Title: A Phase 1 Drug-Drug Interaction Study Between Brigatinib and the CYP3A Substrate Midazolam in Patients With ALK-Positive or ROS1-Positive Solid Tumors

NCT Number: NCT03420742

SAP Approve Date: 19 November 2020

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Brigatinib-1001

A Phase 1 Drug-Drug Interaction Study Between Brigatinib and the CYP3A Substrate Midazolam in Patients With ALK-Positive or ROS1-Positive Solid Tumors

PHASE 1

Version: Final

Date: 19 November 2020

Prepared by:

PPD

Based on:

Protocol Version: Original

Protocol Date: 14 November 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
CK	creatine kinase
C_{max}	maximum observed concentration
CPK	creatine phosphokinase
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP3A	cytochrome P450 3A
DBP	diastolic blood pressure
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HDPE	high-density polyethylene
ICH	International Council on Harmonisation
ILD	interstitial lung disease
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small-cell lung cancer
ORR	objective response rate
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetic(s)
PR	partial response
PTA	posttrial access
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SBP	systolic blood pressure
SI	Système international
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time of first occurrence of maximum observed concentration
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to characterize the effect of repeat-dose administration of brigatinib 180 mg QD on the single-dose pharmacokinetics [PK] of midazolam.

4.2 Safety Objectives

The safety objective of this study is to assess the safety and tolerability of brigatinib in patients with ALK-positive or ROS1-positive solid tumors.

CCI

[redacted]

4.4 Study Design

This study is an open-label, multicenter, phase 1 study designed to evaluate the effect of repeated doses of brigatinib on the single-dose PK of midazolam, a sensitive CYP3A probe substrate to determine if brigatinib, at therapeutic doses, produces clinically meaningful CYP3A induction in vivo, and if so, to inform strategies for the management of potential drug-drug interactions (DDIs) between brigatinib and substrates of CYP3A. The patient population will consist of patients 18 years of age or older who have locally advanced or metastatic solid tumors who meet 1 of the following 4 criteria: 1) patients with locally advanced or metastatic ALK-positive NSCLC who have progressed on or are intolerant to treatment with at least 1 other ALK inhibitor, 2) patients with ALK-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available, 3) patients with locally advanced or metastatic ROS1-positive NSCLC who have progressed on crizotinib therapy or are intolerant to crizotinib, or 4) patients with ROS1-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available. This study will consist of 2 parts: Part A (Cycle 1: PK cycle) and Part B (Cycle 2 and beyond: treatment cycles).

Approximately 20 patients with locally advanced or metastatic ALK-positive or ROS1-positive solid tumors, including NSCLC, will be enrolled in this study to achieve approximately 15 PK-evaluable patients for assessment of the effect of brigatinib on the PK of midazolam.

Part A:

Part A of the study will use a fixed-sequence design over a single 28-day treatment cycle. Patients will receive a 3 mg oral dose of midazolam on Day 1 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the absence of brigatinib. Brigatinib 90 mg will then be orally administered once daily (QD) on Days 2 through 8. If the 90 mg QD brigatinib dose is tolerated by the patient, the brigatinib dose will be

increased to 180 mg QD, starting on Day 9 and continuing through Day 28 (in accordance with the United States [US] prescribing information). For patients who have escalated to brigatinib 180 mg QD, a 3 mg oral dose of midazolam will be administered on Day 21 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the presence of brigatinib.

Any patients in Part A who are not PK evaluable will be replaced.

Figure 4.a Part A

Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Midazolam 3 mg	X																				X							
Brigatinib 90 mg		X	X	X	X	X	X	X																				
Brigatinib 180 mg									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sampling for Midazolam PK	X	X																			X	X						

Note: Red, green, and blue shading indicate dosing days for midazolam 3 mg, brigatinib 90 mg, and brigatinib 180 mg, respectively.

