Title: Brigatinib in Patients With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non–Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: 2002

Brigatinib in Patients with Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non‑Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

PHASE 2

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
ALK+	anaplastic lymphoma kinase-positive
ATC	anatomical therapeutic chemical
CDx	companion diagnostic
CNS	central nervous system
CPK	creatine phosphokinase elevation
CR	complete response
ctDNA	circulating tumor DNA
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
CCI	[redacted]
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GI	gastrointestinal
HRQOL	health-related quality of life
HU	health resource utilization
ICF	informed consent form
iCNS	Intracranial Central Nervous System
iDOR	Intracranial duration of response
iORR	intracranial objective response rate
iPFS	intracranial progression-free survival
IRC	independent review committee
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
QLQ-C30	EORTC core Quality of Life Questionnaire
QLQ-LC13	Quality of Life Questionnaire, Lung Cancer supplementary module

QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TLF	tables, listings, and figures
TRAE	treatment-related adverse event

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is:

- To determine the efficacy of brigatinib, as evidenced by confirmed objective response rate (ORR), in patients with anaplastic lymphoma kinase-positive (ALK+) locally advanced or metastatic non-small-cell lung cancer (NSCLC) whose disease has progressed on therapy with alectinib or ceritinib.

4.2 Secondary Objectives

The secondary objectives are:

- To characterize the durability of efficacy with brigatinib.
- To assess intracranial efficacy of brigatinib.
- To assess the overall survival (OS) with brigatinib.
- To assess the safety and tolerability of brigatinib.
- To collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic (PK) analyses.
- To assess patient-reported symptoms and health-related quality of life (HRQOL) assessed by European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC13.

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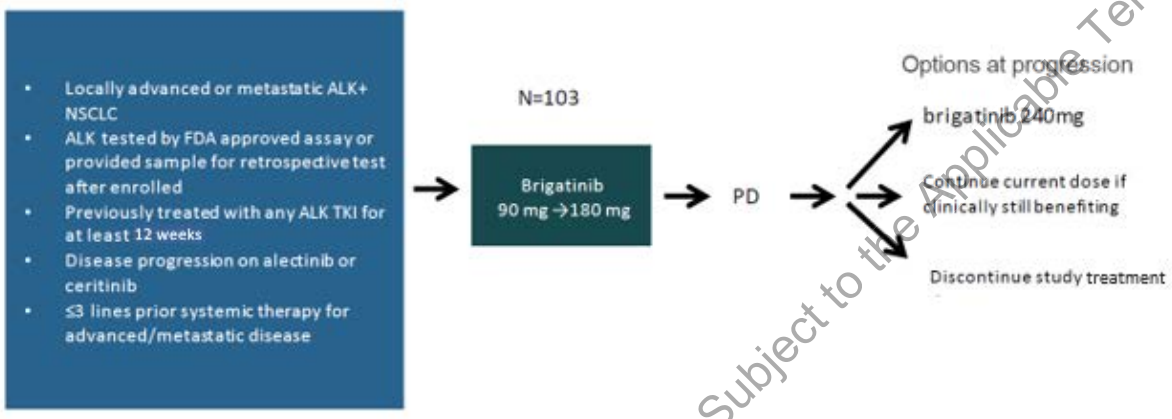
4.4 Study Design

This study is a phase 2, open-label, single-arm, multicenter, international study in patients with ALK+ NSCLC whose disease has progressed on prior alectinib or ceritinib (with or without prior crizotinib and no more than 3 different systemic regimens as treatment for locally advanced/metastatic disease). An estimated 103 patients will be enrolled internationally. Once

enrolled, patients will be treated with brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD. The study scheme is outlined in Figure 1.

Figure 1: Study Scheme



Abbreviations: ALK+, anaplastic lymphoma kinase positive; NSCLC, non–small-cell lung cancer; FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitor, PD, progressive disease.
ALK+ by central laboratory is not required before enrollment.
Strongly encourage (but not mandate) re-biopsy at screening and at progression. Plasma sample to be collected at screening, Cycle 3 Day 1 and Cycle 5 Day 1 and at progression.
Objective of exploratory biomarker analysis: to understand the resistance mechanism.

Patients will continue to be treated with brigatinib until they experience objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as assessed by the investigator, or intolerable toxicity. Upon radiological progression, at the discretion of the investigator, patients who are receiving brigatinib 180 mg QD and have experienced toxicities no greater than Grade 2 during treatment may elect to increase the brigatinib dose to 240 mg QD, or continue study treatment at their current dose if they are still benefiting from treatment at this dose (e.g. absence of clinical symptoms or signs indicating clinically significant disease progression requiring alternative systemic anti-cancer therapy; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g. respiratory failure due to tumor compression, spinal cord compression] requiring urgent use of alternative anticancer-therapy; and no significant, unacceptable or irreversible toxicities related to study treatment). In both scenarios (increase dose or continue at same dose), the medical monitor shall review and approve the case.

Adverse events (AEs) will be assessed from the start of the study drug till 30 days after last dose. Patients' signs and symptoms, laboratory values, vital signs, electrocardiograms (ECGs), and any other relevant special exams as clinically indicated will be obtained to evaluate the safety and tolerability of brigatinib.

Sparse PK samples will be collected during the study to measure plasma concentrations of brigatinib, as outlined in Protocol Appendix A, PK Sampling Schedule.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective 14 June 2010 [5].

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is confirmed ORR, as assessed by the independent review committee (IRC), per RECIST v1.1 in the full analysis (see Section 7.2.1) population.

5.2 Secondary Endpoints

The secondary endpoints are:

- Confirmed ORR, as assessed by the investigator, per RECIST v1.1.
- Duration of response (DOR) as assessed by the IRC.
- DOR as assessed by the investigator.
- Progression-free survival (PFS) as assessed by the IRC.
- PFS as assessed by the investigator.
- Disease control rate (DCR) as assessed by the IRC.
- DCR as assessed by the investigator.
- Time to response as assessed by the IRC.
- Time to response as assessed by the investigator.
- Confirmed intracranial objective response rate (iORR) in patients with iCNS metastases at baseline, as assessed by the IRC.
- Duration of intracranial response (iDOR) in patients with iCNS metastases at baseline, as assessed by the IRC.
- Intracranial progression-free survival (iPFS) in patients with iCNS metastases at baseline, as assessed by the IRC.
- OS.
- Safety/tolerability (CTCAE version 4.03).
- HRQOL assessed with the global health status/quality of life (QOL) and other function and symptom from EORTC QLQ-C30 (version 3.0), and EORTC QLQ-LC13.

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6.0 DETERMINATION OF SAMPLE SIZE

The sample size was determined so that it would allow for stating that the true ORR (expected response rate) is greater than the threshold response rate of 20% for patients previously treated by alectinib or ceritinib. A total of approximately 103 patients will be enrolled. This sample size was calculated to provide at least 90% power to rule out an uninteresting ORR of 20%, assuming the true ORR is 35%. The calculation is based on an exact binomial test with a total one-sided alpha level of 0.025 at primary analysis.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Baseline values are defined as the last valid values collected during the time interval from the screening visit to the first dose date (time) of the study treatment.

