PPD

STATISTICAL ANALYSIS PLAN

STUDY TITLE:

An Open-label, Single-center, Three-part Study in Healthy Subjects to Investigate the Effect of Givinostat on the Pharmacokinetics of Midazolam and Dabigatran, the Effect of Clarithromycin on the Pharmacokinetics of Givinostat and the Pharmacokinetics of Single and Multiple Doses of Givinostat.

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1. SIGNATURE PAGE

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2.2. List of Abbreviations

α	Type I Error (Significance Level)
Ab	Antibody
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADPC	Analysis Data Pharmacokinetic Concentrations
ADPP	Analysis Data Pharmacokinetic Parameters
ADSL	Subject-Level Analysis
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
A_{mean}	Arithmetic Mean
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Concentration *Versus* Time Curve
AUC_{0-t}	AUC from Time Zero to Last Sampling Time with Quantifiable Concentrations
$AUC_{0-\infty}$	AUC from Time Zero to Infinity
$AUC_{0-\tau,ss}$	AUC Corresponding to the Dosing Interval, at Steady State
$AURC_{0-t}$	Area Under the Urinary Excretion Rate Curve from Time 0 to the Last Rate
$\%AUC_{extrap}$	Residual Area or Percentage of Extrapolated Part of $AUC_{0-\infty}$
BDS	Basic Data Structure
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
bpm	Beats Per Minute
C_0	Pre-dose Concentration
CI	Confidence Interval
Cl	Total Body Clearance
CK	Creatine Kinase
Cl/F	Total Body Clearance Affected by the Bioavailability Factor
Cl_R	Renal Clearance
Cl_R/F	Renal Clearance Affected by the Bioavailability Factor
C_{last}	Last Quantifiable Concentration
C_{max}	Maximum Observed Concentration
$C_{max,ss}$	Maximum Observed Plasma Concentration at Steady State
Cr_{CL}	Creatinine Clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV%	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
DM	Demographics
ECG	Electrocardiogram
F	Bioavailability Factor
FDA	Food and Drug Administration
GGT	Gamma-Glutamyltransferase
GLP	Good Laboratory Practices

G_{mean}	Geometric Mean
GMR	Geometric Least Square Means Ratio
GCV%	Geometric Coefficient of Variation
GSD	Geometric Standard Deviation
H_0	Null Hypothesis
H_1	Alternative Hypothesis
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCVAb	Hepatitis C Virus Antibodies
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
INR	International Normalized Ratio
ISCV%	Intra-Subject Coefficient of Variation
IV	Intravenous
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LSmeans	Least Square Means
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MSE	Mean Square Error
MW	Molecular Weight
NCA	Non-Compartmental Analysis
PC	Pharmacokinetic Concentrations
PCL	Protocol Clarification Letter
P-gp	P-Glycoprotein
PP	Pharmacokinetic Parameters
PT	MedDRA Preferred Term
QTcF	Corrected QT Interval by Fridericia
RBC	Red Blood Cell
RDW-CV	Coefficient Variation of the Red Cell Distribution Width
RSQ	Goodness of Fit for the Terminal Elimination Phase
rtf	Rich Text File
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SOC	MedDRA System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Concentration
$T_{max,ss}$	Time to Maximum Observed Concentration at Steady State

TOST	Two One-Sided T-Tests
TSH	Thyroid-Stimulating Hormone
t_0	Time of Dosing (t=0h)
$t_{½}$	Apparent Terminal Elimination Half-Life
ULOQ	Upper Limit of Quantification
V_D	Apparent Volume of Distribution
V_D/F	Apparent Volume of Distribution Affected by the Bioavailability Factor (F)
WBC	White Blood Cell
WHO	World Health Organization
λ_z	Apparent Terminal Elimination Rate Constant
τ	Dosing Interval

3. INTRODUCTION

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications for the Tables, Figures and Listings (TFLs). This document describes the variables and populations, anticipated data transformation and manipulations and other details of the analysis not provided in the Clinical Study Protocol (CSP).
The described analyses are based on the final CSP version 1.0, dated 29NOV2021 [1] and a Protocol Clarification Letter (PCL) dated 25FEB2022. This SAP was finalized prior to data base lock and conduct of the statistical analyses. For each part of the study at the time of the Blind Review Process, a Data Blind Review Process Minute will be prepared and attached to this document (Annex 3).
Additional pharmacokinetic and statistical analysis may be performed to supplement the planned analyses described in this SAP. These supplemental analyses will be identified and presented in the Clinical Study Report (CSR).

4. STUDY OBJECTIVES

4.1. Primary

1. To assess the potential effect of oral clarithromycin on the single dose pharmacokinetics of givinostat (Part 2).

4.2. Secondary

1. To assess the safety and tolerability of concomitant administration of givinostat plus clarithromycin (Part 2).

5. INVESTIGATIONAL PLAN

5.1. Study Design

This is a phase I, open-label, 3-part, fixed-sequence, non-randomized study in healthy male and female subjects.
Study parts may be conducted concomitantly.

5.1.1. Rational for Study Design

The rational for study design detailed in the CSP [1].

In Part 2, the potential of givinostat as DDI victim through P-gp inhibition will be evaluated.

5.1.2. Rational for Dose Selection and Treatment Duration

5.1.2.1. Part 2

Rationale for Clarithromycin Dose and Treatment Duration

A dose of 500 mg clarithromycin will be administered twice-daily to subjects, from Day 4 to Day 10, in order to maximize the possibility to identify a DDI with givinostat. The inhibitory effect will be assessed on Day 8 [1].

5.2. Study Plan

5.2.1. Part 2 – Effect of Oral Clarithromycin on the Single Dose Pharmacokinetics of Givinostat

Subjects will be confined in PPD from Day -1 to Day 11.

On Days 1 and 8, givinostat 50 mg as oral suspension will be administered as a single dose, 1 hour after the planned morning time of clarithromycin administration. Givinostat will be administered following an overnight fasting of at least 8 hours and subjects will remain fasted until at least 3 hours post-dose. Except for water given with clarithromycin (150 mL), no fluids will be allowed from 1 hour before the morning dosing until 2 hours post dose. Water will be provided ad libitum at all other times. Givinostat will be administered with the subjects in a semi-recumbent position and subjects will remain semi-recumbent until at least 3 hours post-dose.
From Day 4 to Day 10, clarithromycin 500 mg film-coated tablets will be administered twice a day, in the morning and in the evening.

The following assessments will be performed:

- Blood collection for pharmacokinetic analysis on Days 1 to 4 and 8 to 11.
- Vital signs measurements (BP, PR and RR) on Days 1 and 4 to 10.
- 12-lead ECG on Days 1, 3, 7 and 8.
- Blood collection for laboratory tests (hematology and biochemistry) on Day 3.

Subjects will be discharged from PPD in the morning of Day 11 if allowed by the investigator based on their medical condition. The following procedures will be performed:

- Physical examination.
- Collection of body weight.
- Vital signs measurements (BP, PR, RR and body temperature).
- 12-lead ECG.
- Safety laboratory assessments (hematology, biochemistry, coagulation and urinalysis).
- Serum pregnancy test for all female subjects.

Subjects will return to PPD 10 to 14 days after the end of study to undergo additional assessments as required as per protocol.

The total duration of Part 2 for each subject will be up to approximately 7 weeks from Screening to Follow-up visit, divided as follows:

- Screening: up to 21 days
- Treatment Period: Days 1 to 11

- Safety follow-up visit: 12±2 days

5.3. Number of Participants and Sample Size Estimation

To ensure enough subjects with evaluable data complete each study part, a total of fifty-four (54) healthy male and female subjects are planned to be enrolled as follows:

- Part 1: twenty-six (26) subjects
- Part 2: twenty (20) subjects
- Part 3: eight (8) subjects

Each subject will participate in one study part only.

5.3.1. Part 2

Assuming an ISCV% of ≤20% for givinostat C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, a true geometric means ratio (givinostat with *vs* without clarithromycin) of 1.00, a significance level (alpha error) of 5%, and a default no-effect boundary of 80.00% to 125.00%, a sample of 16 evaluable subjects results in at least 80% power. Accounting for early-termination subjects, a sample size of 20 subjects will be enrolled.

5.4. Randomization

This is a fixed sequence study. Randomization is not applicable.

5.5. Blinding

The study will be conducted as open label. Blinding procedures are not applicable.

5.6. Statistical Hypothesis

5.6.1. Part 2

Part 2 of the study is designed to assess the potential effect of oral clarithromycin on the single dose pharmacokinetics of givinostat.

As in accordance with the FDA Guidance on DDI studies [2], assessment of DDI will be based upon the 90% CI for the GMR of the primary pharmacokinetic parameters.

This method is equivalent to TOST with the null hypothesis (H_0) of non-comparable bioavailability at the 5% significance level ($\alpha = 0.05$).

Assuming a maximum 20% difference between givinostat co-administered with clarithromycin and administered alone, the interval hypotheses for comparable bioavailability can be formulated as:

$$H_0: \ \mu_T/\mu_R < 0.80 \quad \text{or} \quad \mu_T/\mu_R > 1.25$$

versus H_1: $0.80 \leq \mu_T/\mu_R \leq 1.25$

where μ_T and μ_R are the Geometric LSmeans for givinostat co-administered with clarithromycin and administered alone, respectively.

Hence, the hypothesis is to show comparable bioavailability by rejecting the H_0 of non-comparable bioavailability, i.e., the decision of comparable bioavailability is made based on whether the 90% CI of the givinostat co-administered with clarithromycin-to-givinostat administered alone GMR is within 80.00 – 125.00% [2].

6. STUDY ASSESSMENTS

For each study part, a summary of procedures for study assessments are presented in Section 2 of the CSP (Study Flow-Chart and Study Design Diagram) [1].

6.1. Safety Assessments

Subjects' safety will be monitored during the study.

Safety assessments will include pre-study medical history, physical examination, vital signs, 12-lead ECG, clinical laboratory tests and adverse event (AE) monitoring. Additional safety measurements may be performed at the discretion of the investigator for reasons related to subject safety.

Medications will be mentioned according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

6.1.1. Medical History

Medical history will cover all relevant past or present information related to subject's health at the time of informed consent signature.
Medical history at screening will include past or present relevant cardiovascular, respiratory, renal, genitourinary, gastrointestinal, hepatic, hematological, immunological, endocrine, dermatological, musculoskeletal, neurological, psychiatric, drug and surgical history, or any other diseases or disorders.

Medical history will be referred in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or higher.

Adverse events related to medical history will be identified.

6.1.2. Physical Examination

Physical examination at screening and end-of-study will include: general appearance; skin; head and neck; thorax and abdomen; pulmonary auscultation; cardiac auscultation; abdomen palpation; limbs; brief neurological examination.

6.1.3. Weight, Height and Body Mass Index

The body height and weight values as well as the body mass index (BMI) will be recorded in the electronic case report form (eCRF) and will be determined at Screening. Only body weight will be determined also at admission and end-of-study.

The subjects' body weight will preferably be measured using the same weighing scale for all subjects and throughout the study. The weighing scale should have a precision of at least 0.5 kg.

6.1.4. Vital Signs

Vital signs will include:

- Systolic blood pressure (SBP).
- Diastolic blood pressure (DBP).
- Pulse rate (PR).
- Respiratory rate (RR).
- Body temperature.

6.1.5. 12 Lead Electrocardiogram

A 12-lead ECG will be performed preferably before the blood collection. The corrected QT interval by Fridericia (QTcF) will be analyzed.

6.1.6. Laboratory Safety Tests

The following laboratory parameters will be tested:

- Hematology:
  - Red blood cell (RBC) count.
  - White blood cell (WBC) count.
  - WBC differential count:
    - Neutrophils.
    - Eosinophils.
    - Basophils.
    - Lymphocytes.
    - Monocytes.
  - Hemoglobin.
  - Mean corpuscular volume (MCV).
  - Mean corpuscular hemoglobin (MCH).
  - Mean corpuscular hemoglobin concentration (MCHC).
  - Coefficient variation of the red cell distribution width (RDW-CV).
  - Hematocrit.
  - Platelet count.
  - Mean platelet volume.
- Coagulation:
  - Prothrombin rate.
  - Prothrombin time.
  - Prothrombin time – international normalized ratio (INR).
  - Activated partial thromboplastin time (aPTT).
- General biochemistry:
  - Total bilirubin.

- Direct bilirubin.
- Indirect bilirubin.
- Alkaline phosphatase (ALP).
- Amylase.
- Aspartate aminotransferase (AST).
- Alanine aminotransferase (ALT).
- Lactate dehydrogenase (LDH).
- Cystatin C.
- C-reactive protein.
- Gamma-glutamyltransferase (GGT).
- Creatinine kinase (CK).
- Total protein.
- Albumin.
- Uric acid.
- Triglycerides.
- Total cholesterol.
- Low-density lipoprotein-cholesterol (LDL-C).
- High-density lipoprotein-cholesterol (HDL-C).
- Sodium.
- Potassium.
- Chloride.
- Calcium.
- Magnesium.
- Glucose.
- Creatinine.
- Urea.
- Thyroid-stimulating hormone (TSH).
- Estimated creatinine clearance (Cr_{CL}).

