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Statistical Analysis Plan

Protocol number:

24-0026

Protocol title:

A Phase 1 Study to Evaluate Relative Bioavailability and Food Effect of an ALG-097558 Tablet Formulation and the Drug-Drug Interaction Potential of ALG-097558 and its metabolite ALG-097730 in Healthy Volunteers

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Revision History

Revision summary since final version 1.0.

Version No.	Effective Date	Description of Changes

Table of Contents

List of Abbreviations

Abbreviation	
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Intervals
CRF	Case Report Form
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HEENT	Head, Eyes, Ears, Nose, and Throat
HV	Healthy Volunteers
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NIAID	National Institute of Allergy and Infectious Diseases
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PO	Oral
PSRT	Protocol Safety Review Team
PT	Preferred Term
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODD	WHO Drug Dictionary

1.0 Introduction

This statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in protocol 24-0026: A Phase 1 Study to Evaluate Relative Bioavailability and Food Effect of an ALG-097558 Tablet Formulation and the Drug-Drug Interaction Potential of ALG-097558 and its metabolite ALG-097730 in Healthy Volunteers.

This SAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This version of the SAP is based on the protocol 24-0026 Version 3.0 Jun12 2025, and CRF Version 2.0 Jun04 2025. Changes to these documents may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock and any formal interim analysis.

1.1 Changes to the Planned Analysis

There are no changes to the planned analysis.

2.0 Study Objectives and Endpoints

2.1 Objectives and Associated Endpoints for Part A: DDI Itraconazole

Objectives	Endpoints
Primary	
Evaluate the effect of a CYP3A4 inhibitor/P-gp inhibitor, itraconazole, on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	PK parameters of ALG-097558 and metabolite ALG-097730 in plasma, including but not limited to AUC_{last}, $AUC_{0\text{-}inf}$, T_{max}, C_{max}, C_{min}, C_0 (predose), and $t_{1/2}$ following single dose administration alone or with co-administration of multiple dose itraconazole
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in HV participants when administered as monotherapy or in combination with itraconazole	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)
Exploratory †	
Evaluate the relationship between pharmacokinetics and safety	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data
Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, physical examinations, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK
Evaluate the relationship between the plasma ALG-097558 concentration and its effect on the QT interval on an ECG	2-sided upper 90% confidence interval of the placebo-adjusted change from baseline in QTc

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

2.2 Objectives and Associated Endpoints for Part B: DDI-Dabigatran

Objectives	Endpoints
Primary	
Evaluate the effect of multiple doses of ALG-097558 on the pharmacokinetics of a P-gp substrate, dabigatran	PK parameters of dabigatran (total) in plasma, including but not limited to AUClast, AUC0-inf, Tmax, Cmax, Cmin, C0 (predose), and t1/2 following single dose administration alone or with co-administration of multiple dose ALG-097558
Secondary	
Evaluate the safety and tolerability and PK of multiple doses of ALG-097558 in HV participants when administered alone or in combination with dabigatran	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)
	PK parameters of ALG-097558 and ALG-097730, including but not limited to AUClast, AUC0-inf, Tmax, Cmax, Cmin, C0 (predose), and t1/2 following administration of multiple dose ALG-097558
Exploratory †	
Evaluate the relationship between pharmacokinetics and safety	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data
Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, physical examinations, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

2.3 Objectives and Associated Endpoints for Part C: Relative Bioavailability and Food Effect

Objectives	Endpoints
Primary	
Evaluate the relative bioavailability of 2 different tablet formulations of ALG-097558 and effect of food on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730	Evaluate the relative bioavailability of 2 different tablet formulations of ALG-097558 and effect of food on the pharmacokinetics of ALG-097558 and the metabolite, ALG-097730
Secondary	
Evaluate the safety and tolerability of single doses of ALG-097558 in HV participants	Safety data, including incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs and clinical laboratory results (including biochemistry, blood coagulation, hematology and urinalysis)
Exploratory †	
Evaluate the relationship between pharmacokinetics and safety	Relationship between various PK parameters of ALG-097558 and the metabolite ALG-097730 and safety data
Evaluate the effect of covariates (e.g., body weight, ethnicity) on pharmacokinetics	Evaluate emergent safety, which may include incidence of adverse events by type, intensity, seriousness, and relationship to treatment, vital signs, 12-lead ECGs, clinical laboratory results and other covariates, with PK

† Analyses of exploratory endpoints may be performed at the time of primary and secondary analysis, if the results are available from the research laboratory. Any available results from the exploratory endpoints at the time of compilation of the final CSR may be included.