Part B:

After completion of Part A, patients may continue to Part B to receive the potential therapeutic benefits of brigatinib. Any patients who are replaced because they are not PK evaluable in Part A will also be eligible to continue into Part B. The starting dose of brigatinib in Part B will be the dose that was tolerated by the patient at the end of Part A. Part B of the study will include 28-day treatment cycles in which brigatinib will continue to be dosed QD at the highest tolerated dose (up to 180 mg QD) up to 23 cycles of treatment, or until disease progression (PD), intolerable toxicity, or another discontinuation criterion is met. Patients who cannot escalate to 180 mg QD in Part A will be maintained at 90 mg QD or lower. The available brigatinib daily oral doses for Part A and Part B will include 180, 120, 90, and 60 mg, allowing patients to have their dose reduced in cases of intolerability.

Disease assessments by the investigator, using Response Evaluation Criteria in Solid Tumors, version 1.1(RECIST v1.1), and evaluated by computed tomography and/or magnetic resonance imaging, will be performed during Screening; at 8-week intervals during treatment (ie, on Day 28 [±3 days] of every even-numbered cycle) through Cycle 14; and every 12 weeks (ie, every 3 cycles) thereafter, and at end of treatment (EOT). Safety will be assessed throughout the study, including adverse event reporting through the 30-day follow-up period after EOT. Subsequent therapy will also be collected during the 30-day follow-up period.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of this study are midazolam PK parameters in the presence and absence of brigatinib, including:

- Area under the concentration-time curve from time 0 to infinity (AUC_{∞}).
- Maximum observed concentration (C_{max}).
- Time of first occurrence of C_{max} (t_{max}).

5.2 Secondary Endpoints

There are no secondary endpoints for this study.

5.3 Safety Endpoints

The endpoints for assessing safety and tolerability of brigatinib will include:

- Adverse events (AEs).
- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis [Part B only]).
- Vital signs.

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that approximately 20 patients will be enrolled to obtain approximately 15 PK-evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC_{∞} means of midazolam in the absence and presence of brigatinib. The within-patient coefficient of variation for midazolam AUC_{∞} was estimated to be 28% on the basis of a pooled analysis of data from 5 DDI studies with midazolam conducted in patients with cancer [1,3,4,8,7]. Assuming that the AUC_{∞} ratio for midazolam in the presence versus absence of brigatinib is 1, with a sample size of 15, the 90% CI for the AUC_{∞} ratio is expected to be 0.84 to 1.19 on the basis of the variance assumptions. If the AUC_{∞} ratio for midazolam in the presence versus absence of brigatinib is X, with a sample size of 15, the 90% CI for the AUC_{∞} ratio is expected to be 0.84X to 1.19X on the basis of the variance assumptions.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4.

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. Screening values are used for baseline

values. If screening values are not available Cycle 1 Day 1 values prior to study drug administration are considered as baseline.

For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

For the categorical variables, the count and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. Additional statistics will be tabulated for pharmacokinetic data (see Section 7.9.1).

A month is operationally defined to be 30.4375 days.

Screen failure subjects will be grouped and listed at the end.

7.1.1 Study Definitions

A Patient is enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug for part A.

The data for part A and part B will be presented separately.

Part A

1. Baseline tables, disposition, safety tables

Midazolam + Brigatinib (N=XX)

Part B

1. Baseline tables, disposition, safety tables

Brigatinib 60 mg	Brigatinib 90 mg	Brigatinib 120 mg	Brigatinib 180 mg	Total

2. **Efficacy tables**

ALK-positive NSCLC	ROS1-positive NSCLC	all other ALK-positive solid tumors	all other ROS1-positive solid tumors	Total

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which they were collected. Generally, the window for the visits following start of first dose of study drug will be constructed such that the upper limit of the interval falls half way between the two visits. If a patient has more than 1 assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used. If two visits on different dates have the same distance from the scheduled study day, the data of the visit after the scheduled study day will be used. If there are multiple assessments on the selected study day then for quantitative variables the average value, and for qualitative variables the worst value (or best value, if selected for baseline), will be used.

7.1.4 Conventions for Derivation of Treatment-Emergent Adverse Event (if missing adverse event dates)

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has month and year but day is missing, the event will be considered
  - treatment emergent for Part A if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drug in Part A, and on or before the month and year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.
  - treatment emergent for Part B if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drugs in Part B, and on or before the month and year of the date of the last dose of study drugs in Part B plus 30 days.
- If the start date has year, but day and month are missing, the event will be considered:
  - treatment emergent for Part A if the year of the start date of the event is on or after the year of the date of the first dose of Brigatinib in Part A, and on or before the year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.
  - treatment emergent for Part B if the year of the start date of the event is on or after the year of the date of the first dose of study drugs in Part B, and on or before the year of the date of the last dose of study drugs in Part B plus 30 days.