- Viral Serology:
  - Human Immunodeficiency Virus (HIV):
    - HIV-1 (anti-HIV-1Ab).
    - HIV-2 (anti-HIV-2Ab).
  - Hepatitis B (HBsAg)
  - Hepatitis C (anti-HCVAb).
- Beta-human chorionic gonadotropin (beta-hCG) pregnancy tests:
  - Serum.
  - Urine.
- Urinalysis:
  - pH.
  - Specific gravity.
  - Protein.
  - Hemoglobin.
  - Glucose.
  - Ketones.
  - Bilirubin.
  - Nitrites.
  - Urobilinogen.

    - Microscopy.
- Drugs-of-abuse urine test:
    - Cannabinoids.
    - Opiates.
    - Cocaine.
    - Amphetamines.
    - Benzodiazepines.
- Ethanol urine test.
- Cotinine urine test.
- Follicle-stimulating hormone (FSH) test.
- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) diagnostic tests.

6.1.7. Adverse Events

The occurrence of clinical AEs will be monitored throughout the study.
Clinically significant abnormalities in laboratory safety tests, vital signs and physical examination will be reported as AEs.

Treatment-emergent AEs (TEAEs) are defined as AEs not present prior to first administration of investigational product, or AEs present before first administration of investigational product that worsen after the subject receives the first dose of investigational product. TEAEs that occur after administration of investigational product during the washout of a given period will be assigned to the treatment administered in that period.

The following information will be used for the description of the AEs:

- Reported Term.
- Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) coding.
- MedDRA Preferred Term (PT) coding.
- Start date and time.
- End date and time.
- Seriousness.
- Severity:
    - Mild.
    - Moderate.
    - Severe.
- Relationship (causality) for each treatment administrated, per part.
    - Reasonably Possible.
    - Not Reasonably Possible.
    - Unknown.
- Action taken:
    - Dose Increased.
    - Dose Not Changed.
    - Dose Rate Reduced.
    - Dose Reduced.
    - Drug Interrupted.
    - Drug Withdrawn.

  - Not Applicable.
  - Unknown.
- Concomitant medication.
- Outcome:
  - Fatal.
  - Not Recovered / Not Resolved.
  - Recovered / Resolved.
  - Recovered / Resolved with Sequelae.
  - Recovering / Resolving.
  - Unknown.
- Most recent study treatment taken.
- Last dosing date.

6.1.8. Previous and Concomitant Medications

A previous medication is any medication for which the end date is prior to first dosing.
A concomitant medication is any medication ongoing or initiated after first dosing.

For all study parts, the use of any medications including Over-the-Counter (OTC) products (including herbal medicines such as St John's Wort, homeopathic preparations, vitamins, and minerals) is forbidden from 28 days or within 5 half-lives of the medicinal product, whichever is longer, prior to admission up to last sample for pharmacokinetics assessment, except for medications for the treatment of AEs.

Any medication (previous or concomitant) taken within the period of medication restriction must be recorded in the eCRF. If concomitant medication is ongoing at the follow-up visit, no end date will be provided in the eCRF.

For each study part, previous and concomitant medications used by study participants during the study and their judged impact on the pharmacokinetic assessment will be listed in the respective Data Blind Review Meeting/ Process Minute (Annex 3).

Concomitant medications will be coded according to the WHO ATC classification system.

6.2. Pharmacokinetic Assessments

6.2.1. Blood Sampling for Pharmacokinetic Assessments

In each study part, while subject is confined at the clinical research unit, blood samples will be taken preferably via an indwelling cannula placed in a vein of an upper limb of the subject. During ambulatory visits, blood samples will be taken by direct venipuncture.

The actual time of all pharmacokinetic blood draws will be recorded and reported for all subjects. The pre-dose blood sample will be collected within 30 minutes before dosing. The post-dose blood samples will be collected within ±3 minutes from the scheduled sampling time. Greater deviations will be reported as a protocol deviation and its cause will be recorded.

In case blood sampling for pharmacokinetics and other procedures coincide in time, blood draws

will have priority unless other procedures are necessary for assuring subject's safety.

Syneos Health Clinique will carry out the determination of plasma levels of givinostat and its metabolites (ITF2374, ITF2375, ITF2440 and ITF2563), midazolam, 1-hydroxymidazolam and total and free dabigatran in accordance with the applicable principles of Good Laboratory Practices (GLP), using a previously validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

The planned lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) for:

- givinostat are 1 and 100 ng/mL.
- givinostat metabolite ITF2374 are 1 and 100 ng/mL.
- givinostat metabolite ITF2375 are 1 and 100 ng/mL.
- givinostat metabolite ITF2440 are 10 and 500 ng/mL.
- givinostat metabolite ITF2563 are 2 and 125 ng/mL.
- midazolam are 100 and 100000 pg/mL.
- 1-hydroxymidazolam are 100 and 50000 pg/mL.
- total dabigatran are 1 and 400 ng/mL.
- free dabigatran are 1 and 400 ng/mL.

LLOQ represents a value lower than or equal to 1/20 of estimated C_{max} value. Any adjustment to this range will be documented in the study specific Bioanalytical Report, which will supersede the indicated range.

6.2.1.1. Part 2

A total of forty (40) blood samples will be collected as follows:

- Twenty (20) blood samples of 4 mL each will be collected in sodium heparin tubes at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 60 and 72 hours after the administration of givinostat, on Days 1 and 8, for the determination of givinostat.

6.2.2. Plasma Pharmacokinetic Parameters

The following pharmacokinetic parameters will be derived by standard non-compartmental analysis (NCA) methods from the single-dose plasma concentration *versus* time profiles, for:

- Part 2:
  - givinostat.

Parameter	*Description*
C_{max}	Maximum observed concentration, directly obtained from the observed concentration *versus* time profile.
T_{max}	Time of occurrence of maximum observed concentration.
$AUC_{0\text{-}t}$ [1]	Area under the concentration *versus* time curve (AUC) from time of dosing (t=0h) to the time of the last measurable concentration (t_{last}), calculated by the linear-up/log-down trapezoidal method.
$AUC_{0\text{-}\infty}$	Total AUC extrapolated to infinity, calculated as $AUC_{0-t} + \frac{C_{last}}{\lambda_z}$, where C_{last}

Parameter	*Description*
	is the last measurable concentration and λ_z is the apparent terminal elimination rate constant.
$\%AUC_{extrap}$	Percentage of $AUC_{0-\infty}$ due to extrapolation from the time of the last measurable concentration (t_{last}) to infinity, i.e., residual area, calculated as $100 \cdot \frac{AUC_{0-\infty} - AUC_{0-t}}{AUC_{0-\infty}}$.
λ_z	Apparent first order elimination rate constant associated with the terminal (log-linear) portion of the concentration *versus* time curve. The parameter is estimated by linear least square regression analysis using the last three (or more) non-zero concentrations.
$t_{½}$	Apparent terminal elimination half-life, calculated as $\frac{ln(2)}{\lambda_z}$.

[1] *In Part 2, for givinostat the last sampling time corresponds to 72 hours.*

The upper and the lower timepoints and the number of timepoints used for λ_z estimation, as well as the goodness of fit for the terminal elimination phase (RSQ), will be reported.
No values of λ_z, $AUC_{0-\infty}$, $\%AUC_{extrap}$ and $t_{½}$ will be reported for cases where λ_z cannot be reliably determined.

7. STUDY ENDPOINTS

7.1. Primary

1. Givinostat plasma concentrations and thereof derived pharmacokinetic parameters alone and in combination with clarithromycin (Part 2).

7.2. Secondary

1. Incidence and severity of AEs; changes in vital signs, physical examination, ECG and clinical laboratory tests following administration of givinostat alone and in combination with clarithromycin (Part 2).

8. ANALYSIS POPULATIONS

The analysis populations are defined in accordance with the CSP [1].

For each study part, the subjects to be included in each analysis population will be reported in the respective Data Blind Review Process Minute (Annex 3).

For each study part, explanation of the reasons for exclusion of subjects from any analysis population will be provided in the respective Data Blind Review Process Minute (Annex 3) and in the CSR.

The list of subjects who complete each study part will be presented in Annex 4.

8.1. Part 2

8.1.1. Part 2 Safety Analysis Population

All subjects who receive at least one dose of an IMP in Part 2 of the study will constitute the Part 2 Safety Analysis Population.

Part 2 safety data analysis will be performed for all subjects in the Part 2 Safety Analysis Population.

8.1.2. Part 2 Pharmacokinetic Analysis Population

Part 2 Pharmacokinetic Analysis Population will include all subjects enrolled in Part 2 of the study, who are expected to provide evaluable pharmacokinetic data for at least one IMP, without deviations affecting pharmacokinetic interpretation.

The following reasons justify the exclusion of the pharmacokinetic data of a subject from the Part 2 pharmacokinetic analysis population:

- Protocol violation considered to have a potentially relevant effect on the pharmacokinetic results of the study.

  NOTE: These protocol violations will be reported in the Data Blind Review Process Minute (Annex 3), and their impact will be assessed at the time of pharmacokinetic analysis.
- Subject experienced vomiting or diarrhea.

  NOTE: Subjects that experienced vomiting or diarrhoea during this study part will be reported in the Data Blind Review Process Minute (Annex 3), and their exclusion will be assessed at the time of pharmacokinetic analysis.
- Subject with pre-dose concentration > 5% of the C_{max} value of the corresponding pharmacokinetic profile.

  NOTE: This exclusion will be assessed at the time of pharmacokinetic analysis.
- Subject with lack of any measurable concentrations or only very low plasma concentrations.

  NOTE: This exclusion will be assessed at the time of pharmacokinetic analysis.

8.1.3. Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population

Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population will include all subjects from the Part 2 Pharmacokinetic Analysis Population who are expected to provide evaluable pharmacokinetic data for givinostat administered alone (Day 1) and co-administered with clarithromycin (Day 8), without deviations affecting pharmacokinetic interpretation.

9. DATA REVIEW / TRANSFORMATION

9.1. Data Management

Data handling will be conducted in accordance with the Clinical Data Management section of the CSP and the Data Management Plan developed specifically for this study.

9.2. Acceptance of Data

For each study part, TFLs may start being programmed prior to or during the course of the trial. However, the programming of analysis datasets and TFLs will only be concluded and quality-controlled after database soft lock. Only audited data released by the bioanalytical laboratory will be used for programming the final analysis datasets and TFLs.

9.3. Data Transformation (CDISC)

Before performing the statistical analysis, all data collected (multiple sources) will be integrated into a common repository, using SAS® version 9.4 or higher.

For standardization and submission purpose, all data will be transformed according to Clinical Data Interchange Standards Consortium (CDISC):

- Study Data Tabulation Model (SDTM) version 1.4 or higher.
- SDTM Implementation Guide (SDTMIG) version 3.2 or higher.
- The following analysis datasets will be generated (Analysis Data Model [ADaM] version 2.1 or higher; ADaM Implementation Guide [ADaMIG], version 1.2 or higher) to support the results and ease the programming activities during the statistical analysis:
  - Subject-Level Analysis Dataset (ADSL).
  - Analysis Data Pharmacokinetic Concentrations (ADPC).
  - Analysis Data Pharmacokinetic Parameters (ADPP).
  - Analysis Data Adverse Events (ADAE).
  - Analysis Data Vital Signs (ADVS).
  - Analysis Data Electrocardiogram Parameters (ADEG).
  - Analysis Data Laboratory Test Results (ADLB).

For the scope of this trial, considering the primary and secondary objectives, six (6) Basic Data Structure (BDS) domains will be generated: ADPC, ADPP, ADAE, ADVS, ADEG and ADLB. These six datasets plus ADSL will be updated for each part. These domains will support the descriptive statistical analyses of the pharmacokinetic concentrations, the pharmacokinetic parameters and safety.

<u>ADSL – Subject-Level Analysis Dataset</u>
This analysis domain will contain: general data about the subjects (i.e., age, sex and race), planned and actual allocated treatment analysis, and start and end dates of treatment analysis period. The origin of these data will primarily be the Demographics (DM) and Exposure (EX) SDTM domains. Besides this information, the following variables will be derived:

- *Pharmacokinetic Analysis Set Population Flag 2* – Subjects included in the Part 2 Pharmacokinetic Analysis Population.
- *Drug-Drug Interaction Analysis Set Population Flag 7* – Subjects included in the Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population.

<u>ADPC – Analysis Data Pharmacokinetic Concentrations</u>
This is a BDS dataset that will contain the concentrations for each subject, per treatment analysis, per analyte/metabolite, and per timepoint.
The origin of these data will primarily be the EX and Pharmacokinetic Concentrations (PC) SDTM domains and ADSL ADaM domain.