3.0 Study Design

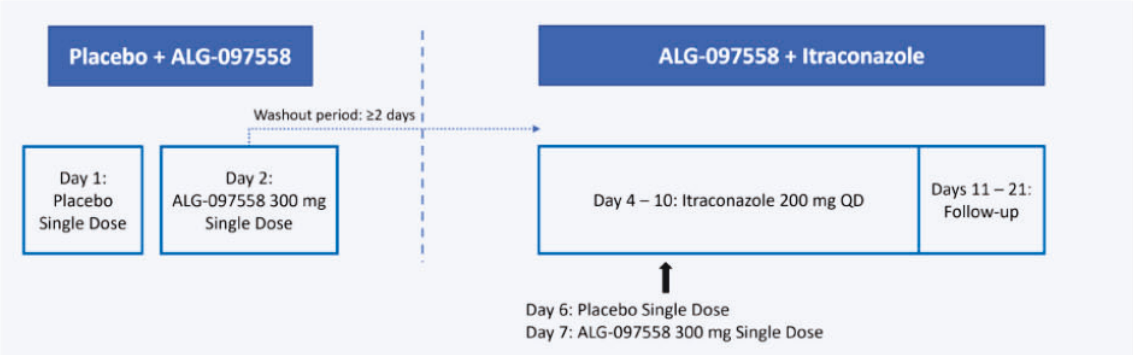
3.1 General Description

This multi-part Phase 1 study consists of 3 parts, all conducted in healthy volunteers (HV).

Part A: Part A: Drug-drug interaction (DDI) - Impact of Itraconazole (CYP3A4/P-gp inhibitor) on PK of ALG-097558

This part is a partially blind and partially placebo-controlled, fixed sequence, crossover study being conducted in up to 12 adult HVs to investigate the effect of itraconazole, a CYP3A4/P-gp inhibitor on the pharmacokinetics of ALG-097558 (Figure 1). Eligible participants will receive a single oral (PO) dose of matching placebo for ALG-097558 on Day 1 in single blind fashion (subject blinded only). Participants will then receive a single PO dose of 300 mg ALG-097558 on Day 2 in open label fashion, followed by a washout period of at least 2 days. Finally, participants will receive multiple PO doses of 200 mg itraconazole solution once daily (QD) on Days 4–10 in open label fashion, a single PO dose of matching placebo for ALG-097558 on Day 6 in single-blind fashion and a single PO dose of 300 mg ALG-097558 on Day 7 in open label fashion. Participants will be followed-up 10 days after administration of the last dose of study drug.
Administration of itraconazole and ALG-097558 will be in the fasted state at the same time on dosing days. Administration of Tablet Formulation 1 (SDD tablet) of ALG-097558 will be used.

