Clinical Study Protocol

NCT Number: NCT03596866

Title: A Phase 3 Randomized Open-label Study of Brigatinib (ALUNBRIG®) Versus Alectinib (ALECENSA®) in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (XALKORI®)

Study Number: Brigatinib-3001

Document Version and Date: Amendment 4.0, 08 March 2021

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

PROTOCOL

A Phase 3 Randomized Open-label Study of Brigatinib (ALUNBRIG®) Versus Alectinib (ALECENSA®) in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (XALKORI®)

Sponsor:	Takeda Development Center Americas, Inc (TDCA) 95 Hayden Avenue Lexington, MA 02421, USA Telephone: +1 (617) 679-7000		
Study Number:	Brigatinib-3001		
IND Number:	IND 110,935	**EudraCT Number:**	2018-001957-29
Compound:	Brigatinib (AP26113)		
Date:	08 March 2021	**Amendment Number:**	4

Amendment History:

Date	Amendment Number	Amendment Type	Region
08 March 2021	4	Substantial	Global
09 March 2020	3	Substantial	Global
07 June 2019	2	Substantial	Global
11 January 2019	1	Nonsubstantial	Germany
15 May 2018	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information are presented in Section 10.0, as is information on reporting product complaints.

Investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in the study manual to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD Date
Oncology Clinical Research, [redacted]

[redacted], PhD Date
Oncology Statistics, [redacted]

[redacted] MD Date
Oncology Clinical Research, [redacted],
Clinical Study Lead

[redacted], PhD Date
Quantitative Clinical Pharmacology, [redacted]

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment Summary of Changes

Protocol Amendment 4 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reasons for this amendment are to:

- Add futility analysis to be performed with the planned interim analysis.
- Add precautions for photosensitivity to sunlight.
- Update the dose modification guidance for creatine phosphokinase (CPK) elevation to align with the current Company Core Data Sheet (CCDS) V3 recommendations.
- Provide updated brigatinib storage conditions.
- Add the descriptions of direct-to-patient (DTP) drug delivery during the pandemic of coronavirus disease 2019 (COVID-19).
- Add criteria to terminate central blinded Independent Review Committee (BIRC) assessment if the primary endpoint is met at the interim analysis (IA) or primary analysis, or not met at the primary analysis.
- Add description of remote source document verification during the pandemic of COVID-19.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
	Description	***Rationale***
Section 2.0 STUDY SUMMARY Section 6.3.1 Duration of an Individual Patient's Study Participation Section 13.1.3.2 Primary Efficacy Endpoint Analyses Section 13.2 IA	A futility analysis will be performed with the interim analysis.	Due to strategic considerations, a futility analysis is added to the interim analysis so that the study could be terminated early if the real efficacy of alectinib and brigatinib in the study population significantly deviates from the study assumption.
Section 8.3 Recommended Dosing and Dose Modification Guidelines	Updated the creatine phosphokinase (CPK) dose modification guidance.	Aligned protocol with the current CCDS V3 dose modification guidance for CPK elevation. An analysis was performed using data from Studies 301 and 201 to evaluate the relationship of CPK increase, brigatinib treatment duration and muscular toxicities. The results suggested that CPK increase was associated with longer duration