Besides this information, the following variables will be derived:

- *Pharmacokinetic Analysis Set Population Flag 1.*
- *Drug-Drug Interaction Analysis Set Population Flag 1*
- *Drug-Drug Interaction Analysis Set Population Flag 2*
- *Drug-Drug Interaction Analysis Set Population Flag 3.*
- *Drug-Drug Interaction Analysis Set Population Flag 4.*
- *Drug-Drug Interaction Analysis Set Population Flag 5.*
- *Drug-Drug Interaction Analysis Set Population Flag 6.*
- *Pharmacokinetic Analysis Set Population Flag 2.*
- *Drug-Drug Interaction Analysis Set Population Flag 7.*
- *Pharmacokinetic Analysis Set Population Flag 3.*
- *Pharmacokinetic Analysis Set Population Flag 4.*

ADPP – Analysis Data Pharmacokinetic Parameters

This is a BDS dataset that will contain the NCA pharmacokinetic parameters (plasma and urine) for each subject, per treatment analysis and per analyte/metabolite.
Besides the original pharmacokinetic parameter value, the dataset will contain the *ln*-transformed value that is necessary to apply for the specified statistical model(s).
The origin of these data will primarily be the DM and Pharmacokinetic Parameters (PP) SDTM domains.
Besides this information, the following variables will be derived:

- *Pharmacokinetic Analysis Set Population Flag 1.*
- *Drug-Drug Interaction Analysis Set Population Flag 1.*
- *Drug-Drug Interaction Analysis Set Population Flag 2.*
- *Drug-Drug Interaction Analysis Set Population Flag 3.*
- *Drug-Drug Interaction Analysis Set Population Flag 4.*
- *Drug-Drug Interaction Analysis Set Population Flag 5.*
- *Drug-Drug Interaction Analysis Set Population Flag 6.*
- *Pharmacokinetic Analysis Set Population Flag 2.*
- *Drug-Drug Interaction Analysis Set Population Flag 7.*
- *Pharmacokinetic Analysis Set Population Flag 3.*
- *Pharmacokinetic Analysis Set Population Flag 4.*

ADAE – Analysis Data Adverse Events Dataset

This is an OCCDS dataset that will contain the adverse events for each subject.
The origin of these data will primarily be the Adverse Events (AE) SDTM domain and ADSL ADaM domain.

ADVS – Analysis Data Vital Signs Dataset

This is a BDS dataset that will contain the vital signs results for each subject, per treatment analysis and per timepoint.
The origin of these data will primarily be the Vital Signs (VS) SDTM domain and ADSL ADaM domain.

ADEG – Analysis Data Electrocardiogram Parameters Dataset

This is a BDS dataset that will contain the electrocardiogram for each subject, per treatment analysis and per timepoint.

The origin of these data will primarily be the ECG Test Results (EG) SDTM domain and ADSL ADaM domain.

ADLB – Analysis Data Laboratory Test Results Dataset
This is a BDS dataset that will contain the safety laboratory test results for each subject and per treatment analysis.
The origin of these data will primarily be the Laboratory Test Results (LB) SDTM domain and ADSL ADaM domain.

10. STATISTICAL METHODS

10.1. General Considerations

Estimation of the pharmacokinetic parameters and drug-drug interaction comparative bioavailability analysis will be conducted on Phoenix® WinNonlin® version 8.2 or higher (Certara USA Inc, Princeton, NJ). All other statistical analysis will be conducted on SAS® version 9.4 or higher.

Statistical analyses and pharmacokinetic analyses will be performed in accordance with the U.S. FDA guidances [2, 3] and PPD applicable Standard Operating Procedures (SOPs).

Unless specified otherwise, continuous variables will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), minimum, median and maximum values. Categorical data will be summarized with frequencies and percentages.
For subjects' characteristics and safety analyses, missing data will not be replaced; descriptive statistics and statistical analysis will be performed based on the available data only. All data recorded on discontinued subjects will be listed.

10.2. Subjects' Disposition

The number of subjects who completed each study part as well as subjects who withdrew prematurely from the study will be summarized by completion status and reason for withdrawal. Subjects who prematurely withdrew from the study will be listed.

The number of subjects included in each analysis population will be summarized, for each study part.

10.3. Protocol Deviations

During the respective Data Blind Review Process, all protocol deviations that occurred during each study part will be assessed in terms of their potential impact on the pharmacokinetic analysis. The result of this assessment will be reported in the respective Data Blind Review Process Minute (Annex 3).

10.4. Plasma Pharmacokinetic Concentrations

For each study part (Part 1, Part 2 and Part 3), for the subjects included in the respective pharmacokinetic analysis population, descriptive statistics [n, geometric mean (G_{mean}), arithmetic

mean (A_{mean}), SD, geometric SD (GSD), coefficient of variation (CV%), geometric CV% (GCV%), two-sided 95% CI of the A_{mean} and G_{mean}, median, minimum and maximum] of the plasma concentrations will be presented for each time point, by analyte, and by administration day. Concentrations below the LLOQ will be taken as missing for the calculation of the log-transformed statistics and as zero for the calculation of the remaining summary statistics.

For each study part (Part 1, Part 2 and Part 3), individual (per subject) and G_{mean} (including 95% CIs) plasma concentration *versus* time profile will be graphically displayed in both linear and semi-logarithmic scales:

- For plotting individual data in linear scale, concentrations below the LLOQ will be substituted by zero.
- For plotting G_{mean} data in linear scale, concentrations below the LLOQ will be substituted by missing.
- For plotting data in semi-logarithmic scale, concentrations below the LLOQ before t_{max}, will be substituted by ½ of the LLOQ value. After t_{max}, concentrations below the LLOQ will be considered as missing. However, in case of two or more consecutive concentrations below the LLOQ, the first value will be replaced by ½ of the LLOQ value and the next values will be considered as missing.

Graphic presentation of individual data will be based on actual blood sampling time, except for pre-dose sampling time which will be assumed as t_0.

Concentration data from non-evaluable periods will be listed and graphically represented separately.

10.5. Plasma Pharmacokinetic Parameters

For each study part, plasma pharmacokinetic parameters will be calculated for the respective pharmacokinetic analysis population.

For each study part, for the subjects included in the pharmacokinetic analysis population, individual plasma pharmacokinetic parameters and descriptive statistics (n, G_{mean}, A_{mean}, SD, GSD, CV%, GCV%, two-sided 95% CI of the A_{mean} and G_{mean}, median, minimum and maximum), will be presented by investigational product.

If a given pharmacokinetic parameter could not be reliably determined for more than ⅓ of the subjects, only the minimum and maximum values will be presented, and the other descriptive statistics will be omitted for that parameter.

Missing pharmacokinetic parameter data will not be imputed.

10.6. Drug-Drug Interaction Comparative Bioavailability Statistical Analysis

10.6.1. Part 2

Formal statistical analysis of pharmacokinetic data will be performed to characterize the following pharmacokinetic interactions:

1. Analysis of the potential effect of oral clarithromycin on the single-dose pharmacokinetics of oral givinostat:

C_{max} and AUC_{0-t} of givinostat when it is administered alone (Day 1) and co-administered with clarithromycin (Day 8) will be the primary pharmacokinetic parameters for the assessment of the potential effect of oral clarithromycin on the single-dose pharmacokinetics of oral givinostat.

An ANOVA will be performed on the *ln*-transformed primary pharmacokinetic parameters. A linear mixed effects model will be applied, using Treatment as fixed effect, assessed at a two one-sided 5% significance level ($\alpha = 0.05$). Subject will be included as random effect. GMR of the Test-to-Reference and corresponding 90% CI will be calculated for the *ln*-transformed primary pharmacokinetic parameters, using givinostat co-administered with clarithromycin as the Test and administered alone as the Reference.

Wilcoxon signed rank test will be used to test for the difference in T_{max}. The 90% CI for median T_{max} difference will be calculated by an exact asymmetric method.

10.7. Safety Data Analysis

Safety and tolerability data will be listed by study part, treatment, study timepoint and subject number and summarized descriptively by study part, treatment and study timepoint.

At each time point, absolute values of safety variables and change from baseline will be summarized with mean, median, SD, SE, minimum, and maximum values. The number of available observations and absolute out-of-range values will be presented. Values outside the investigator's normal range will be flagged in the listing.

For clinical laboratory data and vital signs data, out of range values will be flagged as "H" (High) or "L" (Low) in the Data Listings if the parameter is outside the normal range.
The ECG results will be listed per subject. Any comment on abnormal results will also be provided. Abnormalities in physical examination, ECG, clinical laboratory tests and vital signs will be classified in terms of clinical significance. Clinically significant abnormalities will be reported as adverse events (AEs).

AEs will be tabulated and summarized according to the MedDRA, version 24.1 or higher, and classified by SOC and PT.

All occurring TEAEs will be assigned to the last treatment administered. A separate listing of Serious Adverse Events (SAEs) will be presented, if applicable.

Incidence and frequency of TEAEs will be summarized descriptively by SOC and PT for each investigational product and overall.

11. PRESENTATION OF RESULTS

11.1. Statistical Output Specification

Tables will be generated as Rich Text Files (*.rtf) from SAS®.
Figures and Analysis Outputs will be generated as *.docx files, exported from Phoenix WinNonlin® and/or SAS®.

In-text Tables and Figures will preferably be prepared in portrait format. Listings will preferably be prepared in landscape format.

The CSR will be written according to PPD SOPs and templates for reporting bioavailability/bioequivalence trials.

11.2. Planned Tables, Figures, and Subject Data Listings

The planned Tables, Figures, and Individual Data Listings for the CSR are listed below.

11.2.1. In-text Tables and Figures

For CSR Synopsis:

The following Tables will be produced for direct insertion in the Synopsis of the CSR:

Title
PART 2
Givinostat: Summary Statistics of the Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8)
Givinostat: Potential Effect of Clarithromycin on the Pharmacokinetics of Givinostat: Total Intra-Subject Coefficient of Variation, Geometric Least Square Means, Geometric Least Square Means Ratio and Corresponding 90% Confidence Interval for C_{max} and AUC_{0-t}

The following Figures will be produced for direct insertion in the Synopsis of the CSR:

Legend
PART 2
Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8). A – Linear Scale; B – Semi-Logarithmic Scale

For CSR Body Text:

The following Tables and Figures will be produced for direct insertion in the body text of the CSR:

In-text Tables	**Title**
PART 2	
Table 2.A.	Study Flow-Chart – Part 2
Table 2.B.	Identity of Investigational Products – Part 2
Table 2.C.	Summary of Exposure to Treatment – Part 2
Table 2.D.	Summary of Subjects Disposition – Part 2

In-text Tables	Title
Table 2.E.	Summary of Demographic Data of Pharmacokinetic and Drug-Drug Interaction Comparable Bioavailability Analysis Populations
Table 2.F.	Givinostat: Summary Statistics of the Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8)
Table 2.G.	Givinostat: Potential Effect of Clarithromycin on the Pharmacokinetics of Givinostat: Total Intra-Subject Coefficient of Variation, Geometric Least Square Means, Geometric Least Square Means Ratio and Corresponding 90% Confidence Interval for C_{max} and AUC_{0-t}
Table 2.H.1.	Summary of Treatment-Emergent Adverse Events (TEAEs) – All TEAEs
Table 2.H.2.	Summary of Treatment-Emergent Adverse Events (TEAEs) – Drug-related TEAEs

In-text Figures	Legend
PART 2	
Figure 2.A.	Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8) – Linear Scale
Figure 2.B.	Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8) – Semi-Logarithmic Scale

11.2.2. Tables, Figures and Graphs Referred to But Not Included in the Text (Section 14 of CSR)

At least the following Tables and Figures should be produced for Section 14 of the CSR.
If necessary, additional Tables and Figures should be prepared.

The following Tables and Figures will be compiled in a document, to be considered as Section 14 (Tables, Figures and Graph Referred To But Not Included in the Text) of the CSR.

