]	X		X	X			X								X	X			X		
HIV-1 viral load	X								X												
CD4 cell count	X																			
HBV and HCV testing[l]	X																			
SARS-CoV-2[m]		X							X											
Urine drug and alcohol screen[n]	X	X			X				X								X			

Study Procedure	Screening[a]	Study Day																	Follow-up[e]/ET[f]	Telephone contact[g]
		Period 1 (VES)						Wash out[d]	Period 2 (VES + RFB)											
		−1[b]	1	2[c]	3	4	5		−1[b]	1	2	3	4	5	6	7[c]	8	9	10	
Pregnancy test (women of childbearing potential)[a]	X	X							X											X	X
FSH (postmenopausal women)[a]	X																				
Blood chemistry[a]	X	X					X		X										X	X	
Calculated CL_{cr}[a]	X	X					X		X										X	X	
Coagulation panel	X																				
Hematology[a]	X	X					X		X										X	X	
Urinalysis[a]	X	X					X		X										X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Enrollment			X																		
Confinement[a]		X	X	X					X	X	X	X	X	X	X	X					
VES dosing			X												X						
RFB dosing										X	X	X	X	X	X	X	X	X			
Plasma VES and perpetrator PK[r]			X	X	X	X	X								X	X	X	X	X		
Serum biomarkers[s]			X	X	X		X								X	X	X		X		
Whole blood ISG mRNA[t]			X	X	X	X	X								X	X	X	X	X		

Study Procedure	Screening[a]	Study Day																	Follow-up[e]/ET[f]	Telephone contact[g]
		Period 1 (VES)						Wash out[d]	Period 2 (VES + RFB)											
		−1[b]	1	2[c]	3	4	5		−1[b]	1	2	3	4	5	6	7[c]	8	9	10	
PGx (TLR7 and BCRP)[o]			X																	
Immune cell phenotyping[p]			X	X		X	X								X	X		X	X	
TruCulture cytokine response[w]			X																	

ART = antiretroviral therapy; BCRP = breast cancer resistance protein; CD4 = clusters of differentiation 4; CL_{cr} = creatinine clearance; CRS = cytokine release syndrome; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = interferon-stimulated genes; mRNA = messenger RNA; PGx = pharmacogenetics; PK = pharmacokinetics; RFB = rifabutin; TLR7 = toll-like receptor 7; VES = vesatolimod

a Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.
b Admission to clinic.
c Discharge from clinic.
d There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1. Participants should inform the site of any AE during the washout period.
e Participants will return for an in-clinic follow-up visit 10 (± 3) days after the last dose of VES.
f Assessments will be performed within 72 hours of ET from the study, if possible.
g For participants assigned female at birth of childbearing potential, an at-home urine pregnancy test will be completed 10 days after the last dose of RFB. Participants will be contacted by telephone to report at-home pregnancy test results.
h Collect ART history for at least the past 12 months.
i Every day during confinement, as needed, based on reported signs and symptoms.
j Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after each dose of VES.
k 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after each dose of VES.
l HBV core antibody, HBsAg, and HCV antibody at screening.
m COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed prior to the next scheduled test based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
n On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
o For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required. Urine pregnancy testing is repeated at the follow-up visit and ET visit, if applicable.
p For participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.

q In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day -1 until completion of assessments on Day 7. Participants may remain confined for a longer duration within each treatment period if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.

r VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after each dose of VES. Time windows allowed for PK samples to be collected are provided in Table 8 of the study protocol..

s Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after each dose of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.

t Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30-minute window.

u A PGx sample will be collected on Day 1 (preferably) or at any other time during the study.

v Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30 minute window.

w Whole blood sample for TruCulture cytokine response will be collected on Period 1 Day 1 (predose).

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4

Appendix 2. Data Collection of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table 12-4). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit will be assigned as follows:

i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same participant and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this participant and this visit will be categorized as "Virtual Visit"

iii. Otherwise result is missing

Table 12-4. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits.

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 3. MST List for cytokine release syndrome

The selected PTs of cytokine release syndrome based on GSI developed MST are listed as follows.

	Selected PTs Based on GSI Developed MST
1	Arthralgia
2	Capillary leak syndrome
3	Chills
4	Fatigue
5	Headache
6	Hypotension
7	Hypoxia
8	Influenza
9	Influenza like illness
10	Malaise
11	Myalgia
12	Nausea
13	Pyrexia
14	Shock
15	Tachypnoea
16	Vomiting
17	Cytokine storm
18	Systemic inflammatory response syndrome
19	Cytokine release syndrome
20	Haemophagocytic lymphohistiocytosis
21	Multiple organ dysfunction syndrome
22	Chronic inflammatory response syndrome

GS-US-382-1587 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Pharmacology eSigned	PPD
PPD	Biostatistics eSigned	PPD
PPD	Global Development Lead (GDL) eSigned	PPD