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
	Description	***Rationale***
		of treatment and did not seem to be associated with the frequency of muscular toxicity. Also, review of individual patient data from Studies 301 and 201 showed only 1 report of patient with a Grade 3 CPK elevation as well as a Grade 3 muscular toxicity (Preferred Term: muscular toxicity). Additionally, many of the 49 patients from pooled Studies 301 and 201 with a Grade ≥3 CPK elevation did not report a muscular toxicity event (any grade or Grade ≥3). Based on these analyses, it was concluded that the dose modification for CPK elevations of Grade 3 and 4, without concurrent muscular toxicity, is not warranted and therefore the guidance was modified accordingly.
Section 8.6 Precautions and Restrictions	Added precautions for photosensitivity to sunlight.	Mitigation of photosensitivity to sunlight, which has been observed in patients treated with brigatinib.
Section 8.10 Storage, Handling, and Accountability	Updated the storage condition of brigatinib to "Store at controlled room temperature of 20°C to 25°C with excursions permitted between 15°C to 30°C."	Update of the storage condition of brigatinib to be consistent with Investigational Medicinal Product Dossier and other documents.
Section 8.11 Preparation and Dispensing	Added the description of DTP drug delivery during the COVID-19 pandemic.	Because of the impact of the COVID-19 pandemic, travel restrictions were executed in most of the countries participating in the study, and some of the study centers were temporarily closed. Instructions were provided to establish the DTP process to facilitate the direct delivery of the drugs from the study site to the patient's home to make sure the patients are able to continue the treatment without physically going to the study center.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
	Description	***Rationale***
Section 9.8 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival) and Appendix A Schedule of Events	Provided clarification that the collection of tumor assessment data is not required if the patient has progressed and has started treatment beyond progression during the posttreatment follow-up.	Although the tumor assessment is still a requirement, collection of these data is not required if the patient has progressed and has started treatment beyond progression.
Section 11.2 IRC	Added criteria to terminate BIRC assessment if the primary endpoint is met at the IA or primary analysis, or not met at the primary analysis.	Tumor assessment by BIRC is no longer warranted after primary analysis, and assessment of ongoing patients will continue to be performed by investigators.
Section 14.1 Study-Site Monitoring Visits	Added description of remote source document verification during the COVID-19 pandemic.	Because of the impact of the COVID-19 pandemic, travel restrictions were executed in most of the countries participating the study, and some of the study centers were temporarily closed or limiting entrance of nonpatient personnel. This made the on-site SDV impossible in some of the sites. To ensure data integrity, remote source data verification was allowed and conducted in a small number of sites.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc (TDCA)	**Compound:** Brigatinib (AP26113)	
Title of Protocol: A Phase 3 Randomized Open-label Study of Brigatinib (ALUNBRIG®) Versus Alectinib (ALECENSA®) in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer Patients Who Have Progressed on Crizotinib (XALKORI®)	**IND No.:** IND 110,935	**EudraCT No.:** 2018-001957-29
Study Number: Brigatinib-3001	**Phase:** 3	
Study Design: A phase 3, randomized, open-label, comparative, multicenter, international study of patients with anaplastic lymphoma kinase-positive (ALK+) non–small-cell lung cancer (NSCLC) who have progressed on crizotinib		
Primary Objective: To compare the efficacy of brigatinib to that of alectinib in patients with ALK+ locally advanced or metastatic NSCLC who have progressed on crizotinib as evidenced by progression-free survival (PFS) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.		
Secondary Objectives: 1. To compare the efficacy of brigatinib to that of alectinib as evidenced by overall survival (OS), PFS as assessed by the investigator, objective response rate (ORR), time to response, and duration of response (DOR) (all as assessed by RECIST v1.1). 2. To compare the efficacy of brigatinib in the central nervous system (CNS)to that of alectinib as evidenced by intracranial objective response rate (iORR), intracranial duration of response (iDOR), and time to intracranial progressive disease (iPD) without prior systemic progression as assessed by modified RECIST criteria. 3. To assess the safety and tolerability of brigatinib in comparison with alectinib. 4. To collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic (PK) analyses. 5. To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (v3.0) and its Quality of Life Lung Cancer Module (QLQ-LC13), in patients treated with brigatinib compared with those treated with alectinib. **Exploratory Objectives:** 1. To compare the efficacy in the CNS of brigatinib to that of alectinib as evidenced by iORR, iDOR, and time to iPD, per the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. 2. To explore the molecular determinants of efficacy and safety with brigatinib and alectinib. 3. To evaluate health resource utilization. 4. To use patient reported outcomes to assess morbidity related to CNS symptoms.		
Subject Population: Adult patients with locally advanced or metastatic ALK+ NSCLC whose disease has progressed on crizotinib.		
Number of Subjects: Approximately 246 expected	**Number of Sites:** 100-120 globally.	

Dose Level(s):	**Route of Administration:**
Arm A: Brigatinib 180 mg once daily (QD) with a 7-day lead-in at 90 mg QD. Brigatinib can be taken with or without food. Arm B: Alectinib 600 mg orally twice daily with food.	Oral
Duration of Treatment:	**Period of Evaluation:**
Patients will continue to be treated with brigatinib or alectinib until they experience objective disease progression by the investigator's assessment per RECIST v1.1 or until any other discontinuation criterion is met. Continuation of brigatinib and alectinib beyond progression is permitted, at the investigator's discretion, if there is evidence of continued clinical benefit.	The total estimated duration of the study is approximately 5 years, including approximately 2 years to accrue patients, with approximately 3 years for treatment and follow-up of the last patient.