End-of-Text Tables	Title
14.2. PART 2	
14.2.1. DEMOGRAPHIC DATA – PART 2	
14.2.1.1.	**Demographic Data – Part 2 Safety Analysis Population**
14.2.1.2.	**Demographic Data – Part 2 Pharmacokinetic Analysis Population**
14.2.1.3.	**Demographic Data – Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population**
14.2.1.4.	**Subjects Prematurely Discontinued After First Dosing**
14.2.2. PHARMACOKINETIC DATA – PART 2	
14.2.2.1.	**Deviations from Blood Sampling Schedule**
14.2.2.1.1.	Deviations from Blood Sampling Schedule
14.2.2.1.2.	Missing Blood Samples
14.2.2.1.3.	Other Important Protocol Deviations
14.2.2.2.	**Plasma Concentrations**

End-of-Text Tables	Title
14.2.2.2.1.	Givinostat: Individual Data and Descriptive Statistics of Plasma Concentrations Following Administration of Givinostat Alone (Day 1)
14.2.2.2.2.	Givinostat: Individual Data and Descriptive Statistics of Plasma Concentrations Following Co-Administration of Givinostat and Clarithromycin (Day 8)
14.2.2.3.	**Pharmacokinetic Parameters**
14.2.2.3.1.	Givinostat: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1)
14.2.2.3.2.	Givinostat: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters Following Co-Administration of Givinostat and Clarithromycin (Day 8)
14.2.2.3.3.	Givinostat: Givinostat Co-Administered and Clarithromycin (Day 8)-to-Givinostat Alone (Day 1) Individual Ratios for C_{max}
14.2.2.3.4.	Givinostat: Givinostat Co-Administered and Clarithromycin (Day 8)-to-Givinostat Alone (Day 1) Individual Ratios for AUC_{0-t}
14.2.2.4.	**Log-Linear Regression Parameters for λ_z Estimation**
14.2.2.4.1.	Givinostat: Log-Linear Regression Parameters for λ_z Estimation Following Administration of Givinostat Alone (Day 1)
14.2.2.4.2.	Givinostat: Log-Linear Regression Parameters for λ_z Estimation Following Co-Administration of Givinostat and Clarithromycin (Day 8)
14.2.3. SAFETY DATA – PART 2	
14.2.3.1.	**Adverse Events**
14.2.3.1.1.	Pre-Treatment Adverse Events
14.2.3.1.2.	Treatment-Emergent Adverse Events (I)
14.2.3.1.3.	Treatment-Emergent Adverse Events (II)
14.2.3.2.	**Vital Signs**
14.2.3.2.1.	Descriptive Statistics of Vital Signs Parameters
14.2.3.2.2.	Descriptive Statistics of Change from Baseline of Vital Signs Parameters
14.2.3.2.3.	Shifts in Vital Signs Parameters
14.2.3.3.	**12-Lead ECG**
14.2.3.3.1.	Descriptive Statistics of 12-Lead ECG Parameters
14.2.3.3.2.	Descriptive Statistics of Change from Baseline of 12-Lead ECG Parameters
14.2.3.3.3.	Shifts in 12-Lead ECG Parameters
14.2.3.4.	**Hematology**
14.2.3.4.1.	Descriptive Statistics of Hematology Parameters
14.2.3.4.2.	Descriptive Statistics of Change from Baseline of Hematology Parameters
14.2.3.4.3.	Shifts in Hematology Parameters
14.2.3.5.	**Biochemistry**
14.2.3.5.1.	Descriptive Statistics of Biochemistry Parameters
14.2.3.5.2.	Descriptive Statistics of Change from Baseline of Biochemistry Parameters
14.2.3.5.3.	Shifts in Biochemistry Parameters
14.2.3.6.	**Coagulation**
14.2.3.6.1.	Descriptive Statistics of Coagulation Parameters
14.2.3.6.2.	Descriptive Statistics of Change from Baseline of Coagulation Parameters
14.2.3.6.3.	Shifts in Coagulation Parameters

End-of-Text Tables	Title
14.2.3.7.	**Urinalysis**
14.2.3.7.1.	Descriptive Statistics of Urinalysis Parameters
14.2.3.7.2.	Descriptive Statistics of Change from Baseline of Urinalysis Parameters
14.2.3.7.3.	Shifts in Urinalysis Parameters
14.2.3.8.	**Body Weight**
14.2.3.8.1.	Descriptive Statistics of Body Weight
14.2.3.8.2.	Descriptive Statistics of Body Weight – Male Subjects
14.2.3.8.3.	Descriptive Statistics of Body Weight – Female Subjects
14.2.3.8.4.	Descriptive Statistics of Change from Baseline of Body Weight
14.2.3.8.5.	Descriptive Statistics of Change from Baseline of Body Weight – Male Subjects
14.2.3.8.6.	Descriptive Statistics of Change from Baseline of Body Weight – Female Subjects

End-of-Text Figures	Title
14.2. PART 2	
14.2.2. PHARMACOKINETIC DATA – PART 2	
14.2.2.5.	**Plasma Concentration *Versus* Time Profiles of All Subjects**
14.2.2.5.1.	Givinostat: Plasma Concentration *Versus* Time Profiles of All Subjects Following Administration of Givinostat Alone (Day 1) – Linear Scale
14.2.2.5.2.	Givinostat: Plasma Concentration *Versus* Time Profiles of All Subjects Following Co-Administration of Givinostat and Clarithromycin (Day 8) – Linear Scale
14.2.2.6.	**Individual Plasma Concentration *Versus* Time Profiles**
14.2.2.6.1.	Givinostat: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration and Clarithromycin (Day 8) – Linear Scale
14.2.2.6.2.	Givinostat: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration and Clarithromycin (Day 8) – Semi-Logarithmic Scale

11.2.3. List of Subject Data Listings (Section 16.2 of CSR)

The following Data Listings will be produced for Section 16.2. Subject Data Listings of the CSR.

If necessary, additional Data Listings should be prepared.

Listing No.	Title
16.2. SUBJECTS DATA LISTING	
16.2.2. Part 2	

Listing No.	Title
16.2.2.1.	**Subject Disposition**
16.2.2.1.1.	Subject Disposition
16.2.2.2.	**Protocol Deviations**
16.2.2.2.1.	Blood Sampling Times Deviations
16.2.2.2.2.	Other Protocol Deviations
16.2.2.3.	Excluded Data from the Pharmacokinetic Analysis
16.2.2.3.1.	Plasma Concentrations
16.2.2.3.1.1.	Givinostat: Individual Data of Plasma Concentrations
16.2.2.3.2.	Plasma Concentration Versus Time Profiles
16.2.2.3.2.1.	Givinostat: Individual Plasma Concentration Versus Time Profiles – Linear Scale
16.2.2.3.2.2.	Givinostat: Individual Plasma Concentration Versus Time Profiles – Semi-Logarithmic Scale
16.2.2.4.	Demographic and Other Baseline Data
16.2.2.4.1.	Demographic Data
16.2.2.4.2.	Fertility/Contraception
16.2.2.4.2.1.	Female Fertility/Contraception
16.2.2.4.2.2.	Male Fertility/Contraception
16.2.2.4.3.	Drugs of Abuse, Ethanol and Cotinine
16.2.2.4.4.	Viral Serology at Screening
16.2.2.4.5.	Previous and Concomitant Medication
16.2.2.4.6.	SARS-COV-2 Test
16.2.2.5.	**Compliance**
16.2.2.5.1.	Investigational Product Administration
16.2.2.6.	**Individual Pharmacokinetic Data**
16.2.2.6.1.	Givinostat: Individual Pharmacokinetic Data
16.2.2.6.1.1.	Givinostat: Individual Drug Concentration Data
16.2.2.6.1.2.	Givinostat: Individual Pharmacokinetic Parameters
16.2.2.6.1.3.	Givinostat: Individual Pharmacokinetic Profiles
16.2.2.6.1.4.	Givinostat: Documentation of Statistical Analysis
16.2.2.6.1.4.1.	Givinostat: Non-Compartmental Analysis Output
16.2.2.6.1.4.2.	Givinostat: Non-Compartmental Analysis Plots
16.2.2.6.1.4.3.	Givinostat: Drug-Drug Interaction Analysis Output
16.2.2.7.	**Adverse Event Listings (Each Subject)**
16.2.2.7.1.	Pre-Treatment Adverse Events
16.2.2.7.2.	Treatment-Emergent Adverse Events
16.2.2.7.3.	Serious Adverse Events (I)
16.2.2.8.	**Listings of Laboratory Measurements by Subject**
16.2.2.8.1.	Normal Range of Laboratory Values
16.2.2.8.2.	Hematology (I)
16.2.2.8.3.	Hematology (II)
16.2.2.8.4.	Biochemistry (I)
16.2.2.8.5.	Biochemistry (II)
16.2.2.8.6.	Biochemistry (III)
16.2.2.8.7.	Biochemistry (IV)
16.2.2.8.8.	Biochemistry (V)
16.2.2.8.9.	Coagulation

Listing No.	Title
16.2.2.8.10.	Urinalysis
16.2.2.8.11.	Urine Microscopy
16.2.2.8.12.	Pregnancy Test
16.2.2.8.13.	Additional (Not Planned) Laboratory Safety Tests
16.2.2.9.	**Vital Signs**
16.2.2.10.	**12-Lead ECG**

12. REFERENCES

[1] ITF/2357/55 Clinical Study Protocol, Version 1.0, 29NOV2021
[2] Food and Drug Administration (FDA), Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (2020).

13. APPENDICES

APPENDIX A. Planned Tables, Figures, and Subject Data Listings

A.1. In-text Tables and Figures – For CSR Synopsis

A.1.1. **Part 2**

SYNOPSIS TABLES (1)

Givinostat: Summary Statistics of the Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8)

Parameter (unit)	Givinostat Alone (Day 1) (n = xx)	Givinostat Co-Administered with Clarithromycin (Day 8) (n = xx)
C_{max} (<unitsC>)	xx.xx (xx.x%)	xx.xx (xx.x%)
T_{max} (h)	xx.xx (xx.xx – xx.xx)	xx.xx (xx.xx – xx.xx)
AUC_{0-t} (<unitsA>)	xx.xx (xx.x%)	xx.xx (xx.x%)
$AUC_{0-\infty}$ (<unitsA>)	xx.xx (xx.x%)	xx.xx (xx.x%)
$\%AUC_{extrap}$ (%)	xx.xx (xx.x%)	xx.xx (xx.x%)
λ_z (1/h)	x.xxx (xx.x%)	x.xxx (xx.x%)
$t_{½}$ (h)	xx.xx (xx.x%)	xx.xx (xx.x%)

n – Number of Subjects
Values are geometric mean (G_{mean}) with geometric coefficient of variation (GCV%) within parenthesis
T_{max} values are median with range between parentheses
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: This table will present the summary statistics of the pharmacokinetic parameters calculated for Part 2 Pharmacokinetic Analysis Population. In case a pharmacokinetic parameter could not be calculated for one or more subjects in the Part 2 Pharmacokinetic Analysis Population, the pharmacokinetic parameter should be followed by the # symbol and accompanied by a footnote: '# For <Parameter(s)>, n=xx, for <Investigational Product> product <, and n=xx, for <Investigational Product> product> '.

SYNOPSIS TABLES (2)

Givinostat: Potential Effect of Clarithromycin on the Pharmacokinetics of Givinostat: Total Intra-Subject Coefficient of Variation, Geometric Least Square Means, Geometric Least Square Means Ratio and Corresponding 90% Confidence Interval for C_{max} and AUC_{0-t}

Parameter	Total ISCV%	Geometric LSmeans		GMR (%)	90% CI
		Givinostat Alone (Day 1)	Givinostat Co-Administered with Clarithromycin (Day 8)		
C_{max}	xx.x	xx.xx	xx.xx	xx.xx	xx.xx – xx.xx
AUC_{0-t}	xx.x	xx.xx	xx.xx	xx.xx	xx.xx – xx.xx

Geometric LSmeans values are given in <unitsC> for C_{max} and <unitsA> for AUC
GMR corresponds to the ratio of the Geometric LSmeans of Givinostat Co-Administered with Clarithromycin (Day 8) and the Geometric LSmeans of Givinostat Alone (Day 1)
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: This table will present the results of the analysis of the potential effect of clarithromycin on the pharmacokinetics of givinostat, performed on the Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population.

SYNOPSIS FIGURES (3)

Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8). A – Linear Scale; B – Semi-Logarithmic Scale

Plot the values of giviniostat plasma concentrations (<unitsC>) on the y axis against time (h) on the x axis.
Label x axis with 'Time (h)' and y axis with 'Givinostat Concentration (<unitsC>)'.
Marks on the x axis should be from time 0 to 72 h, at intervals of 4 hours, or multiples.
Plasma concentrations marks for each blood sampling scheduled timepoint should be in (i) bordered circles (in black color) without fill for Givinostat Alone (Day 1), and (ii) solid fill circles (in dark blue color) for the Givinostat Co-Administered with Clarithomycin (Day 8).

These guidelines should be applied on every Figure produced for pharmacokinetic results of this study.

Note: These figures will present the geometric mean concentration versus time profiles calculated for the Part 2 Pharmacokinetic Analysis Population.

A.2. In-text Tables and Figures – For CSR Body Text

A.2.1. Part 2

Table 1.A. Study Flow-Chart – Part 2

Note: To be captured from the Clinical Study Protocol (CSP) and Amendments.

Table 1.B. Identity of Investigational Products – Part 2

Note: To be generated by the Medical Writing (MW).