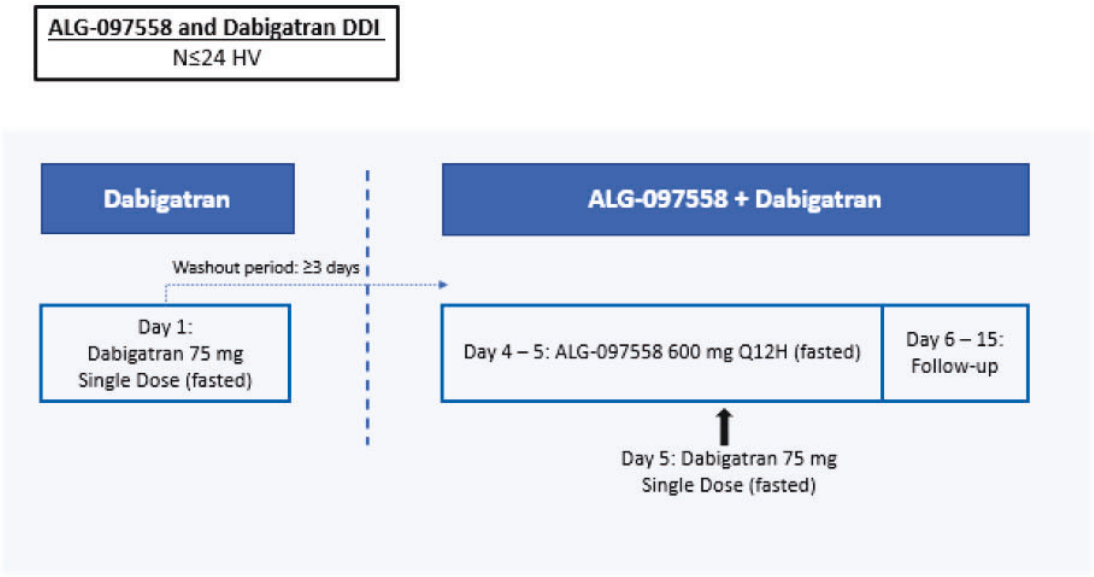
Figure 1. Schematic for Part A: DDI-Itraconazole of 24-0026



Part B: DDI - Impact of ALG-097558 on PK of Dabigatran (P-gp substrate)

This is an open-label, fixed sequence, crossover study being conducted in up to 24 adult HVs to investigate the effect of ALG-097558 on the pharmacokinetics of a single dose of dabigatran, a P-glycoprotein (P-gp) substrate (Figure 2). Eligible participants will receive a single PO dose of 75 mg dabigatran on Day 1, followed by a washout period of at least 3 days. Participants will then receive multiple PO doses of 600 mg ALG-097558 Q12H on Days 4–5 (total of 3 doses) and a single PO dose of 75 mg dabigatran on Day 5. Participants will be followed up 10 days after administration of the last dose of study drug.
The administration of dabigatran and ALG-097558 will be in the fasted state at the same time on dosing days. Administration of Tablet Formulation 1 (SDD tablet) of ALG-097558 will be used.

Figure 2. Schematic for Part B: DDI-Dabigatran of 24-0026

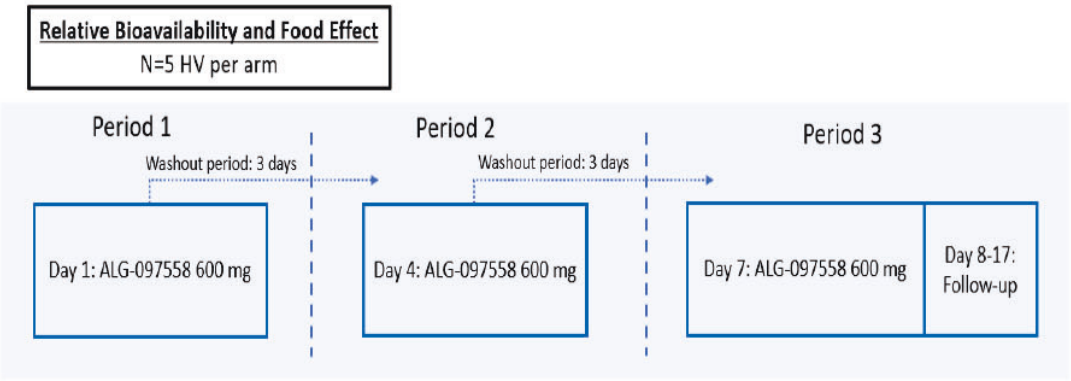


Part C: Relative Bioavailability/Food Effect

This is an open-label, randomized, 3-arm crossover study being conducted in 15 adult HVs. There will be three dosing sequences of which two will compare PK of a single-dose of 600 mg Tablet Formulation 1 (SDD tablet) and Tablet Formulation 2 of ALG-097558 for relative bioavailability. Two sequences will measure the effect of food on the PK of the single-dose of 600 mg Tablet Formulation 2 (Figure 3).

