Statistical Analysis Plan

NCT Number: NCT06132867

Title: A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution Versus an Immediate-Release Tablet in Adult Healthy Subjects

Study Number: Brigatinib-1004

Document Version and Date: Final, 03 November 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: Brigatinib-1004

A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution versus an Immediate-Release Tablet in Adult Healthy Subjects

Phase: 1

Version: Final

Date: 03 Nov 2023

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Protocol Version: Original

Protocol Date: 13 Sep 2023

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
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APPROVAL SIGNATURE

Study Title: A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution versus an Immediate-Release Tablet in Adult Healthy Subjects

Approvals:

As the statistical analysis plan was executed using the Veeva platform, please find the e-signature page at the end of the document.

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

λ_z	terminal disposition phase rate constant
AE	adverse event
AESI	adverse event of special interest
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{∞_pred}	area under the plasma concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration
$AUC_{extrap}\%$	area under the curve from the last quantifiable plasma concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
$AUC_{extrap}\%\_pred$	area under the curve from the last quantifiable plasma concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred}
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
BLQ	below the lower limit of quantitation
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
$CL/F_{\_pred}$	apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRU	Clinical Research Unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMP	data management plan
ET	early termination
ECG	electrocardiogram
Geom CV	geometric coefficient of variation
Geom Mean	geometric mean
GMR	geometric least-squares mean ratio
ICF	Informed Consent Form
ln	natural logarithm
LSM	least-squares mean
Mean	arithmetic mean
MedDRA®	Medical Dictionary for Regulatory Activities®

n	number of observations
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{½z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of first occurrence of C_{max}
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration
$V_z/F_{\_pred}$	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To determine the relative bioavailability of brigatinib after single-dose administration of an oral solution formulation versus an immediate-release tablet formulation.

1.1.2 Secondary Objective

To evaluate the safety and tolerability of brigatinib after single-dose administration of an oral solution formulation and an immediate-release tablet formulation.

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoints for this study are brigatinib pharmacokinetic (PK) parameters after a single-dose of an oral solution formulation and an immediate-release tablet formulation, including:

- *Maximum observed plasma concentration (C_{max})*
- *Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last})*
- *Area under the plasma concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞})*

1.2.2 Secondary Endpoint

The secondary endpoints will be assessed through evaluation of the following parameters:

- *Number of subjects with at least one treatment-emergent adverse event (TEAE) and/or severe adverse event (SAE).*

1.2.3 Exploratory Endpoints

The following PK parameters for brigatinib after administration of each formulation:

- *Time of the first occurrence of C_{max} (t_{max})*
- *Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration (CL/F)*
- *Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration (V_z/F)*
- *Terminal disposition phase half-life ($t_{½z}$)*
- *Terminal disposition phase rate constant (λ_z)*

- *Area under the curve from the last quantifiable plasma concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞} (AUC_{extrap}%)*

Data related to the acceptability and palatability of the oral solution formulation will also be collected.

1.2.4 Additional Endpoints

- Area under the plasma concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration (AUC_{∞_pred})
- Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the predicted value of the last quantifiable concentration (V_z/F_pred)
- Apparent clearance after extravascular administration, calculated using the predicted value of the last quantifiable concentration (CL/F_pred)
- Area under the curve from the last quantifiable plasma concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred} ($AUC_{extrap}\%\_pred$)

1.3 Estimands

Not applicable.

2.0 STUDY DESIGN

This is an open-label, randomized, 2-period, 2-sequence, crossover study in healthy adult subjects to evaluate the relative bioavailability of brigatinib when administered as an oral solution versus as an immediate-release tablet (ALUNBRIG®). A study schematic is shown in Table 2.a.