Table 1.C. Summary of Exposure to Treatment – Part 2

Treatment	Study Day	Number of Subjects
Givinostat 50 mg	Day 1	xx
Clarithromycin 500 mg b.i.d.	Days 4-7	xx
Clarithromycin 500 mg b.i.d + Givinostat 50 mg	Day 8	xx
Clarithromycin 500 mg b.i.d.	Day 9-10	xx

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Table 1.D. Summary of Subjects Disposition – Part 2

Disposition	Number of Subjects
Randomized	**xx**
Discontinued after First Dosing	**xx**
Reason	
- <Reason>	xx
Part 2 Safety Analysis Population	**xx**
Part 2 Pharmacokinetic Analysis Population	**xx**
Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population	**xx**
Completed Part 2 of Study	**xx**

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Table 1.E. Summary of Demographic Data of Pharmacokinetic and Drug-Drug Interaction Comparable Bioavailability Analysis Populations

Demography	Parameter	Pharmacokinetic Analysis Population	Drug-Drug Interaction Comparable Bioavailability Analysis Population
Age (years)	n	xx	xx
	Mean	xx	xx
	SD	xx.x	xx.x
	Median	xx	xx
	Minimum	xx	xx
	Maximum	xx	xx
Sex, n (%)	n	xx	xx
	Male	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)
Race, n (%)	n	xx	xx
	<Race>	xx (xx.x%)	xx (xx.x%)
Weight (kg)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Minimum	xx.x	xx.x
	Maximum	xx.x	xx.x
Height (cm)	n	xx	xx
	Mean	xxx	xxx
	SD	xx.x	xx.x
	Median	xxx	xxx
	Minimum	xxx	xxx
	Maximum	xxx	xxx
Body Mass Index (kg/m^2)	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Minimum	xx.x	xx.x
	Maximum	xx.x	xx.x

n – Number of Subjects; SD – Standard Deviation
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Table 1.F. Givinostat: Summary Statistics of the Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8)

Parameter (unit)	Givinostat Alone (Day 1) (n = xx)	Givinostat Co-Administered with Clarithromycin (Day 8) (n = xx)
C_{max} (<unitsC>)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]
T_{max} (h)	xx.xx (xx.xx – xx.xx)	xx.xx (xx.xx – xx.xx)
AUC_{0-t} (<unitsA>)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]
$AUC_{0-\infty}$ (<unitsA>)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]
$\%AUC_{extrap}$ (%)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]
λ_z (1/h)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]
$t_{½}$ (h)	xx.xx (xx.x%)	xx.xx (xx.x%)
	[xx.xx – xx.xx]	[xx.xx – xx.xx]

n – Number of Subjects
Values are geometric mean (G_{mean}) with geometric coefficient of variation (GCV%) within parenthesis and 95% confidence interval of the G_{mean} within square brackets
T_{max} values are median with range between parentheses
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: This table will present the summary statistics of the pharmacokinetic parameters calculated for Part 2 Pharmacokinetic Analysis Population. In case a pharmacokinetic parameter could not be calculated for one or more subjects in the Part 2 Pharmacokinetic Analysis Population, the pharmacokinetic parameter should be followed by the # symbol and accompanied by a footnote: '# For <Parameter(s)>, n=xx, for <Investigational Product> product <, and n=xx, for <Investigational Product> product> '.

Table 1.G. Givinostat: Potential Effect of Clarithromycin on the Pharmacokinetics of Givinostat: Total Intra-Subject Coefficient of Variation, Geometric Least Square Means, Geometric Least Square Means Ratio and Corresponding 90% Confidence Interval for C_{max} and AUC_{0-t}

Parameter	Total ISCV%	Geometric LSmeans		GMR (%)	90% CI
		Givinostat Alone (Day 1)	Givinostat Co-Administered with Clarithromycin (Day 8)		
C_{max}	xx.x	xx.xx	xx.xx	xx.xx	xx.xx – xx.xx
AUC_{0-t}	xx.x	xx.xx	xx.xx	xx.xx	xx.xx – xx.xx

Geometric LSmeans values are given in <unitsC> for C_{max} and <unitsA> for AUC
GMR corresponds to the ratio of the Geometric LSmeans of Givinostat Co-Administered with Clarithromycin (Day 8) and the Geometric LSmeans of Givinostat Alone (Day 1)
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: This table will present the results of the analysis of the potential effect of clarithromycin on the pharmacokinetics of givinostat, performed on the Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population.

Table 1.H.
Table 1.H.1. Summary of Treatment-Emergent Adverse Events (TEAEs) – All TEAEs

	Givinostat (n = xx)	Clarithromycin (n = xx)	Total (N = xx)
Number of Subjects {Nr. of TEAEs} (% of Subjects)	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
MedDRA System Organ Class (SOC) Preferred Term (PT)			
<TEAEs SOC>	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
<TEAEs SOC>	xx {xx} (xx%)	xx {xx} (xx%)	xx {xx} (xx%)
<Insert as many rows as deemed necessary>			
Severity			
Mild	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
Moderate	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
Severe	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**

MedDRA – Medical Dictionary for Regulatory Activities
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Table 1.H.2. Summary of Treatment-Emergent Adverse Events (TEAEs) – Drug-Related TEAEs

Treatment Groups	Substrate Alone (n = xx)	Steady-state Build-Up (n = xx)		Inhibition Effect (n = xx)	
Treatment Identification	**Givinostat**	**Clarithromycin**	**Clarithromycin**	**Givinostat**	**Total**
Number of Subjects {Nr. of TEAEs} (% of Subjects)	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
MedDRA System Organ Class (SOC) Preferred Term (PT)					
<TEAEs SOC>	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
<TEAEs SOC>	xx {xx} (xx%)	xx {xx} (xx%)	xx {xx} (xx%)	xx {xx} (xx%)	xx {xx} (xx%)
<Insert as many rows as deemed necessary>					
Severity					
Mild	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
Moderate	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**
Severe	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**	**xx {xx} (xx%)**

MedDRA – Medical Dictionary for Regulatory Activities
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Figure 1.A. Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8) – Linear Scale

Figure 1.B. Givinostat: Geometric Mean (95% CI) Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration of Givinostat and Clarithromycin (Day 8) – Semi-Logarithmic Scale

14.1.1. SAFETY DATA

14.2. PART 2

14.2.1. DEMOGRAPHIC DATA – PART 2

14.2.1.1. Demographic Data – Part 2 Safety Analysis Population [2]

14.2.1.2. Demographic Data – Part 2 Pharmacokinetic Analysis Population [2]

14.2.1.3. Demographic Data – Part 2 Drug-Drug Interaction Comparable Bioavailability Analysis Population [2]

[2] *To be generated as follows:*

Subject No.	Sex	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
<Subject ID>	<Male / Female>	<Race>	xx	xxx	xx.x	xx.x
<Insert as many rows as deemed necessary>						
		n	xx	xx	xx	xx
		Mean	xx	xxx	xx.x	xx.x
		SD	xx.x	xx.x	xx.xx	xx.xx
		Median	xx	xxx	xx.x	xx.x
		Minimum	xx	xxx	xx.x	xx.x
		Maximum	xx	xxx	xx.x	xx.x

BMI – Body Mass Index; n – Number of Subjects; SD – Standard Deviation
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.1.4. Subjects Prematurely Discontinued After First Dosing

Subject No.	Time of Discontinuation	Last Treatment Administered	Reason for Discontinuation
<Subject ID>	<Day # >	<Treatment>	<Reason>
<Insert as many rows as deemed necessary>			

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2. PHARMACOKINETIC DATA – PART 2

14.2.2.1. Deviations from Blood Sampling Schedule

14.2.2.1.1. Deviations from Blood Sampling Schedule

Subject No.	Day of Dose	Investigational Product	Analyte	Planned Time (h:min)	Deviation (h:min)	Reason for Deviation
<Subject>	<Day #>	<Investigational Product>	<Analyte>	<Planned blood sampling time>	<Deviation time>	<Reason for deviation (e.g. Difficulty with blood sampling / Subject unavailable at scheduled time)>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2.1.2. Missing Blood Samples

Subject No.	Day of Dose	Treatment	Analyte	Planned Time (h:min)	Reason for Missing Blood Sample
<Subject ID>	<Day #>	<Treatment>	<Analyte>	<Planned blood sampling time>	<Reason for missing blood sample>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2.1.3. Other Important Protocol Deviations

Subject No.	Day of Dose	Treatment	Analyte	Category	Description
<Subject ID>	<Day #>	<Treatment>	<Analyte>	<Deviation category>	<Description of deviation>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2.2. Plasma Concentrations

14.2.2.2.1. Givinostat: Individual Data and Descriptive Statistics of Plasma Concentrations Following Administration of Givinostat Alone (Day 1) [3]

14.2.2.2.2. Givinostat: Individual Data and Descriptive Statistics of Plasma Concentrations Following Co-Administration of Givinostat and Clarithromycin (Day 8) [3]

[3] To be generated as follows:

Subject No.	Pre-dose	Time Post-Dose (h)									
		x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
<Subject ID>	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
<Insert as many rows as deemed necessary>											
n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
G_{mean} (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
A_{mean} (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
GSD (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
GCV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
G_{mean} 95% CI Lower (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
G_{mean} 95% CI Upper (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
A_{mean} 95% CI Lower (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
A_{mean} 95% CI Upper (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Minimum (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Maximum (<unitsC>)	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

n – Number of Subjects; G_{mean} – Geometric Mean; A_{mean} – Arithmetic Mean; GSD – Geometric Standard Deviation; SD – Standard Deviation; GCV% – Geometric Coefficient of Variation; CV% – Coefficient of Variation; G_{mean} 95% CI Lower – Lower Limit of the 95% Confidence Interval for the Geometric Mean; G_{mean} 95% CI Upper – Upper Limit of the 95% Confidence Interval for the Geometric Mean; A_{mean} 95% CI Lower – Lower Limit of the 95% Confidence Interval for the Arithmetic Mean; A_{mean} 95% CI Upper – Upper Limit of the 95% Confidence Interval for the Arithmetic Mean.
BLQ – Below the Limit of Quantification (LLOQ = <LLOQ> <unitsC>) of the assay (taken as missing for the calculation of log-transformed statistics and as zero for the calculation of the remaining summary statistics)
ND – Not Done
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: These tables will present the individual data and descriptive statistics of the plasma concentrations of the Part 2 Pharmacokinetic Analysis Population.

14.2.2.3. Pharmacokinetic Parameters

14.2.2.3.1. Givinostat: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters Following Administration of Givinostat Alone (Day 1) [4]

14.2.2.3.2. Givinostat: Individual Data and Descriptive Statistics of Pharmacokinetic Parameters Following Co-Administration of Givinostat and Clarithromycin (Day 8) [4]

[4] To be generated as follows:

Subject No.	C_{max} (<unitsC>)	T_{max} (h)	AUC_{0-t} (<unitsA>)	$AUC_{0-\infty}$ (<unitsA>)	$\%AUC_{extrap}$ (%)	λ_z (1/h)	$t_{1/2}$ (h)
<Subject ID>	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
<Insert as many rows as deemed necessary>							
n	xx	xx	xx	xx	xx	xx	xx
G_{mean}	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
A_{mean}	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
GSD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
GCV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
G_{mean} 95% CI Lower	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
G_{mean} 95% CI Upper	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
A_{mean} 95% CI Lower	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
A_{mean} 95% CI Upper	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
Minimum	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx
Maximum	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	x.xxx	xx.xx

n – Number of Subjects; G_{mean} – Geometric Mean; A_{mean} – Arithmetic Mean; GSD – Geometric Standard Deviation; SD – Standard Deviation; GCV% – Geometric Coefficient of Variation; CV% – Coefficient of Variation; G_{mean} 95% CI Lower – Lower Limit of the 95% Confidence Interval for the Geometric Mean; G_{mean} 95% CI Upper – Upper Limit of the 95% Confidence Interval for the Geometric Mean; A_{mean} 95% CI Lower – Lower Limit of the 95% Confidence Interval for the Arithmetic Mean; A_{mean} 95% CI Upper – Upper Limit of the 95% Confidence Interval for the Arithmetic Mean.
NC – Not Calculated
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: These tables will present the individual data and descriptive statistics of the pharmacokinetic parameters calculated for Part 2 Pharmacokinetic Analysis Population.

14.2.2.3.3. Givinostat: Givinostat Co-Administered and Clarithromycin (Day 8)-to-Givinostat Alone (Day 1) Individual Ratios for C_{max} [5]

14.2.2.3.4. Givinostat: Givinostat Co-Administered and Clarithromycin (Day 8)-to-Givinostat Alone (Day 1) Individual Ratios for AUC_{0-t} [5]

[5] *To be generated as follows:*

Subject No.	Givinostat Co-Administered and Clarithromycin (Day 8) (<units>)	Givinostat Alone (Day 1) (<units>)	Ratio (%)
<Subject ID>	xx.xx	xx.xx	xx.xx

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2.4. Log-Linear Regression Parameters for λ_z Estimation

14.2.2.4.1. Givinostat: Log-Linear Regression Parameters for λ_z Estimation Following Administration of Givinostat Alone (Day 1) [6]

14.2.2.4.2. Givinostat: Log-Linear Regression Parameters for λ_z Estimation Following Co-Administration of Givinostat and Clarithromycin (Day 8) [6]

[6] *To be generated as follows:*

Subject No.	Lower TLIN (h)	Upper TLIN (h)	No. of Time Points	RSQ
<Subject ID>	xx.xx	xx.xx	xx	x.xx

<Insert as many rows as deemed necessary>

Lower TLIN – Lower Time Point Used in Regression Analysis; Upper TLIN – Upper Time Point Used in Regression Analysis; RSQ – Goodness of Fit for the Terminal Elimination Phase
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.2.5. Plasma Concentration *Versus* Time Profiles of All Subjects

14.2.2.5.1. Givinostat: Plasma Concentration *Versus* Time Profiles of All Subjects Following Administration of Givinostat Alone (Day 1) – Linear Scale

14.2.2.5.2. Givinostat: Plasma Concentration *Versus* Time Profiles of All Subjects Following Co-Administration of Givinostat and Clarithromycin (Day 8) – Linear Scale

Note: These Figures will be extracted from Phoenix® WinNonlin® 8.2 or higher.