On Day 1, eligible participants will receive one of three sequences either a single PO dose of 600 mg ALG-097558 (Tablet Formulation 1) in the fasted state, a single PO dose of 600 mg ALG-097558 (Tablet Formulation 2) in the fasted state, or a single PO dose of 600 mg ALG-097558 (Tablet Formulation 2) in the high-fat fed state followed by a washout period of 3 days on Day 1. On Day 4, participants will receive a different dose from the three sequences, followed by a washout period of 3 days. On Day 7, participants will receive the final dose sequence. Participants will be followed-up 10 days after the administration of the last dose of study drug.

Figure 3. Schematic for Part C: Relative Bioavailability and Food Effect of 24-0026



Participants will be randomized equally (1:1:1) into one of three treatment sequences:

Arm	Period 1	Period 2	Period 3
Sequence 1	Formulation 1 fasted	Formulation 2 fasted	Formulation 2 fed
Sequence 2	Formulation 2 fasted	Formulation 2 fed	Formulation 1 fasted
Sequence 3	Formulation 2 fed	Formulation 1 fasted	Formulation 2 fasted

3.2 Randomization and Blinding

This is an open-label trial with sequential group enrollment for Part A and Part B and randomization will not be utilized for these parts. Part A has a nested single-blind dosing, in which only the participants will be blinded to receiving placebo (matching to the ALG-097558 dose) a day before the ALG-097558 dose on both Day 1 and Day 6, but no randomization. Part B is open-label dosing with no randomization. Part C participants will be randomized to receiving one of the three treatment sequences in different orders (5 participants per arm) but there is no blinding of formulation being received. Participants will be randomized equally (1:1:1) into one of three treatment sequences.

The randomization scheme for Part C will be generated prior to the initiation of the study by a designated statistician/ programmer and utilized by the site.

3.3 Sample Size

Up to approximately 51 (12 in Part A, 24 in Part B and 15 in Part C) participants are planned to be enrolled. No formal sample size/ power calculations were performed, as this trial does not aim to test a statistical hypothesis. The sample size chosen for each study part was based upon precedent set by other trials of similar nature and are deemed sufficient to evaluate the study objectives for this early phase trial.

3.4 Protocol Safety Review Team

This study will use a Protocol Safety Review Team (PSRT), which is an advisory group internal to this trial that may be used for the protocol decision steps based on safety data and other factors that require the team's input and deliberation. PSRT members include the Principal Investigator (PI), the DMID Medical Monitor, and the DMID Medical Officer, with input provided from the DCC. Representatives from the drug developer may be included as non-voting members of the PSRT. The details of the PSRT process will be outlined in the PSRT charter.

3.5 Timing of Analyses

The final analysis will occur once all participants complete their end of study visit or their last scheduled assessment per the Schedule of Assessments (Section 1.3), or the sponsor terminates the study for futility at time of the interim analysis or for any other reason.]

4.0 Analysis Sets

For purposes of analysis, the following populations are defined:

Enrolled Analysis Set: Defined as all participants who sign informed consent and are provided with an enrollment number. The Enrolled Analysis Set will be used for summaries of subject disposition and protocol deviations.

Safety Analysis Set: Defined as all participants who have received at least one dose of their allocated study intervention. Actual treatment assignment will be utilized for reporting. The Safety Analysis Set will be the primary population for all safety reporting.

Pharmacokinetic Analysis Set: Defined as all subjects in the safety analysis population who have sufficient PK data to estimate PK parameters and will be used for all PK analyses.

5.0 General Considerations

5.1 General Data Handling

All analyses will be conducted by using SAS® (SAS Institute, Inc.) version 9.4 or higher.

Study data will be recorded in electronic case report forms (eCRFs) for all screened and randomized patients. The Electronic Data Capture (EDC) vendor for this study is Dr. Vince Clinical Research (ClinSpark).