- If the start date of an event is completely missing, the event will be considered:
  - treatment emergent for Part A for patients who do not continue into Part B.
  - treatment emergent for Part A for patients who continue into Part B if the ending date of the event is before the date of the first dose of study drugs in Part B.
  - treatment emergent for both Part A and Part B for patients who continue into Part B if the ending date does not reflect whether the AE ends prior to the first dose of study drug in Part B.

7.1.5 Conventions for Missing Adverse Event Dates

Table 7.a Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug of Part A or Part B.	Date of first dose of study drug of Part A or Part B accordingly.
		M and/or Y not same as date of first dose of study drug of Part A or Part B.	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug of part A or Part B	Date of last dose of study drug of Part A or Part B accordingly.
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

7.1.6 Conventions for Other Partial Dates

Missing or incomplete dates recorded during the screening visits (e.g date of initial diagnosis) will be imputed based on the algorithm described below:

- If the date of initial diagnosis has a month and year but the day is missing, the 15th will be inserted as the day.

- If the date of initial diagnosis has a year but the month and the day are missing, June 30th will be inserted.

7.2 Analysis Sets

7.2.1 Safety Population

The safety population is defined as all patients who received at least 1 dose of any study drug (brigatinib or midazolam). The safety analyses will be performed using the safety population.

7.2.2 PK-Evaluable Population

The PK-evaluable population is defined as patients who meet all of following 3 criteria:

- Received the protocol-specified dosing regimen during Part A (including the 180 mg brigatinib dose) without dose reductions or interruptions through the completion of PK sampling.
- Did not receive any excluded concomitant medications through the completion of PK sampling.
- Have sufficient midazolam concentration-time data to permit the reliable estimation of PK parameters by noncompartmental analysis methods.

The PK-evaluable population will be used for PK analyses. Patients who are not PK evaluable may be replaced.

7.2.3 Response- Evaluable Population

The response-evaluable population is defined as all patients who had measurable disease at Baseline, received at least 1 dose of any study drug, and had at least 1 post-Baseline response assessment.

7.3 Disposition of Subjects

Separate tabulations of patient disposition data will be generated for Part A and Part B.

For part A, the number of patients in the safety population, PK-evaluable population, response evaluable population, number of patients who discontinued from study treatment, and the reason study treatment was discontinued, the number of patients who discontinued study, and the reason for discontinuing the study will be summarized. The denominator of percentages will be based on the number of patients in the safety population.

For part B, the number of patients in the safety population, response evaluable population, number of patients who discontinued from study treatment, and the reason study treatment was discontinued, the number of patients who discontinued study, and the reason for discontinuing the study will be summarized. The denominator of percentages in the table of disposition data for Part B will be based on the number of patients in the safety populations for Part B.

The reasons for treatment discontinuation will be any one of the following:

- Adverse event.
- Completed maximum number of cycles per protocol.
- Lost to follow-up.
- Progressive disease.
- Protocol deviation.
- Study terminated by sponsor.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Withdrawal by subject.
- Entry into another therapeutic clinical study or start of new anticancer therapy.
- Noncompliance with the study or follow-up procedures.
- Pregnancy.
- Intolerable toxicities.
- Other.

The reasons for study discontinuation will be any one of the following:

- Death.
- Adverse event.
- Completed maximum number of cycles per protocol.
- Lost to follow-up.
- Progressive disease.
- Protocol deviation.
- Study terminated by sponsor.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Withdrawal by subject.
- Entry into another therapeutic clinical study or start of new anticancer therapy.
- Noncompliance with the study or follow-up procedures.
- Pregnancy.

- Intolerable toxicities.
- Other.

Data concerning patient disposition (eg, primary reason off study treatment, primary reason off study, patient population) will be presented in by-patient listings.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Summaries of demographic and baseline characteristics will be presented for subjects in the safety population.