14.2.2.6. Individual Plasma Concentration *Versus* Time Profiles

14.2.2.6.1. Givinostat: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration and Clarithromycin (Day 8) – Linear Scale

14.2.2.6.2. Givinostat: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Givinostat Alone (Day 1) and Co-Administration and Clarithromycin (Day 8) – Semi-Logarithmic Scale

Note: These figures will be extracted from Phoenix® WinNonlin® 8.2 or higher. A figure will be produced for each subject included in the pharmacokinetic analysis population.

14.2.3. SAFETY DATA – PART 2

14.2.3.1. Adverse Events

14.2.3.1.1. Pre-Treatment Adverse Events

Subject No.	SOC MedDRA PT (Reported Term)	SAE? (Yes/No)	Adverse Event Date and Time		Maximal Severity	Causality	Medication Required?	Outcome
			Start	End				
<Subject ID>	<SOC> <TEAE in MedDRA PT> (<TEAE reported term>)	<Yes / No>	DDMMMYYYY-hh:mm>	DDMMMYYYY-hh mm>	<Maximal Severity of the AE>	<Causality of the AE>	<Yes/No>	<Outcome of the AE>

<Insert as many rows as deemed necessary>

SOC – System Organ Class; MedDRA – Medical Dictionary for Regulatory Activities; PT – Preferred Term; SAE – Serious Adverse Event
NK – Not Known
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.3.1.2. Treatment-Emergent Adverse Events (I)

Subject No.	Day of Dose	Treatment	SOC MedDRA PT (Reported Term)	SAE? (Yes/No)	Last Treatment Date and Time	Adverse Event Date and Time	
						Start	Start
<Subject ID>	<Day #>	<Treatment>	<SOC> <TEAE in MedDRA PT> (<TEAE reported term>)	<Yes / No>	<DDMMMYYYY hh:mm>	<DDMMMYYYY hh:mm>	<DDMMMYYYY hh:mm>

<Insert as many rows as deemed necessary>

SOC – System Organ Class; MedDRA – Medical Dictionary for Regulatory Activities; PT – Preferred Term; SAE – Serious Adverse Event
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.3.1.3. Treatment-Emergent Adverse Events (II)

Subject No.	Day of Dose	Treatment	SOC MedDRA PT (Reported Term)	Maximal Severity	Causality	Medication Required?	Outcome
<Subject ID>	<Day #>	<Treatment>	<SOC> <TEAE in MedDRA PT> (<TEAE reported term>)	<Maximal Severity of the TEAE>	<Causality of the TEAE>	<Yes/No>	<Outcome of the TEAE>

<Insert as many rows as deemed necessary>

SOC – System Organ Class; MedDRA – Medical Dictionary for Regulatory Activities; PT – Preferred Term; SAE – Serious Adverse Event
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.3.2. Vital Signs

14.2.3.2.1. Descriptive Statistics of Vital Signs Parameters [9]

14.2.3.2.2. Descriptive Statistics of Change from Baseline of Vital Signs Parameters [9]

14.2.3.2.3. Shifts in Vital Signs Parameters [10]

14.2.3.3. 12-Lead ECG

14.2.3.3.1. Descriptive Statistics of 12-Lead ECG Parameters [9]

14.2.3.3.2. Descriptive Statistics of Change from Baseline of 12-Lead ECG Parameters [9]

14.2.3.3.3. Shifts in 12-Lead ECG Parameters [10]

14.2.3.4. Hematology

14.2.3.4.1. Descriptive Statistics of Hematology Parameters [9]

14.2.3.4.2. Descriptive Statistics of Change from Baseline of Hematology Parameters [9]

14.2.3.4.3. Shifts in Hematology Parameters [10]

14.2.3.5. Biochemistry

14.2.3.5.1. Descriptive Statistics of Biochemistry Parameters [9]

14.2.3.5.2. Descriptive Statistics of Change from Baseline of Biochemistry Parameters [9]

14.2.3.5.3. Shifts in Biochemistry Parameters [10]

14.2.3.6. Coagulation

14.2.3.6.1. Descriptive Statistics of Coagulation Parameters [9]

14.2.3.6.2. Descriptive Statistics of Change from Baseline of Coagulation Parameters [9]

14.2.3.6.3. Shifts in Coagulation Parameters [10]

14.2.3.7. Urinalysis

14.2.3.7.1. Descriptive Statistics of Urinalysis Parameters [9]

14.2.3.7.2. Descriptive Statistics of Change from Baseline of Urinalysis Parameters [9]

14.2.3.7.3. Shifts in Urinalysis Parameters [10]

[9] *To be generated as follows:*

Parameter	Treatment	Study Day	Protocol Time	n	Mean	SD	SE	Median	Minimum	Maximum
<Parameter (unit)>	<Treatment>	<Day>	<Protocol Time>	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
			<Protocol Time>							
			<Protocol Time>							
			<Protocol Time>							
<Insert as many rows as deemed necessary>										

n – number of subjects; SD – Standard Deviation; SE – Standard Error
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

[10] *To be generated as follows:*

Parameter	Study Day	Protocol Time	Classification		Nr. of Subjects
			Baseline	Post-Baseline Assessment	
<Parameter (unit)>	<Day>	<Protocol Time>	<Low/ Normal/ High>	<Low/ Normal/ High>	xx
		<Protocol Time>	<Low/ Normal/ High>	<Low/ Normal/ High>	xx
<Insert as many rows as deemed necessary>					

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

14.2.3.8. Body Weight

14.2.3.8.1. Descriptive Statistics of Body Weight [9]

14.2.3.8.2. Descriptive Statistics of Body Weight – Male Subjects [9]

14.2.3.8.3. Descriptive Statistics of Body Weight – Female Subjects [9]

14.2.3.8.4. Descriptive Statistics of Change from Baseline of Body Weight [9]

14.2.3.8.5. Descriptive Statistics of Change from Baseline of Body Weight – Male Subjects [9]

14.2.3.8.6. Descriptive Statistics of Change from Baseline of Body Weight – Female Subjects [9]

[9] *To be generated as follows:*

Visit	n	Mean	SD	SE	Median	Minimum	Maximum
<Day>	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
<Insert as many rows as deemed necessary>							

n – number of subjects; SD – Standard Deviation; SE – Standard Error
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

A.3. List of Subject Data Listings (Section 16.2 of CSR)

A.3.1. Part 1

16.2. SUBJECTS DATA LISTINGS

16.2.1. PART 1

16.2.1.1. Subject Disposition

16.2.1.1.1. Subject Disposition

Screening No.	Date ICF Signed	Subject Eligible?	Subject Given an Unique Subject No.?	Unique Subject No.	Inclusion Criteria Not Met	Exclusion Criteria Met	Other Reason for Non-Eligibility	Reason for Non-Randomization
<Screening number>	<DDMMMYYYY>	<Yes/No>	<Yes/No>	<Unique Subject No>	<List all inclusion criteria that were not met>	<List all exclusion criteria that were met>	<List other reasons for non-eligibility>	<List reason for non-randomization>

<Insert as many rows as deemed necessary>

ICF – Informed Consent Form
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.2. Protocol Deviations

16.2.1.2.1. Blood Sampling Times Deviations

Subject No.	Treatment	Sampling Timepoint	Sampling Date and Time		Deviation Reason
			Scheduled/Target	Actual	
<Subject ID>	<Treatment>	<Scheduled Time or unscheduled>	<DDMMMYYYY hh:mm>	<DDMMMYYYY hh mm>	<Reason for deviation>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.2.2. Other Protocol Deviations

Subject No.	Protocol Phase	Treatment	Category	Description	Classification
<Subject ID>	<Protocol Phase #>	<Treatment>	<Deviation Category>	<Description of the deviation>	<Important / Not important>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.3. Excluded Data from the Pharmacokinetic Analysis

16.2.1.3.1. Plasma Concentrations

16.2.1.3.1.1. Midazolam: Individual Data of Plasma Concentrations Following Administration of Midazolam IV [9]

16.2.1.3.1.2. 1-Hydroxymidazolam: Individual Data of Plasma Concentrations Following Administration of Midazolam IV [9]

16.2.1.3.1.3. Midazolam: Individual Data of Plasma Concentrations Following Administration of Oral Midazolam [9]

16.2.1.3.1.4. 1-Hydroxymidazolam: Individual Data of Plasma Concentrations Following Administration of Oral Midazolam [9]

16.2.1.3.1.5. Total Dabigatran: Individual Data of Plasma Concentrations Following Administration of Dabigatran Etexilate [9]

16.2.1.3.1.6. Free Dabigatran: Individual Data of Plasma Concentrations Following Administration of Dabigatran Etexilate [9]

[9] *To be generated as follows:*

Subject No.	Day of Dosing	Investigational Product	Pre-dose	Time Post-Dose (h)									
				x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
<Subject ID>	<Day #>	<Investigational Product>	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

<Insert as many rows as deemed necessary>

BLQ – Below the Limit of Quantification (LLOQ = <LLOQ> <unitsC>) of the assay
ND – Not Done
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.3.2. Plasma Concentration *Versus* Time Profiles

16.2.1.3.2.1. Midazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Midazolam IV – Linear Scale

16.2.1.3.2.2. Midazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Midazolam IV – Semi-Logarithmic Scale

16.2.1.3.2.3. 1-Hydroxymidazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Midazolam IV – Linear Scale

16.2.1.3.2.4. 1-Hydroxymidazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Midazolam IV – Semi-Logarithmic Scale

16.2.1.3.2.5. Midazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Oral Midazolam – Linear Scale

16.2.1.3.2.6. Midazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Oral Midazolam – Semi-Logarithmic Scale

16.2.1.3.2.7. 1-Hydroxymidazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Oral Midazolam – Linear Scale

16.2.1.3.2.8. 1-Hydroxymidazolam: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Oral Midazolam – Semi-Logarithmic Scale

16.2.1.3.2.9. Total Dabigatran: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Dabigatran Etexilate – Linear Scale

16.2.1.3.2.10. Total Dabigatran: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Dabigatran Etexilate – Semi-Logarithmic Scale

16.2.1.3.2.11. Free Dabigatran: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Dabigatran Etexilate – Linear Scale

16.2.1.3.2.12. Free Dabigatran: Individual Plasma Concentration *Versus* Time Profiles Following Administration of Dabigatran Etexilate – Semi-Logarithmic Scale

Note: These Figures will be extracted from Phoenix® WinNonlin® 8.2 or higher. A figure will be produced for each subject with data excluded from the pharmacokinetic analysis.

16.2.1.4. Demographic and Other Baseline Data

16.2.1.4.1. Demographic Data

Subject No.	Date ICF Signed	Date of Birth	Sex	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
<Subject ID>	<DDMMMYYYY>	<MMMYYYY>	<M/F>	<Race>	xx	xxx	xx.x	xx.x

<Insert as many rows as deemed necessary>

ICF – Informed Consent Form; BMI – Body Mass Index; M – Male; F – Female
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.2. Fertility/Contraception

16.2.1.4.2.1. Female Fertility/Contraception

Subject No.	Childbearing Potential?	If Yes, Birth Control Method	Breast Feeding?	Comments
<Subject ID>	<Yes/No>	<Birth Control Method>	<Yes/No>	<Comments>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.2.2. Male Fertility/Contraception

Subject No.	Sexually Active?	Agrees to Use Condom?	Female partner agrees to use a highly effective method of contraception?	Agree not to donate sperm from first dose administration until at least 90 days after the last study drug administration?	Comments
<Subject ID>	<Yes/No>	<Yes/No>	<Yes/No>	<Yes/No>	<Comments>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.3. Drugs of Abuse, Ethanol and Cotinine

Subject No.	Investigational Product	Date and Time	Amphetamines	Benzodiazepines	Cocaine	Cannabinoids	Opiates	Ethanol	Cotinine
<Subject ID>	<Investigational Product>	<DDMMMYYYY hh:mm>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.4. Viral Serology at Screening

Subject No.	Actual Date and Time	Protocol Phase	HIV-1 & HIV-2	Hepatitis B	Hepatitis C
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>

<Insert as many rows as deemed necessary>

HIV – Human Immunodeficiency Virus
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.5. Previous and Concomitant Medication

Subject No.	Treatment	Drug Name [ATC Code]	Indication	Pharmaceutical Form	Dose (units)	Frequency	Route	Date and Time	
								Start	End
<Subject ID>	<Treatment>	<Generic name [XXXXXXX]>	<Therapeutic indication>	<Pharmaceutical Form>	<Dose (units)>	<Frequency>	<Route>	<DDMMMYYYY>	<DDMMMYYYY or Ongoing>

<Insert as many rows as deemed necessary>

ATC – Anatomical Therapeutic Chemical
NK – Not Known
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.4.6. SARS-COV-2 Test

Subject No.	Actual Date	Protocol Phase	Result	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY>	<Protocol Phase>	<Not detectable, Detectable, Inconclusive >	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for any of the evaluations.