The final clinical study report (CSR) will be completed when all primary and secondary safety, clinical, and pharmacokinetic (PK) endpoint data are available. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Any available results from the exploratory endpoints at the time of compilation of the final CSR may also be included. Additional exploratory endpoint results may be included in an addendum to the CSR, publication of manuscript(s), or other reports.

No formal statistical safety analysis will be performed for this study. However, summary tables of data will be provided, as appropriate, as follows.

All statistical analysis will be performed by Parts: Part A, Part B and Part C. Within each part, summary statistics will be presented by treatments, where appropriate.

Also, for Part C, summary statistics will be provided by treatment sequence, as appropriate.

Analysis tables will be presented by treatment using the following groupings of subjects:

Part A:

- Placebo (alone)
- ALG-097558 (alone)
- Itraconazole (alone)
- Itraconazole + Placebo
- Itraconazole + ALG-097558
- Overall

Part B:

- Dabigatran (alone)
- ALG-097558 (alone)
- ALG-097558 + Dabigatran
- Overall

Part C:

- Sequence 1
- Sequence 2
- Sequence 3
- Overall

Data will be presented in by-subject data listings. Unless otherwise stated, all listings will be sorted by treatment group, center ID, subject number, and assessment date (and time, if available).

Continuous data will be summarized by treatment group based on n, mean, median, standard deviation (SD), minimum value, and maximum value.

Categorical data will be summarized by treatment arm using frequency counts and percentages. Where applicable, 95% confidence intervals (CIs) will be provided. For categorical measurements collected at separate visits or time points, unless otherwise stated, the denominator of percentages will be the number of subjects with a non-missing value at that visit or time point. For all other categorical measurements, unless otherwise stated, the denominator of percentages will be the number of subjects in the treatment group. If one or more subjects are missing data, the number of missing values may be presented as a separate category with no percentage. Counts of zero will be presented without percentages.

Relative to the number of digits after the decimal in the raw data, summary statistics will have the following number of digits after the decimal:

- Minimum and Maximum: same number of significant digits as the raw data
- Mean, Median, Q1, and Q3: one additional significant digit
- SD or Standard Error (SE): two additional significant digits
- Percentages <100% will be reported to one decimal place and percentages of 100% will be reported with no decimal place.
- Summary statistics will not exceed four digits after the decimal. Some laboratory parameters or other data may require judicious deviation from this rule.

Numbering for data displays will be based on International Conference on Harmonization (ICH) E3.

5.2 General Definitions

Term	Definition
Study Day	• Study Day = date of interest – reference date + 1, when the date of interest >= reference date; • otherwise, Study Day = date of interest – reference date. Note: if either day is missing, reference date calculations will not be performed. Should imputation be performed, then study day may be computed where appropriate.
Baseline	Defined as the last non-missing value collected prior to receiving the first dose of study treatment (based on date and time of administration).
Post-baseline	Defined as values collected after receipt of the first dose of study treatment (based on date and time of administration)
Change from Baseline	Defined as: Post-baseline value – Baseline value
Percent Change from Baseline	Defined as: (Post-baseline value – Baseline value)/Baseline value x 100. Note: To compute percent change from baseline, the baseline value cannot be equal to zero.
Duration on Study (days)	End of study date – enrolled date or randomization date +1
Duration of Adverse Event (days)	• Stop date of event – start date of event + 1 if time is not collected. • (Stop date/time of event – start date/time of event)/24 if time is collected.
Reporting in Months	Divide number of days by 30.4375
Reporting in Years	Divide number of days by 365.25
Reporting in Weeks	Divide number of days by 7
Age (yr)	From CRF

5.3 Data Imputation Rules

Generally, missing data will not be imputed and will be presented as collected in the study database.

The algorithms in the below table should be used for missing dates when needed for determining treatment emergence of adverse events and prior/concomitant designation of medications. All algorithms assume a comparison to first dose date and/or last dose date for categorization. Missing dates will only be imputed for treated subjects. These rules can also be applied to other date-based categorizations by replacing first dose date with the date of interest.