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data, and counts/percentages for categorical data) will be used to summarize patient characteristics, study treatment administration, efficacy, safety and genetic status of biomarkers. Data will also be displayed graphically, where appropriate.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations 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 purpose of reporting efficacy and safety at specific time points, a month will comprise 30.4375 days.

All the statistical analyses will be performed using SAS Statistical Software v9.4 or higher.

7.1.1 Study Definitions

The primary (and secondary) endpoint, confirmed objective response rate (ORR), is defined as the proportion of patients who are confirmed to have achieved CR or PR per RECIST v1.1 after the initiation of study treatment. Confirmed responses are those that persist on repeat imaging ≥4 weeks (allowing a minus 3-day time window) or more after initial response.

Additional secondary efficacy endpoints for this study are defined as follows:

- Duration of response (DOR) is defined as the time between the first documentation of objective tumor response (CR or PR) for patients with a confirmed CR/PR, and the first subsequent documentation of objective progressive disease (PD) or death due to any cause, whichever occurs first. The detailed scheme of progression and censoring for the analysis of DOR is specified in Table 1.
- PFS is defined as the time from the start of study treatment to the first documentation of objective PD or to death due to any cause, whichever occurs first. The detailed scheme of progression and censoring for the analysis of PFS is specified in Table 1.
- DCR is defined as the proportion of patients who have achieved CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study drug, as per RECIST v1.1.
- Time to response is defined as the time interval from the date of the first dose of study treatment until the initial observation of CR or PR for patients with confirmed CR/PR.
- iCNS ORR (iORR) is defined as the proportion of patients who have achieved confirmed CR or PR in the iCNS per a modification of RECIST v1.1 as defined in the IRC charter

after initiation of study treatment, in patients with any intracranial metastases and in patients with at least one measurable intracranial lesion at baseline by the IRC assessment, and in patients with only non-measurable intracranial lesions at baseline by the IRC assessment.

- Duration of intracranial response (iDOR) is defined as the time interval between the first documentation of confirmed objective tumor response (CR or PR) in the iCNS and the first subsequent documentation of objective PD in the iCNS or death due to any cause, in patients with iCNS metastases at enrollment baseline per IRC. The detailed scheme of progression and censoring for the analysis of iDOR is specified in Table 1.
- iCNS PFS (iPFS) is defined as the time interval from the date of the first dose of study treatment until the first date at which iCNS progression is objectively documented by IRC, or death due to any cause, whichever occurs first.

  An iPFS event is defined as, regardless of extracranial tumor status, either a new lesion in iCNS, or the sum of longest diameters of all measurable iCNS lesions increases by at least 20% from the smallest value on study (including baseline). The detailed scheme of progression and censoring for the analysis of iPFS is specified in Table 1.
- Overall Survival (OS) is defined as the time interval from the date of the first dose of the study treatment until death due to any cause. OS will be censored on the date of last contact for patients who are still alive.

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Table 1: The Scheme of Progression and Censoring for PFS. iPFS, DOR, iDOR, PFS240

Situation	Date of progression or censoring	Outcome
1. New anticancer treatment (including palliative radiotherapy and cancer-related surgery) started prior to documented disease progression or death	Date of last adequate radiological assessment prior to initiation of new anticancer treatment (including palliative radiotherapy and cancer-related surgery)	Censored
2. Death or PD **within** 126 days of last evaluable tumor assessment (or first treatment date if there are no post-baseline tumor assessment)	Date of death or first PD whichever occurred first	Progressed
3. Death or PD **more than** 126 days after the last evaluable tumor assessment (or first treatment date if there are no post-baseline tumor assessment)	Date of last adequate radiological assessment prior to the 126-day interval	Censored
4. No progression or death	Date of last adequate radiological assessment or the first dose date if no valid post-baseline assessment	Censored

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of the medication. 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.

7.2 Analysis Populations

7.2.1 Full Analysis Population

All patients who receive at least one dose of brigatinib will be included in the full analysis population.

The full analysis population will be used for the primary efficacy analysis and analyses on all secondary efficacy endpoints, unless otherwise specified.

7.2.2 iCNS Disease Population

The iCNS disease population will consist of those patients in the full analysis population who were determined by the IRC to have iCNS metastases at baseline, regardless of whether they had at least one lesion that qualified as a target lesion in their baseline assessment by IRC.

7.2.2.1 Measurable iCNS Disease population

The measurable iCNS disease population will consist of the patients within the iCNS disease population who were determined the IRC to have had at least one iCNS target lesion in their baseline assessment.

7.2.2.2 Non-Measurable iCNS Disease population

The non-measurable iCNS Disease population will consist of all patients in the iCNS disease population who are not included in the measurable iCNS disease population.

7.2.3 Per-Protocol Population

The per-protocol population will exclude all patients in the full analysis population who do not meet key entry criteria, have no measurable disease at baseline, or have no adequate postbaseline response assessment unless the reason is death or early discontinuation due to disease progression. To specify, the per-protocol population will fulfill the following criteria:

- Histologically or cytologically confirmed locally advanced or metastatic NSCLC
- Have documentation of ALK rearrangement by either:
    - A positive result from any laboratory test approved by the Food and Drug Administration (FDA) (e.g., the Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit or the Ventana ALK [D5F3] CDx [companion diagnostic] Assay or Foundation Medicine's FoundationOne CDx)

  or

    - A positive result from a non–FDA-approved local lab test and have provided tumor sample to the central laboratory
- Previously progressed on either alectinib or ceritinib
- Did not receive prior treatments of both alectinib and ceritinib
- At least one measurable target lesion per RECIST v1.1, as assessed by the investigator
- At least two adequate post-baseline radiographic response assessments unless the reason for no post-baseline radiographic response assessment is one of the following:
    - Death
    - Discontinuation due to documented disease progression per RECIST v1.1
    - Discontinuation due to AE

The per-protocol population will be used for the sensitivity analyses of the primary endpoint and may be used for analyses of selected secondary efficacy endpoints.

7.2.4 Safety Analysis Population

All patients who receive at least one dose of brigatinib will be included in the safety analysis population; therefore, the safety population is identical to the full analysis population. All safety analyses will be performed using the safety population.

7.3 Patient Disposition

The disposition of patients includes the number and percentage of patients for the following categories: patients in each analysis population, patients ongoing treatment, patients discontinued from study treatment, patients ongoing in the study, and patients discontinued from the study. Patients ongoing in the study are defined as patients who are still being followed (either on treatment, or in survival follow-up) at the time of data cut. Patients discontinued from the study are defined as patients who have permanently left the study.

All percentages will be based on the number of patients in the full analysis population, unless otherwise specified below.

The primary reason for study drug and study discontinuation will also be summarized in this table. Frequency distributions will be provided. When calculating percentages for the reasons for study treatment discontinuation, the total number of patients who had permanently discontinued the study treatment will be used as the denominator. When calculating percentages for the reasons for study discontinuation, the total number of patients who prematurely discontinued from the study and are no longer in follow-up will be used as the denominator.