The demographic characteristics consist of:

- Gender
- Age at date of informed consent (continuous)
- Age category 1
  - < 65 years
  - ≥ 65 years
- Height (cm)[use height at screening]
- Weight (kg) [use C1D1]
- Body Surface Area (BSA)

  BSA is calculated for each patient using the following formula:

$$\textbf{BSA} = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

- Ethnicity
- Race
- Country

  The number of subjects enrolled by country will be summarized
  - France.
  - Italy.
  - Netherlands.
  - Spain.

No inferential statistics will be generated.

Demographic data will also be presented in a by-patient listing.

7.4.2 Baseline Characteristics

Baseline characteristics consist of:

- Disease type.
- Solid tumor disease type.
- Histological classification.
- Disease stage at entry.
- Sites of cancer involvement.
- Baseline ECOG performance status.
- Time since initial diagnosis (months) [(date of first dose – date of initial diagnosis)/30.4375].

Separate by-patient listings will also be presented for baseline disease characteristics and ECOG performance status.

7.5 Medical History and Concurrent Medical Conditions

Patient's medical history and surgical history will be presented in a by-patient listing. Medical history will include the medical condition, date of onset and the end date relative to signing Informed Consent (before or ongoing). Surgical history will include type of surgical procedure and date of the procedure.

7.6 Medication History and Concomitant Medications

No summary for medication history.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO standardized medication name (generic name) for Part A and Part B.

Concomitant therapies with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events, please refer section 7.1.5.

Concomitant medications and procedures will be presented in separate by-patient listings.

7.6.1 Prior Therapies

Information on prior therapies will be summarized by safety population.

Summarized information on prior therapies will include:

- Number of patients who received prior Solid Tumor Therapy.
- Number of patients who received prior radiation therapy related to Solid Tumors.
- Number of patients who received bone marrow transplant or stem cell transplant related to Solid Tumors.

- Number of patients who had any prior surgical procedures related to Solid Tumors.
- Number of patients with prior chemotherapy.
- Months from last dose of prior chemotherapy to first study dose.
- Best response to prior chemotherapy.
- Months from last dose of prior radiation to first study dose.
- Best response to prior radiation.
- Months from date of transplant to first study dose.
- Best response to transplant procedure.
- Months from date of surgery related Solid Tumors to first study dose.

By patient listing of prior therapy will be listed including drug name, type of therapy, start date, end date, type pf therapy, prior best response, date of disease progression, reason for discontinuation, and information if the patient is enrolled in part B.

7.7 Study Drug Exposure and Compliance

7.7.1 Study Drugs Dosing Information

Part A

During Part A, patients will receive two single 3 mg doses of Midazolam on Day 1 and Day 21. Patient will also receive 90 mg Brigatinib QD for 7 days (Days 2 to 8) followed by 180 mg Brigatinib QD for 20 days (Days 9 to 28).

Part B

Brigatinib at highest tolerated dose (180, 120, 90, or 60) QD×28 days per cycle. During Part B, patients may receive up to 23 cycles of treatment, or treatment until PD, intolerable toxicity, or another discontinuation criterion is met. If patients are continuing to receive benefit at 23 cycles, they may have the option to continue brigatinib monotherapy at the same dose. The duration of each cycle will be 28 days.

All dosing information for each visit will be presented by Part A and Part B in a by-patient listing.

7.7.2 Extent of Exposure

Extent of exposure will be reported separately for Part A and Part B. Part A will have exposure information for Brigatinib and Midazolam whereas Part B will have exposure information for Brigatinib only.

Exposure to brigatinib and Midazolam will be summarized using the following measures:

- Time (days) on study treatment.

- Total cumulative dose of brigatinib or midazolam administered.
- Dose intensity (mg/day).
- Relative dose intensity (%).

Time on treatment will be defined as the time interval from the first dose date to the last dosing date and computed with the following formula:

Time (days) on treatment= last non-zero dose date – first dose date + 1

Dose intensity will be calculated with the following formula:

Dose intensity = Total cumulative dose/ Time (days) on study treatment.

In Part A, the daily planned brigatinib dose will be 90 mg in the first 7 days (Days 2 to 8), 180 mg from day 9 onward. In Part B, the daily planned dose will be the highest tolerated dose for Brigatinib (180, 120, 90, or 60 mg QD) at the end of Part A.