All dates will be considered to be made of three parts: day, month, and year. Note that if day is non-missing but month is missing, day should be considered missing as well in the algorithms below.

AE/Medication Date	Unknown Information	Known Information	Action
Start date	*day, month, year*	none	Set start date to the first dose date.
Start date	*day, month*	*year*	If *year* = year of first dose, set the date to the first dose date. If *year* < year of first dose, set month and day to December 31st. If *year* > year of first dose, set month and day to January 1st.
Start date	*day*	*month, year*	If *year* = year of first dose and: • *month* = month of first dose, set day to day of first dose. • *month* < month of first dose, set day to last day of month. • *month* > month of first dose, set day to first day of month. If *year* < year of first dose, set day to last day of month. If *year* > year of first dose, set day to first day of month.
Should the imputed start date based on the rules above be after the end date (either fully known for an AE, or fully known or imputed for a medication), use the end date instead of the date that would be imputed based on the rules above.			
Medication end date	*day, month, year*	none	If *ongoing* is checked, set the date to the last dose date. If *ongoing* is not checked, do not impute.
Medication end date	*day, month*	*year*	If *year* = year of last dose, set the date to the last dose date. If *year* < year of last dose, set month and day to December 31st. If *year* > year of last dose, set month and day to January 1st.
Medication end date	*day*	*month, year*	If *year* = year of last dose and: • *month* = month of last dose, set day to day of last dose. • *month* < month of last dose, set day to last day of month. • *month* > month of last dose, set day to first day of month. If *year* < year of last dose: set day to last day of month. If *year* > year of last dose: set day to first day of month.
Should the imputed end date come before a fully known start date then use the start date instead of the date that would be imputed based on the rules above.			

5.4 Visit Windows

Visits will be evaluated as the intended visit regardless of whether or not they are within the planned visit window. Unless otherwise specified, unscheduled visits will not be summarized in tables but will be presented in data listings.

5.5 Pooling of Centers

Pooling of sites is not deemed necessary for the study analyses

6.0 Analysis Methods

6.1 Study Subject Data

6.1.1 Subject Enrollment and Disposition

The number and percentage of subjects in each analysis population and final subject status (completed or withdrawn), including reasons for withdrawal, will be displayed based on the number of enrolled subjects. In addition, the number and percentage of subjects receiving study drug in each part of the study will be presented.

Subjects contributing to each analysis set and final disposition status will be listed.

6.1.2 Protocol Deviations

Protocol deviations will be identified and classified as Non-Significant and Important in the CRF, during the documentation of the protocol deviation.

All protocol deviations will be summarized by Study parts, importance (non-significant/ important), and deviation category (as per the CRF groups). A listing of all protocol deviations will be provided. Enrolled Analysis Set will be used to summarize protocol deviations.

6.1.3 Demographic and Baseline Characteristics

Subject demographics will be summarized and listed for the Safety Analysis Set, by study parts. Demographic data will include age, sex (Male / Female), ethnicity (Hispanic or Latino / Not Hispanic or Latino/ Unknown), race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Other Pacific Islander / White/ Unknown), baseline height (cm), baseline weight (kg), and Body Mass Index (BMI) (kg/m^2).

6.1.4 Medical History

Medical history will be collected during screening. All medical history terms will be coded by using Medical Dictionary for Regulatory Activities (MedDRA), version 27.1 or most current version. A table will be generated to summarize medical history by system organ class (SOC) and preferred term (PT). Data will be summarized for all subjects in the Safety analysis set by study parts. A subject will be counted only once at each level of reporting. Data will also be presented in a by-subject listing, which will include SOC, PT, and the verbatim term.

6.1.5 Prior and Concomitant Medications

The incidence of medication use will be summarized by WHO Drug Dictionary (WHODD), as of September 2024 or most current version, anatomic therapeutic chemical (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. A subject will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment start date (e.g., taken exclusively during the pre-treatment period). Concomitant medications are those which have been identified to have been taken at any point during the on-treatment or post-treatment periods. Prior and concomitant medication use will be summarized separately and presented by Study parts using Safety analysis set.