Main Criteria for Inclusion:

- Male or female, aged 18 years or older or of local legal adult age.
- Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent) or stage IV NSCLC.
- Must meet one of the following criteria:
  - Have documentation of anaplastic lymphoma kinase (*ALK*) rearrangement by a positive result from the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx.
  - Have documented *ALK* rearrangement by a different test and be able to provide a tumor sample to the central laboratory. (Note: central laboratory *ALK* rearrangement testing results are not required to be obtained before randomization.)
- Had progressive disease while on crizotinib, as assessed by the investigator or treating physician. (Note: crizotinib does not need to be the last therapy a patient received. The patient may have received chemotherapy as his/her last systemic anticancer therapy.)
- Treatment with crizotinib for at least 4 weeks before progression.
- Have had no other ALK inhibitor other than crizotinib.
- Have had no more than 2 prior regimens of systemic anticancer therapy in the locally advanced or metastatic setting (other than crizotinib).
  (Note: a systemic anticancer therapy regimen will be counted if it is administered for at least 1 complete cycle at least 1 cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this neoadjuvant or adjuvant therapy.
  *Systemic therapy followed by maintenance therapy will be considered as one regimen if the maintenance therapy consists of a drug or drugs that were used in the regimen that immediately preceded maintenance.
- Have Eastern Cooperative Oncology Group performance status of 0 to 2.
- Have at least 1 measurable (ie, target) lesion per RECIST v1.1.
- Have recovered from toxicities related to prior anticancer therapy to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 grade ≤1. (Note: treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed, if deemed irreversible.)
- Have adequate organ function, as determined by:
  - Total bilirubin ≤1.5 times the upper limit of the normal range (ULN).
  - Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2, using the modification of diet in renal disease equation.

- Alanine aminotransferase/aspartate aminotransferase ≤2.5 × ULN; ≤5 × ULN is acceptable if liver metastases are present.
- Serum lipase ≤1.5 × ULN.
- Platelet count ≥75 × 10^9/L.
- Hemoglobin ≥9 g/dL.
- Absolute neutrophil count ≥1.5 × 10^9/L.

- Suitable venous access for study-required blood sampling (ie, including PK and laboratory safety tests).
- Have the willingness and ability to comply with scheduled visit and study procedures.
- For female patients of childbearing potential, have a negative pregnancy test documented before randomization.
- For female and male patients who are fertile, agree to use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least 120 days after the end of treatment with brigatinib, or alectinib.

(Note: Given that, globally, the patient population that has received crizotinib as the sole ALK inhibitor is decreasing, Takeda reserves the right to amend the inclusion criteria to include crizotinib intolerant patients and/or patients who have progressed on or been found intolerant to ALK inhibitors other than crizotinib, brigatinib, or alectinib.)

Main Criteria for Exclusion:

- Participation in the control (crizotinib) arm of Study AP26113-13-301 (ALTA 1L)
- Received crizotinib within 7 days before randomization.
- Have a history or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
- Have uncontrolled hypertension. Patients with hypertension should be under treatment for control of blood pressure upon study entry.
- Received systemic treatment with strong cytochrome P-450 (CYP) 3A inhibitors, moderate CYP3A inhibitors, strong CYP3A inducers, or moderate CYP3A inducers within 14 days before randomization.
- Treatment with any investigational systemic anticancer agents within 14 days or 5 half-lives, whichever is longer, before randomization.
- Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated nonmelanoma skin cancer or cervical cancer in situ; definitively treated nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
- Received chemotherapy or radiation therapy within 14 days before randomization except for stereotactic radiosurgery or stereotactic body radiation therapy.
- Received anticancer monoclonal antibodies within 30 days of randomization.
- Had major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed.
- Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening (patients with asymptomatic brain metastases or who have stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the 7 days before randomization will be enrolled).

  (Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable [with no requirement for an increasing dose of corticosteroids or use of anticonvulsants] for at least 7 days before randomization.)
- Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
- Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to the

following:

1. Myocardial infarction within 6 months before randomization.
2. Unstable angina within 6 months before randomization.
3. New York Heart Association Class III or IV heart failure within 6 months before randomization.
4. History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician.
5. Any history of clinically significant ventricular arrhythmia.

- Had cerebrovascular accident or transient ischemic attack within 6 months before first dose of study drug.
- Have malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug.
- Have an ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics.
- Have a known history of HIV infection. Testing is not required in the absence of history.
- Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection. Testing is not required in the absence of history.
- Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to this protocol.
- Have a known or suspected hypersensitivity to brigatinib or alectinib or their excipients.
- Life-threatening illness unrelated to cancer.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

The primary endpoint is PFS as assessed by the blinded Independent Review Committee (BIRC) per RECIST v1.1.