16.2.1.5. Compliance

16.2.1.5.1. Investigational Product Administration

Subject No.	Date	Actual Clock Time	Investigational Product	Dose (units)	Investigational Product Formulation	Route of Administration	Hands and Mouth Check?	150 mL of water taken?	Comments
<Subject ID>	<DDMMMYYYY/ N/A>	<hh:mm/ N/A>	<Investigational Product>	<Dose (units)>	<Formulation>	<Route>	<Yes/No/ N/A>	<Yes/No/ N/A>	<Comments>

<Insert as many rows as deemed necessary>

N/A – Not Applicable
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.6. Individual Pharmacokinetic Data

16.2.1.6.1. Midazolam: Individual Pharmacokinetic Data Following Administration of Midazolam IV

16.2.1.6.1.1. Midazolam: Individual Drug Concentration Data Following Administration of Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.1. to 14.1.2.2.3.'

16.2.1.6.1.2. Midazolam: Individual Pharmacokinetic Parameters Following Administration of Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.1. to 14.1.2.3.3.'

16.2.1.6.1.3. Midazolam: Individual Pharmacokinetic Profiles Following Administration of Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.1. to 14.1.2.6.2.'

16.2.1.6.1.4. Midazolam: Documentation of Statistical Analysis Following Administration of Midazolam IV

16.2.1.6.1.4.1. Midazolam: Non-Compartmental Analysis Output

16.2.1.6.1.4.2. Midazolam: Non-Compartmental Analysis Plots

16.2.1.6.1.4.3. Midazolam: Potential Inhibitory Effect Analysis Output

16.2.1.6.1.4.4. Midazolam: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.6.2. 1-Hydroxymidazolam: Individual Pharmacokinetic Data Following Administration of Midazolam IV

16.2.1.6.2.1. 1-Hydroxymidazolam: Individual Drug Concentration Data Following Administration Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.4. to 14.1.2.2.6.'

16.2.1.6.2.2. 1-Hydroxymidazolam: Individual Pharmacokinetic Parameters Following Administration of Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.4. to 14.1.2.3.6.'

16.2.1.6.2.3. 1-Hydroxymidazolam: Individual Pharmacokinetic Profiles Following Administration of Midazolam IV

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.3. to 14.1.2.6.4.'

16.2.1.6.2.4. 1-Hydroxymidazolam: Documentation of Statistical Analysis Following Administration of Midazolam IV

16.2.1.6.2.4.1. 1-Hydroxymidazolam: Non-Compartmental Analysis Output

16.2.1.6.2.4.2. 1-Hydroxymidazolam: Non-Compartmental Analysis Plots

16.2.1.6.2.4.3. 1-Hydroxymidazolam: Potential Inhibitory Effect Analysis Output

16.2.1.6.2.4.4. 1-Hydroxymidazolam: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.6.3. Midazolam: Individual Pharmacokinetic Data Following Administration of Oral Midazolam

16.2.1.6.3.1. Midazolam: Individual Drug Concentration Data Following Administration of Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.7. to 14.1.2.2.9.'

16.2.1.6.3.2. Midazolam: Individual Pharmacokinetic Parameters Following Administration of Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.7. to 14.1.2.3.9.'

16.2.1.6.3.3. Midazolam: Individual Pharmacokinetic Profiles Following Administration of Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.5. to 14.1.2.6.6.'

16.2.1.6.3.4. Midazolam: Documentation of Statistical Analysis Following Administration of Oral Midazolam

16.2.1.6.3.4.1. Midazolam: Non-Compartmental Analysis Output

16.2.1.6.3.4.2. Midazolam: Non-Compartmental Analysis Plots

16.2.1.6.3.4.3. Midazolam: Potential Inhibitory Effect Analysis Output

16.2.1.6.3.4.4. Midazolam: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.6.4. 1-Hydroxymidazolam: Individual Pharmacokinetic Data Following Administration of Oral Midazolam

16.2.1.6.4.1. 1-Hydroxymidazolam: Individual Drug Concentration Data Following Administration Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.10. to 14.1.2.2.12.'

16.2.1.6.4.2. 1-Hydroxymidazolam: Individual Pharmacokinetic Parameters Following Administration of Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.10. to 14.1.2.3.12.'

16.2.1.6.4.3. 1-Hydroxymidazolam: Individual Pharmacokinetic Profiles Following Administration of Oral Midazolam

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.7. to 14.1.2.6.8.'

16.2.1.6.4.4. 1-Hydroxymidazolam: Documentation of Statistical Analysis Following Administration of Oral Midazolam

16.2.1.6.4.4.1. 1-Hydroxymidazolam: Non-Compartmental Analysis Output

16.2.1.6.4.4.2. 1-Hydroxymidazolam: Non-Compartmental Analysis Plots

16.2.1.6.4.4.3. 1-Hydroxymidazolam: Potential Inhibitory Effect Analysis Output

16.2.1.6.4.4.4. 1-Hydroxymidazolam: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.6.5. Total Dabigatran: Individual Pharmacokinetic Data Following Administration of Dabigatran Etexilate

16.2.1.6.5.1. Total Dabigatran: Individual Drug Concentration Data Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.13. to 14.1.2.2.15.'

16.2.1.6.5.2. Total Dabigatran: Individual Pharmacokinetic Parameters Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.13. to 14.1.2.3.15.'

16.2.1.6.5.3. Total Dabigatran: Individual Pharmacokinetic Profiles Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.9. to 14.1.2.6.10.'

16.2.1.6.5.4. Total Dabigatran: Documentation of Statistical Analysis Following Administration of Dabigatran Etexilate

16.2.1.6.5.4.1. Total Dabigatran: Non-Compartmental Analysis Output

16.2.1.6.5.4.2. Total Dabigatran: Non-Compartmental Analysis Plots

16.2.1.6.5.4.3. Total Dabigatran: Potential Inhibitory Effect Analysis Output

16.2.1.6.5.4.4. Total Dabigatran: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.6.6. Free Dabigatran: Individual Pharmacokinetic Data Following Administration of Dabigatran Etexilate

16.2.1.6.6.1. Free Dabigatran: Individual Drug Concentration Data Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.2.16. to 14.1.2.2.18.'

16.2.1.6.6.2. Free Dabigatran: Individual Pharmacokinetic Parameters Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.3.16. to 14.1.2.3.18.'

16.2.1.6.6.3. Free Dabigatran: Individual Pharmacokinetic Profiles Following Administration of Dabigatran Etexilate

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.1.2.6.11. to 14.1.2.6.12.'

16.2.1.6.6.4. Free Dabigatran: Documentation of Statistical Analysis Following Administration of Dabigatran Etexilate

16.2.1.6.6.4.1. Free Dabigatran: Non-Compartmental Analysis Output

16.2.1.6.6.4.2. Free Dabigatran: Non-Compartmental Analysis Plots

16.2.1.6.6.4.3. Free Dabigatran: Potential Inhibitory Effect Analysis Output

16.2.1.6.6.4.4. Free Dabigatran: Potential Induction Effect Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.1.7. Adverse Event Listings (Each Subject)

16.2.1.7.1. Pre-Treatment Adverse Events [7]

16.2.1.7.2. Treatment-Emergent Adverse Events [7]

[7] To be generated as follows:

Subject No.	Day of Dose	Treatment	Reported Term	Serious?	Maximal Severity	Causality	Action Taken	Medication Required?	Outcome	Adverse Event Start Date and Time	Adverse Event End Date and Time	Comments
<Subject ID>	<Day #>	<Investigational Product>	<AE Reported Term>	<Yes/No>	<Mild, Moderate or Severe >	<Not Reasonably Possible or Reasonably Possible>	<Dose Increased, Dose Not Changed, Dose Rate Reduced, Dose Reduced, Drug Interrupted, Drug Withdrawn, Not Applicable or Unknown>	<Yes or No>	<Fatal, Not Recovered / Not Resolved, Recovered / Resolved, Recovered / Resolved with Sequelae, Recovering / Resolving or Unknown>	<DDMMM YYYY hh:mm>	<DDMMM YYYY hh mm or Ongoing>	<Comments>

<Insert as many rows as deemed necessary>

NK – Not Known
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "Investigational Product" column will only be generated for Table 16.2.1.7.2. If an Adverse Event is related to Medical History, that information will be reported in 'Comments'. The "Comments" column will only be generated if there are reported comments for the adverse events.

16.2.1.7.3. Serious Adverse Events (I)

Subject No.	Treatment	Reported Term	Reason for Seriousness	Details
<Subject ID>	<Treatment>	<AE Reported Term>	<Reason>	<SAE details>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.8. Listings of Laboratory Measurements by Subject

16.2.1.8.1. Normal Range of Laboratory Values

				Normal Range				
				Female		Male		
Category	**Analyte**	**Age**	**Units**	**LLN**	**ULN**	**LLN**	**ULN**	**Qualitative**
<Category>	<Laboratory Analyte>	<Age interval>	<Units>	<Lower Limit>	<Upper Limit>	<Lower Limit>	<Upper Limit>	<Qualitative Values>

<Insert as many rows as deemed necessary>

LLN – Lower Limit Normal; ULN – Upper Limit Normal
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

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16.2.1.8.2. Hematology (I)

Subject No.	Actual Date and Time	Protocol Phase	Hemoglobin (g/dL)	RBC (10^12/L)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW-CV (%)	Total WBC (10^9/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xx	xx	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

RBC – Red Blood Cell; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Hemoglobin; MCHC – Mean Corpuscular Hemoglobin Concentration; RDW-CV – Coefficient Variation of the Red Cell Distribution Width; WBC – White Blood Cell
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.3. Hematology (II)

Subject No.	Actual Date and Time	Protocol Phase	Neutrophils (10^9/L)	Eosinophils (10^9/L)	Basophils (10^9/L)	Lymphocytes (10^9/L)	Monocytes (10^9/L)	Platelets (10^9/L)	Mean Platelet Volume (fL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx	xx	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.4. Biochemistry (I)

Subject No.	Actual Date and Time	Protocol Phase	AST (IU/L)	ALT (IU/L)	GGT (IU/L)	LDH (IU/L)	ALP (IU/L)	CK (IU/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.5. Biochemistry (II)

Subject No.	Actual Date and Time	Protocol Phase	Creatinine (mg/dL)	eGFR	Urea (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mg/dL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.6. Biochemistry (III)

Subject No.	Actual Date and Time	Protocol Phase	Magnesium (mg/dL)	Glucose (mg/dL)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	Albumin (g/dL)	Total Protein (g/dL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.7. Biochemistry (IV)

Subject No.	Actual Date and Time	Protocol Phase	Uric Acid (mg/dL)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Indirect Bilirubin (mg/dL)	TSH (mIU/L)	Chloride (mmol/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.8. Biochemistry (V)

Subject No.	Actual Date and Time	Protocol Phase	Amylase (g/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	FSH (mg/dL)	C-Reactive Protein	Cystain C	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.9. Coagulation

Subject No.	Actual Date and Time	Protocol Phase	Prothrombin Rate (%)	Prothrombin Time (sec)	INR	aPTT (sec)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx	xx.x	x.xx	xx.x	<Reason>

<Insert as many rows as deemed necessary>

INR – International Normalized Ratio; aPTT – Activated Partial Thromboplastin Time
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.10. Urinalysis

Subject No.	Actual Date and Time	Protocol Phase	pH	Specific Gravity	Protein	Hemoglobin	Glucose	Ketones	Bilirubin	Nitrites	Urobilinogen	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx.x	x.xxx	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; NCR – Not Clinically Relevant; CR – Clinically Relevant; RU - Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.11. Urine Microscopy

Subject No.	Actual Date and Time	Protocol Phase	Squamous Epithelial Cells (/uL)	Erythrocytes (/uL)	Leukocytes (/uL)	Observations	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Qualitative Value>	xx	xx	<Observations>	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.8.12. Pregnancy Test

Subject No.	Actual Date and Time	Protocol Phase	Matrix	Result	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Serum or Urine>	<Positive or Negative>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the of the evaluations.

16.2.1.8.13. Additional (Not Planned) Laboratory Safety Tests

Subject No.	Actual Date and Time	Protocol Phase	Investigational Product	Parameter	Results	Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	<Investigational Product>	<Parameter>	<Results>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.1.9. Vital Signs

Subject No.	Scheduled Time	Actual Date and Time	Protocol Phase	Treatment	SBP (mmHg)	DBP (mmHg)	Pulse Rate (beats/min)	Body Temperature (ºC)	Respiratory Rate (beats/min)	If Unscheduled, Reason
<Subject ID>	<Scheduled Time or Unscheduled>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Treatment>	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.1.10. 12-Lead ECG

Subject No.	Scheduled Time	Actual Date and Time	Protocol Phase	Treatment	QTcF (msec)	Result	If Abnormal, Reason	If Abnormal, Clinically Significant?	If Unscheduled, Reason
<Subject ID>	<Scheduled Time or Unscheduled>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Treatment>	xxx	<Abnormal/ Normal>	<Reason for being considered abnormal>	<Yes / No>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for any of the evaluations.