6.1.5.1 Prohibited Medications and Procedures

Subjects are prohibited from using any prescribed or non-prescribed systemic or topical medications, including herbal medications, within 14 days of the first dose of IP with the exceptions in Section **Error! Reference source not found.** of the protocol. The use of prohibited medications/ procedures will be captured in the protocol deviation summary.

6.1.6 Study Drug Exposure and Compliance

Mean number of doses for each treatment, calculated as the cumulative number of doses received by all subjects divided by the number of subjects, for the treatment, will be summarized by study parts, and overall (as appropriate), using Safety Analysis Set.

A listing of treatments administrated will be provided by study parts. The listing will include the days on which each dose of treatment was administrated.

6.2 Efficacy

Not applicable.

6.3 Interim Analysis

Not applicable

6.4 Pharmacokinetics, Primary Endpoints' Analysis

The Pharmacokinetic analysis and endpoints will be explained in a separate PK Analysis Plan.

6.5 Safety

All safety analyses will be performed using the safety analysis set. For all safety endpoints, descriptive statistics will be presented by Study Parts and timepoint (where applicable). In summaries of change from Baseline safety variables, only subjects with both Baseline and post Baseline data will be included. No formal hypothesis tests will be performed for any safety endpoint.

6.5.1 Adverse Events

Adverse events (AEs) will be recorded from signing informed consent through the end of the trial. AEs will be coded according to the MedDRA dictionary 27.1 or the most current version.

AEs will be considered treatment-emergent if the event was a pre-existing condition that becomes more severe or becomes serious after start of study drug, or if the onset of the event occurs after the start of study drug.

All AEs or Serious Adverse Events (SAEs) will be assessed for severity according to the toxicity grading scales in Division of AIDS (DAIDS) scale v2.1 (July 2017) and will be recorded in the CRF (Grade 1 - Mild, Grade 2 – Moderate, Grade 3 - Severe, Grade 4 - Potentially Life-threatening and Grade 5 - Death).

An overview of treatment emergent adverse events (TEAEs) will be produced, including counts and percentages of subjects with any incidences of: TEAEs, TEAEs related to investigational product/Itraconazole/Pradaxa (dabigatran etexilate), SAEs, TEAEs leading to study drug discontinuation and fatal SAEs.

Summaries of AEs by SOC and PT will be sorted by descending overall incidence of SOC and PT and will include the following types:

- AEs
- TEAEs
- TEAEs related to investigational product/Itraconazole/Pradaxa (dabigatran etexilate)
- DAIDS Grade 3 or higher TEAEs

- DAIDS Grade 3 or higher TEAEs related to investigational product/ Itraconazole/ Pradaxa (dabigatran etexilate)
- SAEs
- Serious TEAEs
- Serious TEAEs related to investigational product/Itraconazole/Pradaxa (dabigatran etexilate)
- TEAEs leading to treatment discontinuation
- TEAEs with fatal outcomes

When calculating the incidence of AEs, each AE will be counted only once for a given subject within a MedDRA category (e.g., overall, system organ class, or preferred term). When AEs are summarized within levels of another AE assessment (e.g., relatedness or severity), AEs will be counted once per subject at the worst level of the assessment (e.g., strongest relationship to study drug or greatest severity).

A comprehensive listing of all AEs will be provided in a by-subject data listing. In addition, the following listings will be provided:

- TEAEs related to investigational product/Itraconazole/Pradaxa (dabigatran etexilate)
- SAEs
- TEAEs leading to treatment discontinuation
- TEAEs with fatal outcomes

AEs will also be assessed for relationship to study drug (assessed by the investigators and reported on the CRF), and seriousness. Any missing severity/relationship assessments will be reported as missing.

6.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will include chemistry, coagulation, hematology, serology, and urinalysis. Clinical laboratory parameters will be reported based on the International System of Units (SI). Clinical safety laboratory evaluations collected at check-in (Day -1) will serve as baseline.