In Part A, Midazolam 3 mg will be administered on Day 1 and Day 21. The dose intensity of Midazolam will be calculated on the basis of 2 days of Midazolam in Part A.

Relative dose intensity will be defined as the proportion of the planned dose received by subjects.

Relative dose intensity will be calculated as follows:

Relative dose intensity = Total cumulative dose administered /Total dose planned x 100%.

Total person years for a treated subject will be calculated using the following formula:

Total person years = Time (days) on study treatment / 365.25.

The total person years in an analysis population will be the sum of the total person years of all the subjects in this population.

Dosing administration data for both Part A and Part B will also be presented in separate by-patient listings.

CCI

[redacted]

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

CCI

[redacted]

CCI

CCI

7.9.1 Pharmacokinetic Analysis

The PK-evaluable population will be used for all PK analyses.

Individual and mean plasma midazolam concentration data after dosing on Day 1 and Day 21 of Part A (Cycle 1) will be plotted over time and listed with and without brigatinib coadministration. Plasma PK parameters of midazolam administered in the absence and presence of brigatinib for individual patients will be calculated using noncompartmental analysis methods. Descriptive statistics for plasma midazolam concentrations and PK parameters (including but not limited to C_{max}, t_{max}, and AUC_{∞}) will be calculated with and without brigatinib coadministration.

For the estimation of the effect of brigatinib on midazolam PK, the ratios of geometric mean midazolam AUC_{∞} and C_{max} (with vs without brigatinib coadministration) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance calculated via a mixed-effects analysis of variance (ANOVA) fitting terms for treatment (midazolam with or

without brigatinib coadministration). Patient will be treated as a random effect in the model. After log transformation, AUC_{∞} and C_{max} will be separately analyzed. Point estimates and adjusted 90% CIs for the difference in treatment will be calculated and then exponentially back transformed to provide point and CI estimates for the ratios of interest.

Predose plasma concentrations of brigatinib on Days 21 and 22 of Part A (Cycle 1) and on Day 1 of Cycle 2 (Part B) will be listed and summarized using descriptive statistics. Individual and mean predose plasma concentrations of brigatinib will be plotted over time.

Additional details regarding the pharmacokinetic analyses are provided in the Clinical Pharmacology Analysis Plan.

7.9.2 Pharmacodynamic Analysis

Not applicable. No pharmacodynamic analyses are planned for this study.

7.10 Other Outcomes

Not applicable

7.11 Safety Analysis

Safety analyses will be conducted separately for Part A and Part B.

Safety evaluations will be based on the incidence, severity, type of AEs, vital signs, and clinical laboratory results.

These analyses for Part A will be performed by the safety population for Part A. Safety analyses for Part B will be performed by dose of Brigatinib using the safety population.

7.11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later (based on version at time of database lock). Treatment-emergent AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of brigatinib will be tabulated. An AE will be considered a Treatment-emergent AE (TEAE) if it first occurs worsens on or after the first dose date and before the last dose date + 30 days.

AEs will be tabulated by system organ class (SOC), high level term(HLT), and preferred term (PT) for Part A, and for Part B separately, and for the Period A and B combined. Treatment-emergent AEs will be tabulated by MedDRA system organ class and preferred term and will include the following categories

- Treatment-emergent adverse events.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs (presented by grade and overall).
- Grade 3 or higher drug-related TEAEs (presented by grade and overall).

- Most commonly reported TEAEs (at least 10% of all patients, sorted by preferred term).
- Serious TEAEs.
- Serious drug-related TEAEs.
- Treatment-emergent AEs resulting in study drug dose reduction.
- Treatment-emergent AEs resulting in study drug dose modification (as defined as dose interruption, dose reduction, or permanently discontinued).
- On-study deaths.

Patients reporting the same event more than once will have that event counted only once within each system organ class, and once within each preferred term.

The number and percentage of subjects experiencing treatment emergent AEs resulting in discontinuation of study drug (action on study drug=DISCONTINUED FROM STUDY) will be summarized by MedDRA system organ class, and preferred term.

All adverse events will also be reported in by-patient listings separately for Part A, and Part B.