A.3.2. **Part 2**

16.2.2. PART 2

16.2.2.1. Subject Disposition

16.2.2.1.1. Subject Disposition

Screening No.	Date ICF Signed	Subject Eligible?	Subject Given an Unique Subject No.?	Unique Subject No.	Inclusion Criteria Not Met	Exclusion Criteria Met	Other Reason for Non-Eligibility	Reason for Non-Randomization
<Screening number>	<DDMMMYYYY>	<Yes/No>	<Yes/No>	<Unique Subject No>	<List all inclusion criteria that were not met>	<List all exclusion criteria that were met>	<List other reasons for non-eligibility>	<List reason for non-randomization>

<Insert as many rows as deemed necessary>

ICF – Informed Consent Form
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.2. Protocol Deviations

16.2.2.2.1. Blood Sampling Times Deviations

Subject No.	Treatment	Sampling Timepoint	Sampling Date and Time		Deviation Reason
			Scheduled/Target	Actual	
<Subject ID>	<Treatment>	<Scheduled Time or unscheduled>	<DDMMMYYYY hh:mm>	<DDMMMYYYY hh mm>	<Reason for deviation>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.2.2. Other Protocol Deviations

Subject No.	Protocol Phase	Treatment	Category	Description	Classification
<Subject ID>	<Protocol Phase #>	<Treatment>	<Deviation Category>	<Description of the deviation>	<Important / Not important>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.3. Excluded Data from the Pharmacokinetic Analysis

16.2.2.3.1. Plasma Concentrations

16.2.2.3.1.1. Givinostat: Individual Data of Plasma Concentrations

Subject No.	Day of Dosing	Investigational Product	Pre-dose	Time Post-Dose (h)									
				x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
<Subject ID>	<Day #>	<Investigational Product>	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

<Insert as many rows as deemed necessary>

BLQ – Below the Limit of Quantification (LLOQ = <LLOQ> <unitsC>) of the assay
ND – Not Done
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.3.2. Plasma Concentration *Versus* Time Profiles

16.2.2.3.2.1. Givinostat: Individual Plasma Concentration *Versus* Time Profiles – Linear Scale

16.2.2.3.2.2. Givinostat: Individual Plasma Concentration *Versus* Time Profiles – Semi-Logarithmic Scale

Note: These Figures will be extracted from Phoenix® WinNonlin® 8.2 or higher. A figure will be produced for each subject with data excluded from the pharmacokinetic analysis.

16.2.2.4. Demographic and Other Baseline Data

16.2.2.4.1. Demographic Data

Subject No.	Date ICF Signed	Date of Birth	Sex	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
<Subject ID>	<DDMMMYYYY>	<MMMYYYY>	<M/F>	<Race>	xx	xxx	xx.x	xx.x

<Insert as many rows as deemed necessary>

ICF – Informed Consent Form; BMI – Body Mass Index; M – Male; F – Female
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.2. Fertility/Contraception

16.2.2.4.2.1. Female Fertility/Contraception

Subject No.	Childbearing Potential?	If Yes, Birth Control Method	Breast Feeding?	Comments
<Subject ID>	<Yes/No>	<Birth Control Method>	<Yes/No>	<Comments>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.2.2. Male Fertility/Contraception

Subject No.	Sexually Active?	Agrees to Use Condom?	Female partner agrees to use a highly effective method of contraception?	Agree not to donate sperm from first dose administration until at least 90 days after the last study drug administration?	Comments
<Subject ID>	<Yes/No>	<Yes/No>	<Yes/No>	<Yes/No>	<Comments>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.3. Drugs of Abuse, Ethanol and Cotinine

Subject No.	Investigational Product	Date and Time	Amphetamines	Benzodiazepines	Cocaine	Cannabinoids	Opiates	Ethanol	Cotinine
<Subject ID>	<Investigational Product>	<DDMMMYYYY hh:mm>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>	<Positive / Negative>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.4. Viral Serology at Screening

Subject No.	Actual Date and Time	Protocol Phase	HIV-1 & HIV-2	Hepatitis B	Hepatitis C
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>

<Insert as many rows as deemed necessary>

HIV – Human Immunodeficiency Virus
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.5. Previous and Concomitant Medication

Subject No.	Treatment	Drug Name [ATC Code]	Indication	Pharmaceutical Form	Dose (units)	Frequency	Route	Date and Time	
								Start	End
<Subject ID>	<Treatment>	<Generic name [XXXXXXX]>	<Therapeutic indication>	<Pharmaceutical Form>	<Dose (units)>	<Frequency>	<Route>	<DDMMMYYYY>	<DDMMMYYYY or Ongoing>

<Insert as many rows as deemed necessary>

ATC – Anatomical Therapeutic Chemical
NK – Not Known
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.4.6. SARS-COV-2 Test

Subject No.	Actual Date	Protocol Phase	Result	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY>	<Protocol Phase>	<Not detectable, Detectable, Inconclusive >	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for any of the evaluations.

16.2.2.5. Compliance

16.2.2.5.1. Investigational Product Administration

Subject No.	Date	Actual Clock Time	Investigational Product	Dose (units)	Investigational Product Formulation	Route of Administration	Hands and Mouth Check?	150 mL of water taken?	Comments
<Subject ID>	<DDMMMYYYY/ N/A>	<hh:mm/ N/A>	<Investigational Product>	<Dose (units)>	<Formulation>	<Route>	<Yes/No/ N/A>	<Yes/No/ N/A>	<Comments>

<Insert as many rows as deemed necessary>

N/A – Not Applicable
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.6. Individual Pharmacokinetic Data

16.2.2.6.1. Givinostat: Individual Pharmacokinetic Data

16.2.2.6.1.1. Givinostat: Individual Drug Concentration Data

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.2.2.2.1. to 14.2.2.2.2.'

16.2.2.6.1.2. Givinostat: Individual Pharmacokinetic Parameters

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.2.2.3.1. to 14.2.2.3.2.'

16.2.2.6.1.3. Givinostat: Individual Pharmacokinetic Profiles

Note: The following sentence should be inserted in this section: 'No further information is provided; refer to sections 14.2.2.6.1. to 14.2.2.6.2.'

16.2.2.6.1.4. Givinostat: Documentation of Statistical Analysis

16.2.2.6.1.4.1. Givinostat: Non-Compartmental Analysis Output

16.2.2.6.1.4.2. Givinostat: Non-Compartmental Analysis Plots

16.2.2.6.1.4.3. Givinostat: Drug-Drug Interaction Analysis Output

Note: The documentation of statistical analysis will be extracted Phoenix® WinNonlin® 8.2 or higher.

16.2.2.7. Adverse Event Listings (Each Subject)

16.2.2.7.1. Pre-Treatment Adverse Events [7]

16.2.2.7.2. Treatment-Emergent Adverse Events [7]

[7] *To be generated as follows:*

Subject No.	Day of Dose	Treatment	Reported Term	Serious?	Maximal Severity	Causality	Action Taken	Medication Required?	Outcome	Adverse Event Start Date and Time	Adverse Event End Date and Time	Comments
<Subject ID>	<Day #>	<Investigational Product>	<AE Reported Term>	<Yes/No>	<Mild, Moderate or Severe >	<Not Reasonably Possible or Reasonably Possible>	<Dose Increased, Dose Not Changed, Dose Rate Reduced, Dose Reduced, Drug Interrupted, Drug Withdrawn, Not Applicable or Unknown>	<Yes or No>	<Fatal, Not Recovered / Not Resolved, Recovered / Resolved, Recovered / Resolved with Sequelae, Recovering / Resolving or Unknown>	<DDMMM YYYY hh:mm>	<DDMMM YYYY hh mm or Ongoing>	<Comments>

<Insert as many rows as deemed necessary>

NK – Not Known
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "Investigational Product" column will only be generated for Table 16.2.2.7.2. If an Adverse Event is related to Medical History, that information will be reported in 'Comments'. The "Comments" column will only be generated if there are reported comments for the adverse events.

16.2.2.7.3. Serious Adverse Events (I)

Subject No.	Treatment	Reported Term	Reason for Seriousness	Details
<Subject ID>	<Treatment>	<AE Reported Term>	<Reason>	<SAE details>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.8. Listings of Laboratory Measurements by Subject

16.2.2.8.1. Normal Range of Laboratory Values

				Normal Range				
				Female		Male		
Category	**Analyte**	**Age**	**Units**	**LLN**	**ULN**	**LLN**	**ULN**	**Qualitative**
<Category>	<Laboratory Analyte>	<Age interval>	<Units>	<Lower Limit>	<Upper Limit>	<Lower Limit>	<Upper Limit>	<Qualitative Values>

<Insert as many rows as deemed necessary>

LLN – Lower Limit Normal; ULN – Upper Limit Normal
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

.

16.2.2.8.2. Hematology (I)

Subject No.	Actual Date and Time	Protocol Phase	Hemoglobin (g/dL)	RBC (10^12/L)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW-CV (%)	Total WBC (10^9/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xx	xx	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

RBC – Red Blood Cell; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Hemoglobin; MCHC – Mean Corpuscular Hemoglobin Concentration; RDW-CV – Coefficient Variation of the Red Cell Distribution Width; WBC – White Blood Cell
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.3. Hematology (II)

Subject No.	Actual Date and Time	Protocol Phase	Neutrophils (10^9/L)	Eosinophils (10^9/L)	Basophils (10^9/L)	Lymphocytes (10^9/L)	Monocytes (10^9/L)	Platelets (10^9/L)	Mean Platelet Volume (fL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx	xx	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.4. Biochemistry (I)

Subject No.	Actual Date and Time	Protocol Phase	AST (IU/L)	ALT (IU/L)	GGT (IU/L)	LDH (IU/L)	ALP (IU/L)	CK (IU/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.5. Biochemistry (II)

Subject No.	Actual Date and Time	Protocol Phase	Creatinine (mg/dL)	eGFR	Urea (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mg/dL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.6. Biochemistry (III)

Subject No.	Actual Date and Time	Protocol Phase	Magnesium (mg/dL)	Glucose (mg/dL)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	Albumin (g/dL)	Total Protein (g/dL)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.7. Biochemistry (IV)

Subject No.	Actual Date and Time	Protocol Phase	Uric Acid (mg/dL)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Indirect Bilirubin (mg/dL)	TSH (mIU/L)	Chloride (mmol/L)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.8. Biochemistry (V)

Subject No.	Actual Date and Time	Protocol Phase	Amylase (g/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	FSH (mg/dL)	C-Reactive Protein	Cystain C	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	xx	xxx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.9. Coagulation

Subject No.	Actual Date and Time	Protocol Phase	Prothrombin Rate (%)	Prothrombin Time (sec)	INR	aPTT (sec)	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx	xx.x	x.xx	xx.x	<Reason>

<Insert as many rows as deemed necessary>

INR – International Normalized Ratio; aPTT – Activated Partial Thromboplastin Time
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.10. Urinalysis

Subject No.	Actual Date and Time	Protocol Phase	pH	Specific Gravity	Protein	Hemoglobin	Glucose	Ketones	Bilirubin	Nitrites	Urobilinogen	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	xx.x	x.xxx	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Qualitative Value>	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; NCR – Not Clinically Relevant; CR – Clinically Relevant; RU - Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.11. Urine Microscopy

Subject No.	Actual Date and Time	Protocol Phase	Squamous Epithelial Cells (/uL)	Erythrocytes (/uL)	Leukocytes (/uL)	Observations	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Qualitative Value>	xx	xx	<Observations>	<Reason>

<Insert as many rows as deemed necessary>

L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant; RU – Relevance Unknown
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.8.12. Pregnancy Test

Subject No.	Actual Date and Time	Protocol Phase	Matrix	Result	If Unscheduled, Reason
<Subject ID>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Serum or Urine>	<Positive or Negative>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the of the evaluations.

16.2.2.8.13. Additional (Not Planned) Laboratory Safety Tests

Subject No.	Actual Date and Time	Protocol Phase	Treatment	Parameter	Results	Reason
<Subject ID>	<DDMMMYYYY hh mm>	<Protocol Phase>	<Treatment>	<Parameter>	<Results>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

16.2.2.9. Vital Signs

Subject No.	Scheduled Time	Actual Date and Time	Protocol Phase	Treatment	SBP (mmHg)	DBP (mmHg)	Pulse Rate (beats/min)	Body Temperature (ºC)	Respiratory Rate (beats/min)	If Unscheduled, Reason
<Subject ID>	<Scheduled Time or Unscheduled>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Treatment>	xx	xx	xx	xx	xx	<Reason>

<Insert as many rows as deemed necessary>

SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure
L – Low; H – High; CR – Clinically Relevant; NCR – Not Clinically Relevant
Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for one of the evaluated parameters.

16.2.2.10. 12-Lead ECG

Subject No.	Scheduled Time	Actual Date and Time	Protocol Phase	Treatment	QTcF (msec)	Result	If Abnormal, Reason	If Abnormal, Clinically Significant?	If Unscheduled, Reason
<Subject ID>	<Scheduled Time or Unscheduled>	<DDMMMYYYY hh:mm>	<Protocol Phase>	<Treatment>	xxx	<Abnormal/ Normal>	<Reason for being considered abnormal>	<Yes / No>	<Reason>

<Insert as many rows as deemed necessary>

Program: <SAS Program>
Execution Date/Time: <ddMMMyyyy HH:MM>

Note: The "If Unscheduled, Reason" column will only be generated if there is an Unscheduled Reason for any of the evaluations.

14. ANNEXES

Annex 3: Data Blind Review Process Minute – Part 2
Annex 4: List of Subjects Dosed – Part 2