Key Secondary Endpoint:

OS.

Other Secondary Endpoints:

1. PFS, as assessed by the investigator per RECIST v1.1.
2. ORR, as assessed by the investigator and BIRC per RECIST v1.1.
3. DOR, as assessed by the investigator and BIRC.
4. Time to response, as assessed by the investigator and BIRC.
5. iORR, as assessed by BIRC per modified RECIST v1.1 (as described in protocol and BIRC charter).
6. iDOR, as assessed by the BIRC per modified RECIST v1.1.
7. Time to iPD, as assessed by the BIRC per modified RECIST v1.1.
8. HRQoL assessed with the global health status/quality of life and other function and symptom domains from EORTC QLQ-C30 (v3.0) and EORTC QLQ-LC13.

Safety Endpoints:

Safety assessments will include physical and laboratory examinations, vital signs, and electrocardiograms. Adverse events will be graded according to the NCI CTCAE v4.03.

Exploratory Endpoints:

1. CNS efficacy outcomes as assessed by the BIRC per RANO-BM criteria (iORR, iDOR, and time to iPD).
2. Molecular determinants of efficacy and safety with brigatinib and alectinib.
3. HRQoL measured by EuroQoL–5 Dimensions–5 Levels (EQ-5D-5L) questionnaires.
4. Items from the EORTC Quality of Life Brain Cancer Module (QLQ-BN20) used to assess morbidity related to CNS symptoms.
5. To evaluate health resource utilization.

Statistical Considerations:

The primary analysis of the primary endpoint will be performed using a 2-sided stratified log-rank test (stratification factors: presence of intracranial CNS metastases at baseline [yes vs no] and best prior response to crizotinib therapy as assessed by the investigator [complete response/partial response vs any other response/status unknown]) to compare BIRC-assessed PFS of patients randomized to brigatinib with the BIRC-assessed PFS of patients randomized to alectinib. The overall (2-sided) type I error rate will be controlled at 0.05. The primary analysis will be based on the intent-to-treat population. The Kaplan Meier (K-M) survival curves and K-M estimates (if estimable), along with their 2-sided 95% CIs, will be provided for each treatment group. Additionally, hazard ratios will be estimated using the stratified Cox regression model with the stratification factors.

The interim analysis (IA) for efficacy and futility will be performed after the first 115 events have been observed, and the final analysis of the primary endpoint will be performed after 164 events have been observed. An O'Brien-Fleming Lan-DeMets alpha spending function will be used to control the overall alpha level at 0.05 2-sided. A gamma spending function will be used for the futility stopping boundary. Futility is nonbinding. OS, the key secondary endpoint, will be formally tested for statistical significance only once when PFS per BIRC is statistically significant.

Further details of statistical analyses including the data handling rules will be provided in the statistical analysis plan.

Sample Size Justification:

For the purposes of this sample size calculation, the median PFS for alectinib is estimated as 9 months and the PFS for brigatinib is estimated to be 15 months on the basis of the outcomes observed in previous single-arm studies. Approximately 246 patients will be randomized in a 1:1 fashion to receive brigatinib or alectinib. A total of 164 events (progression or death among the randomized patients) will provide 90% power to detect a 6-month improvement in PFS (hazard ratio=0.60). This power projection is based on a 2-sided log-rank test, and is controlled at the 2-sided 0.05 level, adjusting for the proposed IA plan. The number of events is fixed, but the enrollment number may change based on an assessment of the overall event rate pooled across treatment groups before the close of enrollment.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the study manual. The identified vendors in the study manual for specific study related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALK	anaplastic lymphoma kinase
ALK+	anaplastic lymphoma kinase-positive
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRC	blinded Independent Review Committee
CFR	Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CR	complete response
CT	computed tomography
CYP	cytochrome P-450
DOR	duration of response
DTP	direct-to-patient
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOPE	early onset pulmonary events
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL–5 Dimensions–5 Levels
EQ VAS	EQ visual analogue scale
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Conference on Harmonisation
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
iDOR	intracranial duration of response
IEC	independent ethics committee
iORR	intracranial objective response rate
iPD	intracranial progression without prior systemic progression

IRC	Independent Review Committee
IRB	institutional review board
ITT	intent-to-treat
LD	longest diameter(s)
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
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
QD	once daily
QLQ-BN20	Quality of Life Brain Cancer Module
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Lung Cancer Module
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SLD	sum of the longest diameters
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States