A by-subject listing of treatment-emergent AEs resulting in discontinuation of study drug and treatment-emergent AEs resulting in dose modifications (dose interruption, dose reduction, or permanently discontinued) will be generated.

A by-subject listing of the deaths will be presented. By-subject listings of the deaths will be presented separately for Part A and for Part B. An on-study death is defined as a death that occurs between the first dose of study drug and within 30 days of the last dose of study drug. Deaths with start dates that are completely or partially missing will be imputed to the date of last contact.

7.11.1.1 Overall Summary

The number and percentage of patients who experience any of the following treatment emergent adverse events will be summarized

- Any adverse event.
- Drug-related adverse event.
- Grade 3 or higher adverse event.
- Drug-related Grade 3 or higher adverse event.
- Serious adverse event.
- Drug related serious adverse event.
- Adverse events resulting in study drug dose modification (as defined as dose interruption, dose reduction, or permanently discontinued).
- On-study deaths.

7.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT. Similar summary will be generated for treatment emergent drug-related SAEs.

By-patient listings of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment emergent AE status) for Part A and Part B. The drug-related SAEs will also be presented for Part A and Part B.

7.11.1.3 Deaths

By-subject listings of the deaths will be presented for Part A and Part B. All deaths occurring on-study will be displayed. On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

All deaths will be summarized for Part A and Part B, including deaths occurring on-study and death during follow-up separately.

7.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC, HLT, and PT separately for Part A and Part B.

By-patient listing of AEs resulting in discontinuation of study drug will be presented.

7.11.1.5 Adverse Events Resulting in Dose Reduction

The number and percent of patients experiencing at least one adverse event resulting in dose reduction will be summarized by MedDRA SOC, HLT, and PT separately for Part A and Part B.

A by-patient listing of AEs resulting in dose reduction of study drug will be presented.

7.11.1.6 Adverse Events Resulting in Dose Interruption

The number and percent of patients experiencing at least one adverse event resulting in dose interruption will be summarized by MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose interruption of study drug will be presented.

7.11.1.7 Adverse Events Resulting in Dose Modification

The number and percent of patients experiencing at least one adverse event resulting in dose modification (including as dose interruption, dose reduction, or permanently discontinued) will be summarized by MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose modification of study drug will be presented.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization, ignoring the non-numeric qualifier.

Descriptive statistics for the baseline values, actual values (and/or change from Baseline) in clinical laboratory parameters will be tabulated by scheduled time point for part A and Part B. Urinalysis will be done during part A only.

Hematology includes hematocrit, hemoglobin, WBC count with 5-part differential (lymphocyte, monocytes, neutrophils, eosinophils, basophils), platelets.

Chemistry includes albumin and total protein, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Amylase, Bilirubin (total and direct/indirect), BUN, calcium, bicarbonate, creatine kinase, creatinine, chloride, glucose, LDH, lipase, phosphate, magnesium, potassium, sodium, urate. Magnesium and Urate analysis will be done for part A only.

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.03. The number and proportion of patients with shifts in NCI CTCAE toxicity grades from baseline to the worst post baseline toxicity grade will be summarized. If necessary, graphical displays will be used to show changes in laboratory measures over time for each individual patient; 1) line graphs of individual tests over time for each patient; and 2) scatter plots of baseline versus worst post-baseline values.

Figures of mean actual values at each scheduled visit will also be generated for these clinical laboratory parameters in Système international (SI) units.

Graphical displays will be used to show changes in laboratory measures over time for patients separately for Part A and Part B:

1. Box graphs of individual tests over time.
2. Scatter plots of baseline versus worst post-baseline values for all patients. These will be generated for only selected labs in Table 7.d.