A listing will present data concerning patient disposition.

7.3.1 Screen Failures

Patients who signed an informed consent form (ICF) but did not start study treatment will be counted as a screening failure. Frequency distributions and reasons for screen failure will be provided. When calculating percentages for reasons for screen failure, the total number of patients counted as a screen failure will be used as the denominator.

7.3.2 Patient Eligibility

Frequency distributions will be provided. When calculating percentages for the primary reasons for patient not being eligible, the total number of ineligible patients will be used as the denominator.

7.3.3 Number of Patients Who Were Enrolled

Frequency distribution of the number of patients enrolled by region, country, and site will be provided.

7.3.4 Important Protocol Deviations

Frequency distribution will be provided for each deviation category. A patient who has several deviations will be counted once in each appropriate category. A patient who has several deviations that can be classified into the same category will be counted only once.

7.4 Demographic and Baseline Disease Characteristics

Demographic and baseline characteristics will be analyzed in the full analysis population, as listed in Table 2 and Table 3. Continuous prognostic factors will be summarized by means,

medians, standard deviations, and ranges; categorical prognostic factors will be summarized by counts/percentages. Other prognostic factors (e.g., by categorizing the continuous prognostic factors and re-categorizing the categorical prognostic factors) may also be included in the analysis.

Table 2: Demographics

Parameters	Categories for categorical parameters
Age (continuous)	
Age (categorical)	Grouping 1: 18-64, ≥65 years Grouping 2: 18-49, 50-64, 65-74, ≥75 years
Sex	Male, Female
Race	White, Black or African American, Asian (Asian Indian, Chinese, Japanese, Korean, Not Reported), Other (includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not Reported)
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
Geographic Region	Asia Pacific (China, Other), Europe, North America, Australia.
Weight (continuous)	
Height (continuous)	

Table 3: Baseline Disease Characteristics

Parameters	Categories for categorical parameters
Stage at Initial diagnosis	IA, IB, IIA, IIB, IIIA, IIIB, IV, Unknown or not staged
Stage at study entry	IIIA, IIIB, IV
Time since initial diagnosis (continuous)	
Time since advanced stage diagnosis (continuous)	
Histopathological classification at study entry	Squamous, Non-squamous (including Adenocarcinoma, Adenosquamous Carcinoma, Large cell, Unknown, Other)
Lung involvement at study entry	Left, Right, Both, Neither
Sites of cancer involvement at study entry	All options from eCRF
Metastatic Sites at Baseline	All options from eCRF
Number of sites of cancer involvement at study entry	0, 1, 2, 3+
iCNS metastases as assessed by iCNS IRC Measurable iCNS metastases as assessed by IRC Non-measurable only iCNS metastases as assessed by IRC	Yes, No Yes, No Yes, No
Brain metastases as assessed by investigator Measurable brain metastases as assessed by investigator Non-measurable only brain metastases as assessed by investigator	Yes, No Yes, No Yes, No
Tobacco use history	Never, Former, Current
ECOG Performance Status	0, 1, 2+

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be given using the full analysis population A general medical history will be listed for all patients, with medical history defined as any start date prior to the first dose date.

Concurrent medical conditions, defined as any medical condition during treatment period, will be given by system organ class (SOC) and preferred term (PT), as coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A patient with multiple occurrences of medical history or concurrent medical condition with a SOC will be counted only once in that SOC. A patient with multiple occurrences of medical history or concurrent medication with a PT will be counted only once within that preferred term. Frequency distributions will be provided.

Prior cancer therapies will be summarized as given in Table 4.

Table 4: Prior Cancer Therapies

Parameters	Categories for categorical parameters
Type of prior anti-cancer therapy	Target therapy (Alectinib, Ceritinib, Crizotinib), Chemotherapy, Immunotherapy, Other
Number of prior systemic anticancer regimens	1, 2, 3+
Overall best response to prior anti-cancer regimen	Complete or Partial response, Other (include all other options from eCRF)
Overall best response to prior TKI therapy • Overall best response to Alectinib • Overall best response to Ceritinib • Overall best response to Crizotinib	Complete or Partial response, Other (include all other options from eCRF)
Overall best response to prior Chemotherapy	Complete or Partial response, Other (include all other options from eCRF)
Overall best response to prior Immunotherapy	Complete or Partial response, Other (include all other options from eCRF)
Reason for stopping prior anti-cancer regimen	Progressive Disease, Other (include all other options from eCRF)
Reason for stopping prior TKI • Reason for stopping prior Alectinib • Reason for stopping prior Ceritinib • Reason for stopping prior Crizotinib	
Any prior radiotherapy	Yes, No
Prior radiotherapy on the brain	Yes, No
Best response to prior radiotherapy on brain	Complete or Partial response, Other (include all other options from eCRF)
Prior radiotherapy on the lung	Yes, No
Best response to prior radiotherapy on lung	Complete or Partial response, Other (include all other options from eCRF)

Mutation status will be summarized as given in Table 5.

Table 5: Mutation status

Parameters	Categories for categorical parameters
ALK rearrangement detected	Yes, No
ALK mutation	List categories from eCRF, including categories from 'Other'
Number of ALK mutations	0, 1, 2+
Type of ALK testing used	Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit, Ventana ALK [D5F3] CDx [companion diagnostic] Assay, Foundation Medicine's FoundationOne CDx, All other.

7.6 Medication History and Concomitant Medications

Medication history and concomitant medications will be analyzed in the full analysis population. General medication history, defined as any medications with start date prior to the first dose date, will be listed for all patients in the full analysis set. Concomitant medications, defined as any

medication taken during treatment period, will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from screening through the end of the on-study period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO generic drug term and sorted in decreasing frequency based on the number of reports. A patient who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

The number and percentage of patients with subsequent anti-cancer therapy will be given. Subsequent anti-cancer therapies will be categorized as target therapy, chemotherapy, immunotherapy, and other (including investigational drugs), all per medical review.

7.7 Efficacy Analysis

7.7.1 Primary Efficacy Endpoint Analysis

The best response (CR, PR, SD, or PD), according to RECIST v1.1, will be derived for each patient in the full analysis population (see Section 7.2.1). Patients with no measurable disease at baseline as assessed by the IRC or no adequate postbaseline response assessment will be included as non-responders, unless their overall response is CR. The primary efficacy endpoint confirmed ORR is calculated as the proportion of patients who are confirmed to have achieved CR or PR per IRC after the initiation of study treatment, using the following formula: ORR = (# IRC-confirmed CR or PR)/(# full analysis patients)*100%. The exact 2-sided 95% binomial confidence interval for IRC-confirmed ORR will be calculated along with a p-value from exact binomial test.

Confirmed responses are those meet the following criteria:

1) Part of a pattern leading to confirmed response found in Table 6.
2) Persist on repeat imaging 4 weeks (allowing a minus 3-day time window) or more after initial response.
3) The date of the first scan with CR/PR must be on or after 6 weeks (allowing a minus 3-day time window) relative to the first dose date.