Observed values and changes from baseline for laboratory evaluations will be summarized at each visit (where collected) by study parts. All laboratory parameters will be provided in subject data listings; a separate listing for all values over time for subjects with any post-baseline abnormal laboratory results (all visits) will be provided.

The number and percent of subjects with a DAIDS toxicity grade of 2 or higher will be tabulated by laboratory evaluation with defined DAIDS grading at each visit. Subjects with missing values post-baseline will be excluded from the summary. The denominator for percentages will be the number of subjects with at least one post-treatment assessment for the laboratory parameter in question.

Shift tables displaying the shift from baseline to the worst value of DAIDS grade will be presented based on the most extreme change that it recorded in the CRF.

Figures showing the mean and standard deviation for ALT, AST and Total Bilirubin will be provided.

6.5.3 Vital Signs

Vital signs include respiratory rate (bpm), heart rate, oral temperature (°C), systolic and diastolic blood pressure (mmHg), and weight (kg). Observed values and changes from baseline for vital signs will be summarized at each visit and time point. Vital signs values will also be listed. Vital signs collected on Day 1 before dosing will serve as baseline.

The percentage of subjects with values marked as abnormalities and designated as clinically significant or not clinically significant by the investigator will be summarized both overall and by visit, including unscheduled visits. Vital signs values will also be listed; a separate listing will be provided for subjects with any post-baseline clinically significant vital sign.

6.5.4 Electrocardiograms

For Parts B and C, single 12-lead Electrocardiogram (ECGs) will be collected during screening and at several post treatment days/timepoints. In Part A, triplicate ECGs will be collected at Screening and on Days 1, 2, 6, and 7 before dosing with the ECGs taken at least 3 minutes apart within a 15 minute time period. Triplicate ECGs will be conducted using Holter monitoring when that is in use. ECGs collected on Day 1 before dosing will serve as baseline.

ECG parameters include heart rate (bpm), pulse rate, QRS, QT and QTcF. Observed values and changes from baseline for ECG parameters will be summarized at each visit and time point. For triplicate reads taken, the mean of the reads will serve as the observed value at the specific visit.

The percentage of subjects with overall interpretation marked as abnormalities and designated as clinically significant or not clinically significant by the investigator will be summarized both overall and by visit, including unscheduled visits. ECG values will also be listed by study parts.

Potentially clinically significant abnormalities will also be summarized both overall and by visit, including unscheduled visits. Potentially clinically significant abnormalities are defined based on the table below from Section 15 in the protocol.

Abnormality Code	ECG Parameter			
	HR bpm	PR (ms)	QRS (ms)	QTc (ms)
Actual Value				
Abnormally low	<45	Not applicable	–	–
Abnormally high	≥120	>220	≥120	–
Borderline prolonged QT	–	–	–	≥450 and ≤480
Prolonged QT	–	–	–	>480 and ≤500
Pathologically prolonged QT	–	–	–	>500
Change from Baseline				
Normal QTc change	–	–	–	ΔQTc <30
Borderline QTc change	–	–	–	ΔQTc ≥30 and ≤60
Abnormally high QTc change	–	–	–	ΔQTc >60

6.5.5 Physical Examinations

A comprehensive physical examination will be performed at the screening visit and several post treatment days/timepoints. A full physical examination will include assessments of the following organs and organ systems: skin, HEENT (head, eyes, ears, nose, and throat), neck, lungs, heart, liver, spleen, abdomen, extremities, lymph nodes (axillary and cervical), and nervous system. Height and weight will be measured, and BMI calculated, at the screening visit only.

A symptom-directed (targeted) physical examination will be performed if indicated at all other timepoints specified in the Schedule of Assessments. Interim or unscheduled physical examinations will be performed at the discretion of the participating site PI or appropriate sub-investigator, if necessary, to evaluate AEs or abnormal clinical laboratory test results.

Physical examinations will be presented in subject data listings for subjects in the Safety Analysis Set