Table 2.a: Study Schematic

Pretreatment		**Treatment Periods 1 & 2 (a)**			
Screening	**Check-in (b) (Periods 1 & 2)**	**Dosing and Study Assessments**	**PK Assessments**		**Follow-up (c)**
Within 28 days of first dosing	Day -1	Day 1	Days 1-4 (d)	Days 6 & 8 (d)	14 (±2) Days following last dose
	◄---------- Confinement (d) ----------►				

- *Treatment A (test formulation): 90 mg oral solution dose of brigatinib administered in a fasted state*
- *Treatment B (reference formulation): 90 mg tablet dose of brigatinib administered in a fasted state*

Approximately 12 subjects will be randomly assigned in a 1:1 ratio to one of the treatment sequences, as part of a crossover design (Table 2.b):

Table 2.b Description of Treatment Sequences in the Study

Sequence	Approximate number of subjects	Period 1	Period 2
AB	6	A	B
BA	6	B	A

A= Oral solution dose of brigatinib, fasted state; B= Tablet dose of brigatinib, fasted state.

Subjects will be admitted to the clinical facility on Day -1, the day prior to brigatinib administration in each dosing period. On Day 1 of each period, a single 90 mg dose of brigatinib will be administered. Blood samples for the measurement of plasma concentrations of brigatinib will be collected predose and up to 168 hours postdose following each brigatinib dose. For each dosing period, subjects will be housed starting on Day -1, at the time indicated by the clinical research unit (CRU), until the morning of Day 4 after the 72 hour postdose blood draw and/or study procedures. There will be a washout period of at least 14 days between brigatinib administration in each study period. Subjects will return for dosing and/or study procedures. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee. As per site preference, subjects may be confined throughout the study (ie, washout period and/or return visit[s]).

The follow-up contact will occur 14 (±2) days post the last dose of study drug by telephone. If abnormal, potentially clinically significant findings are noted during this phone follow-up, subjects may then be brought back to the clinic for re-evaluation per the Investigator's discretion. SAEs should be followed up until resolution or permanent outcome.

The planned dose levels/treatments of brigatinib to be evaluated are outlined in Table 2.c.

Table 2.c Planned Brigatinib Dose Levels/Treatments

Treatment	Brigatinib Dose	Formulation	State
A	90 mg	Oral Solution	Fasted
B	90 mg	Tablet	Fasted

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The sample size calculation was based on the expected 2-sided 90% confidence intervals (CIs) for the difference in the paired, natural logarithm (ln)-transformed AUC_∞ means of brigatinib after administration as an oral solution versus an immediate-release tablet. The within-subject percent coefficient of variation (CV%) for brigatinib AUC_∞ was estimated to be 12% on the basis of data from previous clinical studies conducted in healthy subjects (Studies AP26113-15-106 and AP26113-16-110). If the observed geometric mean ratio (GMR) for brigatinib AUC_∞ after administration as an oral solution versus a tablet is 1, with a sample size of 8, the 90% CIs for the GMR is expected to be 0.89 to 1.12 on the basis of the variance assumptions. It is anticipated that a total of approximately 12 subjects will be enrolled to obtain at least 8 PK-evaluable subjects. Subjects will be randomized into 2 treatment sequences, as indicated in Table 2.b.

5.0 ANALYSIS SETS

5.1 Safety Set

All subjects who received at least one dose of the study drug will be included in the safety evaluations.

5.2 PK Set

All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonlin® Version 8.3.4, or higher. All statistical analyses will be conducted using SAS® Version 9.4 or higher. All relevant data recorded in the case report form (CRF) and clinical laboratory data will be listed by subject and treatment. All table, figure, and listing (TFL) shells and numbering list will be included and specified in the TFL Shells document.

For PK data, the number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (geom mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values.

Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the individual data. GMRs and 90% CIs for the GMRs will be reported to 2 decimal places. Intra-subject CV%s will be reported to 1 decimal place.

Noncompartmental analyses of PK parameters will be used in this study. Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK parameters, unless they are deemed questionable (eg, BLQ value between measurable values), in which case they will be treated as missing and excluded from the concentration summary statistics and the PK analysis. BLQ values treated as missing/excluded from the summary statistics and PK analysis will be footnoted accordingly. Values of 0 will not be included in the calculation of geom mean and geom CV%.