Table 7.d Selected Labs

Panel	Test	CTCAE Shift Table	Box Graphs	Scatter Plots	Summary Tables
Chemistry	Albumin	X	X		X
	ALT	X	X		X
	AST	X	X		X
	Alkaline Phosphatase	X	X		X
	Carbon Dioxide		X		X
	Direct Bilirubin	X	X		
	Total Bilirubin	X	X		X
	Blood urea nitrogen		X	X	X
	Calcium	X	X		X
	Chloride		X	X	X
	Creatinine	X	X		X
	Creatinine Clearance		X	X	X
	Glucose	X	X		X
	Lactate dehydrogenase (LDH)		X	X	X
	Magnesium	X	X		X
	Lipase		X		X
	Phosphate	X	X		X
	Potassium	X	X		X
	Sodium	X	X		X
	Urate	X	X		X
Hematology	Platelets	X	X		X
	Hemoglobin	X	X		X
	Leukocytes	X	X		X
	Neutrophils (ANC)	X	X		X
	Monocytes		X		X

Creatinine clearance and estimated glomerular filtration rate (GFR) will be derived using the Cockcroft-Gault and Modification of Diet in Renal Disease formulas as follows:

Cockcroft-Gault equation:

For males:

$$\text{Creatinine Clearance} = \frac{((140 - \text{age[years]}) * \text{weight[kg]})}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85 * ((140 - \text{age[years]}) * \text{weight[kg]})}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

A cap value of 125 will be set to creatinine clearance values (calculated from Cockcroft-Gault equation) higher than 125.

Modification of Diet in Renal Disease equation:

eGFR (mL/min/1.73 m^2)=175×(serum creatinine in mg/dL)$^{-1.154}$×(age in years)$^{-0.203}$×(0.742 if female)×(1.212 if African American)

For purposes of the scatterplots, the worst value will be the largest value observed after baseline for BUN and BUN/creatinine ratio. The worst value will be the smallest value observed after baseline for creatinine clearance and GFR

All chemistry and hematology lab data will also be presented in by-patient listings separately for Part A and Part B safety population.

7.11.3 Vital Signs

For part A and part B descriptive statistics for vital sign results (diastolic and systolic blood pressure, heart rate, body weight and body temperature) will be summarized overtime as follows:

- Baseline value (screening or C1D1 if screening is not available).
- Actual value at scheduled time point.
- Change from baseline.

Vital signs data will also be presented in by-patient listings, separately for Part A and Part B.

Graphical displays will be used to show vital sign parameters over time, separately for the Part A by dose, and for Part B by treatment arm:

- Individual patient line graphs of temperature, diastolic BP, systolic BP, and HR over time for each dose level. These will be summarized for measurements taken in the supine position.
- Box plots over time for temperature, diastolic BP, systolic BP and HR during Cycle 1 will be generated. These will be summarized for measurements taken in the supine position.

7.11.4 12-Lead ECGs

The observed value and changes from Baseline of ECG parameters will be summarized for Baseline and post-Baseline visits of the data collection.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not Applicable.

7.13 Changes in the Statistical Analysis Plan

Not Applicable.

8.0 REFERENCES

1. Clinical Pharmacology and Biopharmaceutics Review: Crizotinib, Application No. 202570Orig1s000. Center for Drug Evaluation and Research. March 2011.
2. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
3. Gibbons JA, de Vries M, Krauwinkel W, Ohtsu Y, Noukens J, van der Walt JS, et al. Pharmacokinetic Drug Interaction Studies with Enzalutamide. Clin Pharmacokinet 2015;54(10):1057-69.
4. Han TH, Gopal AK, Ramchandren R, Goy A, Chen R, Matous JV, et al. CYP3A-mediated drug-drug interaction potential and excretion of brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive hematologic malignancies. J Clin Pharmacol 2013;53(8):866-77.
5. Kaplan EL and Meier P. Nonparametric Estimation from Incomplete observations. J Am
6. Statistical Assoc. 1958;53:457-481.
7. Morcos PN, Cleary Y, Guerini E, Dall G, Bogman K, De Petris L, et al. Clinical Drug-Drug Interactions Through Cytochrome P450 3A (CYP3A) for the Selective ALK Inhibitor Alectinib. Clin Pharmacol Drug Dev 2017;6(3):280-91.
8. Stroh M, Talaty J, Sandhu P, McCrea J, Patnaik A, Tolcher A, et al. Lack of meaningful effect of ridaforolimus on the pharmacokinetics of midazolam in cancer patients: model prediction and clinical confirmation. J Clin Pharmacol 2014;54(11):1256-62.
9. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Nov-2020 21:11 UTC