Table 6: Derivation of confirmed ORR

Overall response First time point	Overall response Subsequent time point	Confirmed Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria[b] for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria[b] for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria[b] for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria[b] for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria[b] for SD duration met, otherwise NE

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
[b] Minimum criteria for SD is that measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks

A response pattern of PR-SD-PR, PR-NE-PR or CR-NE-CR will be defined as a confirmed PR/CR. If the time interval of two PRs/CRs is at least 4 weeks (allowing a minus 3-day time window), regardless of how many NE, the first PR will be considered confirmed.

The best response in target lesions per RECIST v1.1 will be calculated as the maximum decrease (or the minimum increase if no decrease) in percentage in the sum of the longest dimensions of the target lesions at a single assessment as compared with baseline. The best response will be displayed using a waterfall plot in the full analysis population.

Supportive sensitivity analyses will be performed for confirmed ORR assessed by the IRC in the per-protocol population. Supportive sensitivity analyses will also be performed in patients confirmed to be ALK+ by an FDA approved test via local or central assessment and within subgroups defined by age, sex, race, geographic region, prior anticancer therapies (including prior alectinib vs prior ceritinib, with/without chemotherapy; with/without prior crizotinib), and other prognostic factors. Continuous prognostic factors affecting the ORR may be explored using simple logistic regression models.

7.7.2 Secondary Efficacy Endpoint Analyses

Confirmed ORR, as assessed by the investigator (per RECIST v1.1) in both the full analysis and per-protocol populations will be used to assess the robustness of the primary analysis of the primary endpoint. Investigator-confirmed ORR will be found in the full analysis population and per-protocol population, calculated in the same manner as primary endpoint calculation of ORR. The exact two-sided 95% binomial confidence intervals will be calculated for investigator-confirmed ORR in both populations.

The intracranial ORR (iORR) will be analyzed in all the following populations: iCNS Disease population, measurable iCNS disease population, and non-measurable only iCNS disease population. Confirmed iORR, as assessed by the IRC, will be calculated in the same manner as the primary endpoint of confirmed ORR. The exact two-sided 95% binomial confidence intervals will be calculated. Derivation of confirmed iORR will follow the patterns as outlined for the primary endpoint of confirmed ORR.

The disease control rate (DCR) will be assessed by the investigator and IRC in the full analysis population, and the exact two-sided 95% binomial confidence intervals will be calculated. The calculations of the DCR will be as follows:

- DCR in the full analysis population, per investigator = (# investigator-assessed CR or PR or SD)/ (# full analysis patients)*100%;
- DCR in the full analysis population, per IRC= (# IRC-assessed CR or PR or SD)/ (# full analysis patients)*100%;

In general, the calculation of time-to-event (in months) efficacy endpoints will be as follows:

- DOR = date of PFS event or censoring – date of first response (CR or PR, whichever is first recorded) + 1
- PFS = date of progression or death or censoring – date of first study dose + 1
- iPFS = date of iCNS disease progression or death due to any cause or censoring – date of first study dose + 1
- Time to response = date of first confirmed response (CR or PR, whichever occurs first) – date of first study dose + 1
- iDOR = date of iPFS event or censoring – date of first response in the iCNS (CR in the iCNS or PR in the iCNS, whichever is first recorded) + 1
- OS = date of death or last contact – date of first study dose + 1

For time-to-event efficacy endpoints (DOR, PFS, iPFS, iDOR, OS), median values and the associated 2-sided 95% CIs will be estimated using Kaplan-Meier method (Kaplan and Meier, 1958). The PFS rates, iPFS rates and OS rates will be calculated every 6 months, and the associated 2-sided 95% CIs will be computed. Time to event analyses endpoints DOR, and iDOR, will be analyzed using confirmed responders only.

Summary statistics for time to response and iCNS response will be provided for confirmed responders only.

The secondary efficacy endpoints of DOR, PFS, OS and time to response will be analyzed in the full analysis population and in the subgroup of patients who have progressed on prior alectinib. iPFS and iDOR will be analyzed in the iCNS disease population.

Additionally, a sensitivity analysis will be performed for PFS by removing the censoring rule due to more than 1 missing radiological assessment (rule # 3 in Table 1).

7.7.3 Additional Efficacy Endpoint Analyses

Confirmed ORR240, as assessed by the investigator (per RECIST v1.1), will be analyzed in patients who dose-escalate to 240 mg QD after initial progression at 180mg QD. The new baseline for confirmation of response after escalation to 240 mg QD will be defined as the last observed value prior to escalation. The best response (CR, PR, SD, or PD), according to RECIST v1.1, will be derived for each patient that dose escalates to 240 mg QD. The ORR240 is calculated using the following formula:

- ORR240 = (# investigator-confirmed CR or PR in patients that dose-escalate to 240mg QD)/(# patients that dose-escalate to 240 mg QD)*100%.

The exact 2-sided 95% binomial confidence interval for investigator-confirmed ORR240 will be calculated.

PFS240, as assessed by investigator per RECIST v1.1, will be analyzed in patients who dose escalate to 240 mg QD after initial progression at 180 mg QD. The calculation of PFS240 will be as follows: PFS240 = date of progression or death or censoring – date of first dose at 240 mg QD + 1. The median value and associated 2-sided 95% CI for PFS240 will be estimated using the Kaplan-Meier method.

7.8 Statistical Hypotheses

The primary null hypothesis to be tested is that the proportion of patients achieving IRC-confirmed ORR is not different than an uninteresting threshold rate of 20%, i.e.,

H_0: ORR = 20%

The alternative hypothesis is that the confirmed IRC-confirmed ORR is greater than an uninteresting threshold rate of 20%, i.e.,

H_A: ORR > 20%

The key subgroup hypothesis to be tested is:

Confirmed ORR in patients previously treated with alectinib is not different than an uninteresting threshold rate of 20%.

7.9 Statistical Decision Rules

The primary null hypothesis will be tested at a one-sided alpha level of 0.025 using exact binomial test. If the primary null hypothesis is rejected, we will conclude that ORR for brigatinib treatment in patients previously treated with alectinib or ceritinib is significantly greater than the threshold response rate of 20%.

A fixed sequential testing procedure will be used to test between the primary endpoint and the key subgroup hypothesis; that is, the subgroup hypothesis will be tested only if the primary efficacy endpoint is statistically significant in the full analysis population. If the primary endpoint is achieved in patients previously treated with alectinib or ceritinib, then a subgroup analysis of confirmed ORR in patients previously treated with alectinib will be performed and tested at a one-sided alpha level of 0.025 using exact binomial test.

7.10 Pharmacokinetic Analysis

7.10.1 Pharmacokinetic Analysis

Plasma concentration-time data will be presented in a by-patient listing. This listing will include nominal collection time, actual PK sample collection date/time, and brigatinib concentration. A table of plasma concentration-time data for brigatinib will be provided, summarized by time point. These analyses will be done using the safety population.

PK data collected in this study will contribute to population PK and exposure/response (safety and efficacy) analyses. These analyses may include data from other brigatinib clinical studies. The analysis plan for the population PK and exposure/response analyses will be separately defined and the results of these analyses will be reported separately.