A subject's PK parameter data will be included in the listings, but may be excluded from the descriptive and inferential statistics if one or more of the following criteria are met:

- A predose (0 hour) concentration is greater than 5% of that subject's C_{max} value for the same treatment
- A subject did not meet inclusion/exclusion criteria that may have an effect on brigatinib PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol defined study procedures, including but not limited to dosing, dose timing, sample collection, meal timing, etc (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject may be excluded due to vomiting within twice the median t_{max} of brigatinib (2 × ~2 hours = 4 hours)

The details on PK parameter calculations and TFLs will be outlined in the clinical pharmacology analysis plan (CPAP) and TFL Shells document including specifics on the following:

- Insufficient data to determine a reliable $t_{1/2z}$ value and other λ_z-dependent parameters
- PK parameters presented by treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter Phoenix® WinNonlin® output file used to generate the TFLs

- PK parameter ratios for C_{max}, AUC_{last}, AUC_{∞}, AUC_{∞_pred} presented in end-of-text tables.
- Linear mixed-effects model results presented in in-text and end-of-text tables
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures
- Listings of concentration data for individual subjects in Appendix 16.2.5 of the clinical study report (CSR).
- Individual concentration-time figures presented in Appendix 16.2.6 of the CSR.

Continuous demographic and safety data will be summarized descriptively. For categorical variables, the count and percentages of each reported value will be tabulated, where applicable. The denominator for the percent calculation will be the number of subjects in the safety set for overall summaries, and the number of subjects dosed with each treatment in by-treatment summaries. For continuous variables, n, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers. Unless otherwise stated, baseline is defined as the last observation, including recheck or unscheduled events, prior to dosing in each period.

6.1.1 Handling of Treatment Misallocations

Subjects with any treatment misallocations will be analyzed based on the treatment the subjects actually received.

6.2 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form (ICF), date of first dose of brigatinib, date of last dose of brigatinib, date of last subject's discontinuation, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Drug Dictionary, and SAS version used for creating the datasets.

6.3 Disposition of Subjects

Disposition of all randomized subjects (number of subjects who dosed, completed the study, discontinued from the study, and reason(s) for discontinuation(s)) will be summarized by randomized treatment sequence and overall. Treatment sequence, study completion status, date of completion, and whether brigatinib was discontinued will be listed by subject. Reasons for discontinuation of brigatinib and/or study and dates of discontinuation will be listed, if applicable.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by randomized treatment sequence and overall based on the safety set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and body mass index [BMI]) and the number and percentages of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). The last height, weight, and BMI measured prior to dosing will be used in the summaries. All demographic data will be listed by subject as recorded on the CRF, including date of informed consent and protocol version.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history will include any significant conditions or diseases that resolved at or before signing the ICF. All medical history reported by the subject will be recorded regardless of when it may have occurred. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Medical history and concurrent medical conditions will be listed based on safety set.

Any medical condition starting or worsening after taking the first dose of brigatinib will be classified as a TEAE. All medical history will be coded using MedDRA® version specified in the data management plan (DMP). If available, the medical history and concurrent medical condition listings will include the coded term (preferred term and system organ class [SOC]), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history includes any relevant medication stopped at or within 28 days before signing the ICF. Concomitant medication includes any medication other than brigatinib taken at any time between screening and the end of the study (including follow-up contact). All medication history and concomitant medications recorded during the study will be coded with the WHO Drug Dictionary version specified in the DMP and listed based on the safety set. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after study completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Efficacy Analysis

Not applicable

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship(s) of TEAEs, and changes from baseline in the subjects' clinical laboratory results, vital signs, and 12-lead electrocardiograms (ECGs) using the safety set. Clinically significant laboratory values and vital signs will be reported as AEs, as applicable. All safety data will be listed by subject, treatment, and assessment time points, including rechecks, unscheduled assessments, and early termination (ET), chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators. Postdose recheck, unscheduled, or ET results will not be used in summaries.

Tables summarizing safety data by assessment time point will only include summaries for baseline and post-baseline time points.

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, relationship to brigatinib (related or not related), frequency, outcome, dates and times of onset and resolution, and action relative to the AE as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA® version specified in the DMP. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after the first dose of brigatinib administered in the study. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time.

If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the most recent treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment-emergent and attributed to the first treatment received. If severity is missing, the AE will be counted as severe (Grade 3), and if relationship is missing, the AE will be counted as related.

TEAEs will be tabulated by treatment (including overall), SOC, and preferred term. Summary tables will include number of subjects reporting the TEAE as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs (i.e., those events reported by >1 subject in any treatment, excluding serious adverse events (SAEs) will also be summarized. The denominators for percent calculations will be the number of subjects dosed for each treatment. In addition, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

Additional TEAE summary tables will be presented by severity and relationship to brigatinib. If a subject has multiple TEAEs with different severity levels within the same preferred term, the subject will be counted in the most severe category only. For relationship to brigatinib, if a subject has both related and unrelated TEAEs with the same preferred term, the subject will be counted as having related TEAEs.

An overview summary of TEAEs table, including number of subjects with TEAEs, treatment-emergent SAEs, treatment-related TEAEs, treatment-related SAEs, deaths, TEAEs by severity, and AEs leading to discontinuation will be provided.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the CSR.

6.7.2 Adverse Events of Special Interest

AEs of special interest (AESI) will be identified in the AE listings. Specific AESI will be flagged according to an excel file to be provided by Takeda, containing applicable standardized MedDRA queries and MedDRA preferred terms. AESI will include the following categories:

- early onset pulmonary events
- later-onset pneumonitis
- bradycardia
- hypertension
- gastrointestinal events
- elevated creatine phosphokinase
- clinical/chemical Pancreatitis
- increased insulin/hyperglycemia events
- vision impairment events
- photosensitivity
- hepatotoxicity
- peripheral neuropathy
- skin and subcutaneous events

6.7.3 Clinical Laboratory Evaluation

Clinical laboratory tests will be measured as described in Table 6.a:

Table 6.a Collection of Laboratory Samples

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
Serum Chemistry, Hematology, Coagulation	Screening		NA
	1	Day -1 Check-in Day 1 Hour 8 Day 3 Hour 48	Baseline Day 1 Day 3

Clinical Laboratory Panels	Time Point		
	Period	CRF/Listing Day and Hour	Table
	2	Day -1 Check-in Day 1 Hour 8 Day 3 Hour 48 Day 8 Hour 168	Baseline Day 1 Day 3 Day 8
Urinalysis	Screening		Baseline
	2	Day 8 Hour 168	Day 8

Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listings will reflect the data found in the final subject CRFs.
If applicable, an ET assessment will be performed.
NA = Not Applicable

For all numeric values of laboratory test results, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment at each scheduled visit using the International System of Units (SI). Change from baseline will be summarized in a similar manner. The mean value calculated for each assessment time point will be compared to the reference range and flagged if outside of the reference range (* if above the reference range and ^ if below the reference range). In the event there is more than one reference range for a laboratory test, the comparison will be made against the lowest of the lower ranges and the highest of the higher ranges. Postdose unscheduled, recheck, or ET assessments will not be used in summaries. Only baseline and post-baseline time points will be summarized. All clinical laboratory data will be listed by subject. Urine drug screen will be performed at screening and check-in, and results will be listed by subject.

Out-of-normal range flags will be recorded as high (H) and low (L) for numerical results and did-not-match (*) for categorical results. For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above normal (H), normal (N), or below normal (L)) with the postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Any clinically significant laboratory results, as determined by the Investigator, will be recorded as AEs.

6.7.4 Vital Signs

Vital signs will be measured as described in Table 6.b:

Table 6.b Collection of Vital Signs

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Blood Pressure, Heart Rate	Screening		NA

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
	1, 2	Day 1 Predose Day 1 Hour 1 Day 1 Hour 4 Day 2 Hour 24 Day 3 Hour 48 Day 4 Hour 72 Day 6 Hour 120 Day 8 Hour 168*	Baseline Hour 1 Hour 4 Hour 24 Hour 48 Hour 72 Hour 120 Hour 168*
Respiration, Temperature	Screening		NA
	1, 2	Day 1 Predose Day 2 Hour 24 Day 3 Hour 48 Day 8 Hour 168*	Baseline Hour 24 Hour 48 Hour 168*

Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listing will reflect the data found in the final subject CRFs.
If applicable, an ET assessment will be performed.
NA = Not applicable; *Period 2 only

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment and time point. Change from baseline will be summarized in a similar manner. Postdose unscheduled, recheck assessments, or ET results will not be used in analysis. Only baseline and post-dose results will be summarized. Vital sign data will be listed by subject.