7.11 Other Outcomes

7.11.1 Subgroup Analyses

If the primary endpoint is achieved in patients previously treated with alectinib or ceritinib, then a subgroup analysis of confirmed ORR in patients progressed on alectinib will be performed and tested at a 1-sided alpha of 0.025.

Other subgroups of interest include:

- Age (patients ≥ 65 years vs. patients < 65 years)
- Sex (male vs female)
- Race (Asian vs. Non-Asian)
- Patients with any brain metastases at baseline, per investigator (yes vs. no)
    - Prior radiotherapy status to the brain (yes vs. no)
- Region (Asia, China, rest of world)
- Smoking status (never vs former/current)

- Prior TKI treatments (alectinib vs. ceritinib)
- Prior chemotherapy (yes vs. no)
- Prior crizotinib treatment (yes vs. no)
- Best response to prior ceritinib or alectinib treatment (CR/PR vs. other)
- Best response to any ALK TKI (crizotinib, alectinib or ceritinib) (CR/PR vs. other)
- Number of prior ALK TKI therapies (1 prior vs. 2 prior)

For the subgroup analysis by region, patients in China is defined as patients enrolled in mainland China and Chinese authority accredited sties in Hong Kong (Site 21001, 21003 and 21005).

7.12 Safety Analysis

Safety evaluations will be based on the incidence, severity, type of adverse events, clinically significant changes, or abnormalities in the patient's physical examination, vital signs, and clinical laboratory results.

Exploratory analyses may also be performed on other safety parameters, as deemed appropriate, and within subgroups defined by age, sex, race, prior anticancer therapies, medical history, and other prognostic factors. These analyses will be based on the Safety Analysis population.

7.12.1 Study Treatment Exposure

Exposure to study treatment over time will be summarized using the following measures:

- Time on treatment (days)
- Total amount of administrated treatment (mg)
- Dose intensity (mg/day)
- Relative dose intensity (%)
- Dose interruption of at least 3 days
    - Number of patients with at least one occurrence
    - Number of patients who resume any dosing after interruption
    - Number of patients who resumed at the original dose prior to interruption
    - Total duration (days) of time off study drug for one interruption episode
    - Longest off study drug duration across all patients (days)
- Dose reduction of at least 3 days
    - Number of patients with at least one occurrence
    - Number of patients who returned to dosing after reduction

Time on treatment is defined as the time interval from the first study dose date to the last dosing date and is computed using the following formula: Time (days) on treatment = date of last non-zero dose – date of first dose + 1.

Total amount of administered treatment is defined as the cumulative dose of study drug (mg), measured from the first dose to the last dose of brigatinib.

Dose intensity will be calculated with the following formula: Dose intensity = total amount of administered treatment / total # of days received dose.

Relative dose intensity (%) is defined as the proportion of the expected dose received by patients and will be calculated separately for: 90/180 mg QD and 240 mg QD. The expected daily dose will be 90mg in the 7-day lead-in period and 180 mg from day 8 onward. If the patient escalates to 240 mg, the expected daily dose will be 240 mg from that day onward, unless they de-escalate to 180 mg. Relative dose intensity for the three separate dosing groups will be calculated as follows:

- Relative Dose Intensity, 90/180 mg QD phase = (Total Dose Administered in 90/180 mg QD phase/Total Dose Expected in 90/180 mg QD phase) *100
- Relative Dose Intensity, 240 mg QD phase = (Total Dose Administered in 240 mg QD phase/Total Dose Expected in 240 mg QD phase) *100

Dose modifications will be summarized by dose interruption and dose reduction. A patient will be identified as having a dose interruption if this patient has no exposure to study drug for at least 3 consecutive days. A patient will be identified as having dose reduction if this patient had a period of reduced dosage of at least 3 consecutive days, as long as the dose received was less than the target dose but greater than 0 mg on some of the days in this period. Periods of time in which a patient alternates between reduced dosing and dose interruptions will be handled in the following manner:

- The entire period of time between the receipt of the target dose and either resumption at the target dose or discontinuation of treatment will be considered as a single dose reduction period.
- Any period of 3 or more days with no receipt of study drug within that dose reduction period will also be treated as a dose interruption.

Safety will be assessed from the first dose of study treatment for all patients and from the date of escalation to 240 mg QD in patients who escalate after PD.

7.12.2 Adverse Events

All AEs entered in the clinical database (including treatment-emergent and non-treatment-emergent AEs) will be listed in by-patient listings, or available for review in appropriate datasets. AEs will be tabulated by 90/180 mg QD (AE data will be truncated at time of starting 240 mg if a patient escalates) and 240 mg QD (AE data will start at time of first dose of 240 mg) dose groups separately.

Treatment-emergent AEs (TEAEs) are defined as any AE that starts/worsens on or after the first dose of study treatment and no later than 30 days after the last dose date (or the first dose date of brigatinib 240mg if it is within 30 days of the last dose date of brigatinib180mg), and will be tabulated by primary SOC and PT. TEAEs also include those with partially or completely missing start date since there is not enough evidence that the event started before the first dose of study treatment. AEs will be tabulated according to MedDRA by SOC and PT and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher
- Grade 3 or higher drug-related TEAEs
- TEAEs resulting in study drug discontinuation
- TEAE resulting in either dose interruption or dose reduction
- Serious AEs (SAEs) including study drug-related SAEs
- Fatal SAEs, i.e., death within 30 days of last dose of study drug, or related to study drug (if > 30 days)
- Summary of Deaths (including Cause of Death)

A summary table of TEAEs will be provided, including the proportion of patients with at least 1 TEAE, study drug-related TEAE, Grade 3 or 4 TEAE, Grade 3 or 4 study drug-related TEAE, SAE, study drug-related SAE, Grade 3 or 4 SAE, Grade 3 or 4 study drug-related SAE, TEAE resulting in study drug interruption, dose reduction, or dose discontinuation, SAE leading to death and study drug-related. This summary table will be repeated for the safety analysis set in following subgroups:

- Age (patients ≥ 65 years vs. patients < 65 years)
- Race (Asian vs. Non-Asian)
- Region (Asia, China, rest of world)

For the subgroup analysis by region, patients in China is defined as patients enrolled in mainland China and Chinese authority accredited sites in Hong Kong (Site 21001, 21003 and 21005).

The frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity), will be described. Listings of laboratory test results and CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

In addition, TEAEs will be summarized by causal relationship to study treatment (in the opinion of the investigator) and action taken on study treatment, including dose modifications, interruptions and discontinuation.

AEs in special categories will also be summarized in terms of number of patients with at least one event in the category, and by the number of patients with at least one event for each constituent preferred term. The special categories to be analyzed will include at minimum those listed in Appendix 9.2, and will align with the risk profile of brigatinib.

7.12.3 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA primary SOC, and PT.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent status).

7.12.4 Deaths

All deaths occurring on-study treatment (including 30 days after last dose) and during follow-up will be displayed (regardless of treatment-emergent status). Deaths will be summarized by timing (within 30 days after last dose date, more than 30 days after last dose), and reason.

7.12.4.1 Imputation Rule for Missing Causal Relationship of Treatment-Emergent Adverse Events

If there is inadequate information regarding the investigator's assessment of relationship to study treatment, the relationship to the study treatment will be imputed as related to study drug for treatment-emergent AEs.

7.12.4.2 Imputation Rule for Missing Onset Date and Resolution Date of Adverse Events

In general, the imputation will be conservative such that onset dates will be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Resolution date will be imputed first and then used to impute onset date.

Imputation for Resolution Data:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of:
    - Last day of the month (28, 29, 30 or 31 depending on in which month the adverse event resolved)
    - Data cutoff date
    - Death date
- If day and month are missing (UU-UUU-YYYY), impute as the earliest of:
    - December 31 (31-DEC-YYYY)
    - Data cutoff date
    - Death date
- If date is completely missing (e.g., AE is ongoing), impute as earliest of:
    - Data cutoff date

- Treatment discontinuation date + 30 days
- Death date

Imputation for Onset Data:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of:
  - If year and month are the same as year and month of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is the same as year of first dose date and month is after month of first dose date, impute as first date of month
  - If year is the same as year of first dose date and month is before month of first dose date, impute as latest of first day of the month or informed consent date
  - If year is after year of first dose date, impute as first day of month
  - If year is before year of first dose date, impute as latest of first day of the month or informed consent date
- If day and month are missing and year is non-missing (UU-UUU-YYYY), impute as follows:
  - If year is the same as year of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is after year of first dose date, impute as January 1 (01-JAN-YYYY)
  - If year is before year of first dose date, impute as latest of first day of the year (01-JAN-YYYY) or informed consent date
- If date is completely missing:
  - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
  - If resolution date (or imputed resolution date) is prior to first dose date, impute as informed consent date.

7.12.4.3 Derivation of Treatment-Emergent Adverse Event Flag

Treatment-emergent AEs are new or worsening AEs with an onset date on or after the first dose date and within 30 days of the last dose date of study drug. In the case of missing onset date, impute using the rules defined in previous section.

7.12.4.4 Calculation Specifications for Treatment-Emergent Adverse Events

Time to onset is defined as the time interval from the first dose date until the onset date of a treatment-emergent AE. In case of a missing onset date, a date imputed with the rules in Section 7.12.4.2 will be used. Time to onset will be computed with the following formula: time to onset= AE onset date - first dose date + 1.

Time to initial onset of an individual treatment-emergent AE is defined as the time interval from the first dose date until the earliest onset date of the treatment emergent AEs of the same nature. In case of a missing onset date, a date imputed with the rules in Section 7.12.4.2 will be used. Time to initial onset will be computed with the following formula: time to initial onset = earliest AE onset date - first dose date + 1.

Age at onset (in years) will be computed by the following formula and rounding down to the nearest integer: age at onset = floor ((AE start date - birth date + 1)/365.25).

Dose at onset (in mg) will be defined as the dose received by patients on AE onset date, regardless of treatment arm. Dose at onset will not be defined if the occurrence of a treatment-emergent AE is post treatment discontinuation.

Dose by onset will be defined as the last non-zero dose received by AE onset date.

7.12.5 Clinical Laboratory Evaluations

Laboratory and vital signs data in standard units will be summarized using summary statistics and graphically at baseline and at each cycle for which adequate data are available. Laboratory data will also be graded according to the NCI CTCAE v4.03 when applicable.

For patients who have escalated to 240 mg, their new baseline will be defined as the last observed value prior to escalation.

Change from baseline to the worst on-study result will also be summarized by shift in CTCAE grade for selected laboratories.

If a laboratory value is reported using a nonnumeric qualifier (e.g., less than (<) or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

7.12.6 12-Lead ECGs

For consistency, the Fridericia correction (QTcF = QT interval/(RR)1/3 interval) method will be used for all calculations of heart rate-corrected QT (calculated) intervals.

The following Electrocardiogram results will be summarized:

- Heart Rate (<60 bpm, <50 bpm, bradycardiac, tachycardiac)
- QT Interval >500 ms with baseline <=500 ms
- QTcF Maximum Change (No increase, >1-<30 ms, 30-60 ms, >60 ms)

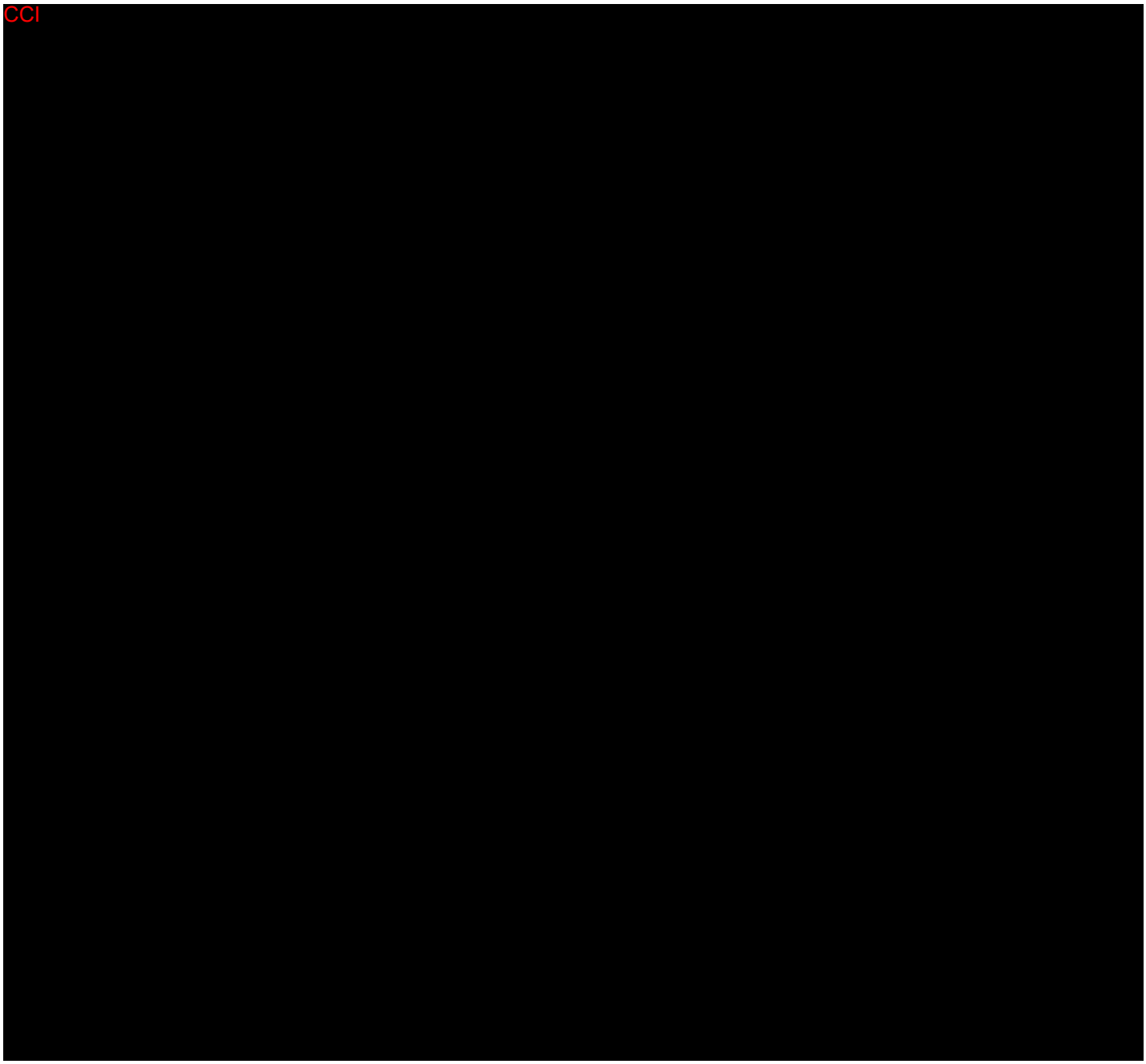
- QTcF (>500 ms & baseline<=500 ms, >480 ms & baseline<=480 ms, >450 ms & baseline<=450 ms)