6.7.5 12-Lead Electrocardiogram

ECGs will be measured as described in Table 6.c:

Table 6.c Collection of ECGs

Parameter	Time Point		
	Period	CRF/Listing Day and Hour	Table
Heart Rate, PR, QRS, QT, QTcF, RR	Screening		NA
	1, 2	Day 1 predose Day 1 Hour 8 Day 8 Hour 168*	Baseline Hour 8 Hour 168*

Time points in the CRF/Listing column are based on the protocol, and it should be noted that the data listing will reflect the data found in the final subject CRFs.
If applicable, an ET assessment will be performed.
NA = Not applicable; *Period 2 only

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for ECG parameters by treatment and time point. Change from baseline will be summarized in a similar manner. Postdose unscheduled, recheck assessments, or ET results will not be used in analysis. Only baseline and post-dose results will be summarized. ECG data will be listed by subject.

6.7.6 Palatability Assessment (Treatment A)

A palatability questionnaire will be given following Treatment A (oral solution). Results will be listed by subject and summarized.

6.7.7 Physical Examinations

Full physical examinations will be performed at screening, check-in and 8 hours post-dose in each period, and on Day 8 of Period 2. Additional physical examinations may be performed at other times at the discretion of the Investigator. Physical examination findings will be presented in the data listings by subject.

6.7.8 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented.

6.7.9 Extent of Exposure and Compliance

The dates, times, and doses of brigatinib will be listed by subject and study period.

6.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma brigatinib concentrations will be collected as outlined in Table 6.d below:

Table 6.d Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Period	Scheduled Time (Hours)*
Brigatinib	Plasma	1 and 2	Predose and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the CRF.

Plasma concentrations of brigatinib will be listed and summarized descriptively by treatment and PK sampling time using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual subject concentration-time profiles will be plotted by treatment on linear and semi-log scales. The arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear (with and without SD) and semi-log scales. For summary statistics and arithmetic mean concentration-time plots, the nominal PK sampling time will be used. For individual subject concentration-time plots, the actual PK sampling time will be used.

The PK parameters will be calculated from plasma brigatinib concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after brigatinib dosing. The PK parameters will be summarized by treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive statistics.

A linear mixed-effects analysis of variance model will be used for the analysis on the ln-transformed brigatinib PK parameters (C_{max}, AUC_{last}, AUC_{∞} and AUC_{∞_pred}). The model will include sequence, treatment, and period as fixed effects. Subject nested within sequence will be

included as a random effect. Each model will include calculation of LSM as well as the difference between treatment LSM. Geometric mean ratios and 90% CIs will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred}. These ratios will be expressed as a ratio of test treatment (ie, oral solution, Treatment A) relative to the reference treatment (ie, tablet, Treatment B).

The following SAS code will be used to perform the analysis:

```
PROC MIXED;
CLASS TREAT PERIOD SEQUENCE SUBJECT;
MODEL LN<Parameter> = TREAT PERIOD SEQUENCE / DDFM = KR;
RANDOM SUBJECT(SEQUENCE);
ESTIMATE "Treatment A vs Treatment B" TREAT 1 -1 / CL ALPHA=0.1 E;
RUN;
```


6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.10 Interim Analyses

Not applicable.

6.11 Preliminary Analysis

A preliminary PK analysis will be completed as described in the CPAP and Section 6.8 of the SAP, with the following changes: 1) QCed data will be used (not QAed); 2) nominal times (not actual sampling times) will be used to calculate PK parameters; and 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.3.4 or higher.

6.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

This SAP is aligned with the analysis planned in the protocol.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

Not applicable.

9.3 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analyses provided in the CSR.