Electrocardiogram results will also be presented in a listing.

7.12.7 Other Observations Related to Safety

{Not applicable}

CCI



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[redacted]

7.14 Changes in the Statistical Analysis Plan

The original SAP (v1.0) was finalized on 5 Dec 2019.

The SAP amendment 1 (v.2.0) was finalized on 05 June 2020. Major changes in this SAP Amendment 1 include:

1. Medical history is defined as any start date prior to the first dose date instead of informed consent date.
2. It is clarified that a p-value will be generated from exact binomial test for the primary endpoint in FAS and for patients previously treated with alectinib if the primary objective is met.
3. The 126-day restriction for the confirmation of a response is removed so that a confirmation scan >126 days after the initial response can be used to confirm the initial response.
4. Time to response will be analyzed only for confirmed responders using summary statistics.
5. An additional sensitivity analysis will be performed for PFS by removing the censoring rule due to more than 1 missing radiological assessment (rule # 3 in Table 1).
6. Adverse events of special categories are updated based on the current brigatinib project standard.
7. A summary table for ECG is added.

8.0 REFERENCES

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[5] Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services v4.03. June 14, 2010. Publication No. 09-5410.

9.0 APPENDICES

9.1 Schedules of Events

Schedule of Events: Study Assessments for All Patients

	Screening Period	Treatment Through 30 Days After Last Dose									Follow-up Period
Assessment	**Screening**	**Cycle 1 [a]**			**Every Cycle (Starting at Cycle 2)**	**Cycle 3 Day 1 and Cycle 5 Day 1**	**Every 2 Cycles (From Cycle 2 to Cycle 14)**	**Every 3 Cycles After Cycle 14**	**End of Treatment [b]**	**30 Days After Last Dose [b]**	**Follow-up [c]**
Day	**D -14 to D0**	**D1**	**D8**	**D15**	**D1**	**D1**	**D28**	**D28**			
Informed consent (main)	X										
Demographics	X										
Medical/surgical history	X										
Diagnosis and cancer history	X										
Prior cancer therapy [d]	X										
Prior ALK+ test report including test method [e]	X										
Physical examination	X	X	X	X	X				X	X	
Vital signs	X	X	X	X	X				X	X	
ECOG performance status	X	X		X	X				X	X	
Hematology	X [f]	X [f]	X	X	X				X	X	
Chemistry	X [f]	X [f]	X	X	X				X	X	
Insulin [g]	X [f]	X [f]	X		X				X	X	
Testosterone level (men only)	X [f]	X [f]			X				X	X	
ECG	X	X			X				X	X	
AEs	Throughout study [h]										
Concomitant medications	Until last dose [i]										

Footnotes are on last table page.

Schedule of Events: Study Assessments for All Patients (continued)

	Screening Period	Treatment Through 30 Days After Last Dose									Follow-up Period
Assessment	**Screening**	**Cycle 1** [a]			**Every Cycle (Starting at Cycle 2)**	**Cycle 3 Day 1 and Cycle 5 Day 1**	**Every 2 Cycles (From Cycle 2 to Cycle 14)**	**Every 3 Cycles After Cycle 14**	**End of Treatment** [b]	**30 Days After Last Dose** [b]	**Follow-up** [c]
Day	**D -14 to D0**	**D1**	**D8**	**D15**	**D1**	**D1**	**D28**	**D28**			
Pregnancy test (women with child bearing potential) [j]	X	X							X		
Disease assessment	X [p]						X [k]	X [k]	X		
Plasma sample for brigatinib PK		Refer to Appendix A, PK Sampling Schedule									
Archival (banked) tumor tissue sample	X [l]										
Optional tumor tissue rebiopsy sample	X [i]								X [m, q]		
Plasma sample for ctDNA	X					X			X [m, q]		
PRO assessment (EORTC QLQ-C30 and QLQ-LC-13)	X	X			X				X	X	
CCI											
HU assessment		X			X				X	X	
Subsequent anticancer therapy/survival [o]											X

Footnotes are on the following page.

AEs, adverse events; ALK+, anaplastic lymphoma kinase positive; C, Cycle; ctDNA, circulating tumor DNA; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; HU, health resource utility; NSCLC, non–small-cell lung cancer; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily.

[a] 1 cycle = 28 days. The allowed visit day window is ±3 days, starting from Cycle 2, with the exception of disease assessment.

[b] This visit shall be scheduled with a ±7-day window. If patient has the last dose equals or more than 30 days before the decision of permanent discontinuation from study treatment is made, the end-of-treatment visit and 30 days after last dose visit can be combined as one visit.

[c] Survival follow-up shall be scheduled with a ±14-day window.

[d] The prior cancer therapy need to include the detail of prior treatment, starting and ending time, and the best response to each treatment.

[e] The assay and sample type of prior ALK test will also be collected.

[f] If the blood tests are performed within 3 days of first dose, the Cycle 1 Day 1 tests are not required to be repeated, unless clinically indicated.

[g] Glucose and insulin will be tested concurrently.

[h] Assessment for early pulmonary symptoms must be performed during the visit on Day 8. The AEs and SAEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug. After this period, only SAEs suspected by the investigator to be related to the study treatment must be reported.

[i] Concomitant medications must be reported from the time informed consent is signed until at least the 30-days-after-last-dose assessment, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues. After study drug is discontinued, only new anticancer therapy to the ALK+ NSCLC need to be reported.

[j] Pregnancy test must be known to be negative before the study drug administration and be performed within 7 days before the first dose of brigatinib (Cycle 1 Day 1) and should be repeated every 3rd cycle on treatment (i.e., C3D1, C6D1, etc.).

[k] Every 8 weeks ±7 days for 14 cycles, then every 3 cycles (12 weeks) ±7 days. Imaging of chest, abdomen and brain will occur at each assessment for all patients until disease progression is observed. If patients continue to receive the study drug beyond progression, the tumor assessment will be managed according to local clinical practice and no need to be collected in eCRF. If a patient discontinues study drug for reasons other than disease progression and has not yet started another systemic anticancer therapy, the patient shall continue to be followed for radiological tumor assessment and only enters follow-up phase once the radiological tumor progression is observed or another systemic anticancer therapy is started.

[l] Archival tumor sample from recent biopsy after patient progresses on alectinib or ceritinib is highly encouraged. If the original ALK+ was not tested by an FDA-approved method, then archived or fresh tumor tissue is mandatory.

[m] For patients who dose escalate to 240 mg QD, the end-of-treatment, 30-days-after-last-dose, and follow-up assessments will not be performed until after the last dose of brigatinib at 240 mg QD. Dose escalation to 240 mg QD can proceed immediately following medical monitor approval with adherence to the Schedule of Events for treatment continuation at 240 mg QD after progression on the following page.

[n] CCI [redacted]

[o] This refers to other anticancer therapy after brigatinib is discontinued.

[p] Tumor radiological imaging used as baseline disease assessment before ICF was signed is allowed to be used if they were generated through patients' regular medical care and within the required window.

[q] If study treatment is stopped for a reason other than disease progression, the re-biopsy and ctDNA shall be collected after confirmed disease progression occurs. If study treatment is continued beyond progression, the re-biopsy and ctDNA shall only be collected at the initial progression. They are not required to be repeated once these patients further progress and stop the treatment entirely.

Schedule of Events – Treatment Continuation at 240 mg QD After Progression

		Treatment Through 30 Days After Last Dose								Follow-up Period
Assessment	**Before Dose Escalation (14 Days)** [a]	**Escalation Cycle 1** [b]		**Every Escalation Cycle (Starting at Cycle 2)**	**Cycle 3 Day 1 and Cycle 5 Day 1**	**Every 2 Escalation Cycles** [c] **(From Escalation Cycle 2 to Cycle 14)**	**Every 3 Escalation Cycles after Escalation Cycle 14**	**End of Treatment**	**30 Days After Last Dose**	**Follow-up**
Day	**D1** [d]	**D1**	**D15**	**D1**						
Informed consent to 240 mg	X									
Physical examination	X	X	X	X				X	X	
Vital signs	X	X	X	X				X	X	
ECOG performance status	X	X	X	X				X	X	
Hematology	X [e]	X [e]	X	X				X	X	
Chemistry	X [e]	X [e]	X	X				X	X	
Insulin [f]	X [e]	X [e]		X				X	X	
Testosterone level (men only)	X [e]	X [e]		X				X	X	
ECG	X	X		X				X	X	
AEs		Throughout study								
Concomitant medications		Until last dose [g]								
Pregnancy test [h]	X						X	X		
Disease assessment						X [c]	X [c]	X		
Plasma sample for brigatinib PK		Refer to Appendix A, PK Sampling Schedule								

Footnotes are on last table page.

Schedule of Events – Treatment Continuation at 240 mg QD After Progression (continued)

		Treatment Through 30 Days After Last Dose								Follow-up Period
Assessment	**Before Dose Escalation (14 Days) [a]**	**Escalation Cycle 1 [b]**		**Every Escalation Cycle (Starting at Cycle 2)**	**Cycle 3 Day 1 and Cycle 5 Day 1**	**Every 2 Escalation Cycles [c]**	**Every 3 Escalation Cycles**	**End of Treatment**	**30 Days After Last Dose**	**Follow-up**
Day	**D1 [d]**	**D1**	**D15**	**D1**						
Plasma sample for ctDNA	X				X			X [i]		
Optional tumor tissue rebiopsy sample at disease progression	X							X [I, J]		
PRO assessment	X	X		X				X	X	
HU assessment				X						
Subsequent anticancer therapy/survival										X

Abbreviations: AEs, adverse events; ALK+, anaplastic lymphoma kinase-positive; C, Cycle; ctDNA, circulating tumor DNA; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; HU, health resource utility; NSCLC, non–small-cell lung cancer; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily.

[a] Last visit on 180 mg QD can be used as rebaseline assessment before dose escalation.

[b] 1 cycle = 28 days.

[c] Every 8 weeks ±7 days for 14 cycles, then every 3 cycles (12 weeks) ±7 days. Imaging of chest, abdomen and brain will occur at each assessment for all patients until disease progression is observed. If patients continue to receive the study drug beyond progression, the tumor assessment will be managed according to local clinical practice and no need to be collected in eCRF.

[d] Performed before first dose at 240 mg QD. The week and day listed in this table are counted from the first day of 240 mg dose.

[e] If the blood tests are performed within 3 days of first dose, the Cycle 1 Day 1 tests are not required to be repeated, unless clinically indicated.

[f] Glucose and insulin will be tested concurrently.

[g] Concomitant medications must be reported from the time informed consent is signed until at least the 30-days-after-last-dose assessment, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues. After study drug is discontinued, only new anticancer therapy to the ALK+ NSCLC need to be reported.

[h] Pregnancy test should be repeated every 3rd cycle on treatment (ie, C3D1, C6D1, etc).

[i] At disease progression.

[J] If study treatment is stopped for a reason other than disease progression, the re-biopsy and ctDNA shall be collected after confirmed disease progression occurs. If study treatment is continued beyond progression, the re-biopsy and ctDNA shall only be collected at the initial progression; they are not required to be repeated once these patients further progress and stop the treatment entirely.

PK Sampling Schedule

All Patients

The PK samples outlined in the schedule below are to be collected in all patients.

PK Sampling Time	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1
Predose (within 4 h before dosing)		X	X	X	X	X
1 h postdose (±15 min)	X	X	X			
4 h postdose (±30 min)	X	X	X			

PK, pharmacokinetics.

For Patients Receiving 240 mg Brigatinib Postprogression

The PK samples outlined in the schedule below are to be collected in patients who receive the 240 mg brigatinib dose postprogression.

PK Sampling Time [a]	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1
Predose (within 4 h before dosing)	X	X	X	X	X
1 h postdose (±15 min)	X				
4 h postdose (±30 min)	X				

PK, pharmacokinetics.
[a] Cycle and day listed in this table are counted from the first day of the 240 mg brigatinib dose.

9.2 Adverse Events in Special Categories

Selection of AEs for special categories will be performed through the use of Standardized MedDRA Queries based on SMQs, Modified MedDRA Queries (MMQs), or Customized MedDRA Queries (CMQs). The adverse events in special categories will be listed and updated as new events occur and/or MedDRA versions change over the course of the study.

The following special categories of adverse events will be analyzed:

- Bradycardia events
- Hypertension events
- Gastrointestinal (GI) Events
- Pancreatic Chemical Events
- Pancreatic Clinical Events
- Elevated Insulin Events
- Hepatic Events
- Hyperglycemia Events
- Creatine Phosphokinase (CPK) Elevation

- Peripheral Neuropathy
- Pulmonary Events
- Skin and Subcutaneous Events
- Vision Impairments Events

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	08-Jun-2020 21:45 UTC