4.0 INTRODUCTION

4.1 Background

4.1.1 Epidemiology and Pathology

Lung cancer is one of the most common cancers in the world—1.8 million new cases in 2012 or 12.9% of all new cancers worldwide [1]. Globally, lung cancer accounted for 1.6 million cases and 1.4 million deaths in 2008 [2]. It is the leading cause of cancer death in the United States (US) and in the European Union (EU). In the US, an estimated 234,030 new cases of lung cancer will be diagnosed by the end of 2018, and 154,050 deaths are estimated to occur due to the disease [3]. In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 with 268,000 deaths in that year [1]. Five-year survival rates remain low: 17.7% and 13% in the US and Europe, respectively [4,5]. In Japan, lung cancer is ranked as the third most frequent cancer; approximately 113,000 new cases were diagnosed in 2012 and approximately 71,500 deaths in that year (ganjoho.jp/reg_stat/statistics/index.html, Accessed 07 March 2018 [in Japanese]). Most lung cancer cases are diagnosed at advanced stages and about 78% of newly diagnosed patients have regional/distant disease [1,6].

Historically, lung cancers have been stratified on the basis of histologic criteria and are generally divided into 2 categories: small-cell lung cancer and non–small-cell lung cancer (NSCLC). NSCLC is the most prevalent histologic class, accounting for more than 80% of all lung cancers [7,8], and includes a number of subtypes such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and bronchioloalveolar carcinoma [9]. More recently, attention has turned to stratifying patients with lung cancer on the basis of molecular alterations since it has become clear that histologically identical tumors are driven by different oncogenes and are therefore likely to respond differently to therapeutic intervention, such as therapies directed at epithelial growth factor receptor (*EGFR*) mutant, ALK receptor tyrosine kinase (*ALK*) rearranged, ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*) rearranged, or B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) V600E mutant NSCLC. The focus herein is on NSCLC that contain oncogenic rearrangements in the *ALK* gene, and the role of brigatinib, a novel small molecule inhibitor, in the treatment of anaplastic lymphoma kinase-positive (ALK+) NSCLC.

4.1.2 ALK+ NSCLC

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults [10]. The first genetic rearrangement of *ALK* seen in NSCLC involved a fusion between the echinoderm microtubule associated protein like 4 gene (*EML4)* and the *ALK* tyrosine kinase domain. *EML4-ALK* has the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts to induce tumor formation [11]. Since then, a number of additional ALK fusion partners have been described in NSCLC that are believed to result in aberrant signaling and oncogenic transformation [12,13].

Estimates of the frequency of *ALK* rearrangement in the overall population of patients with NSCLC range from 2% to 7% [14,15], which represent, based on proportionality of total populations in the US and EU, approximately 7000 to 25,000 patients in the US and *5800* to 20,000 patients in the EU with ALK+ NSCLC in 2016. *ALK* rearrangements are more common among patients with adenocarcinoma histology, patients who have never smoked, and patients who have wild-type *EGFR* and KRAS proto-oncogene, GTPase (*KRAS*) [10].

4.1.3 Current Treatment for ALK+ NSCLC

While the standard treatment algorithm for patients with unselected NSCLC has historically involved frontline treatment with chemotherapy, recent clinical trials have demonstrated that patients with ALK+ locally advanced or metastatic NSCLC respond well to treatment with the ALK inhibitors (crizotinib, alectinib, and ceritinib). Crizotinib received accelerated approval from the US Food and Drug Administration (FDA) in 2011 on the basis of results from 2 single-arm studies [16]. The efficacy of crizotinib has been confirmed in a randomized study of crizotinib versus chemotherapy [16,17].

ALK-dependent mechanisms of resistance, observed in approximately 30% of patients [18], include the acquisition of secondary mutations in ALK that interfere with crizotinib binding, and/or amplification of the *ALK* fusion gene. More than 10 secondary mutations in *ALK* have been associated with crizotinib resistance in patients, with the most common being L1196M and G1269A [19,20]. The central nervous system (CNS) is the first site of progression in approximately 50% of patients treated with crizotinib [21,22], suggesting inadequate penetration of crizotinib into the brain (ie, pharmacologic failure) as the primary cause of resistance in these patients. Therefore, an ALK inhibitor that can overcome secondary resistance mutations in ALK, has adequate penetration into the CNS, and is less susceptible to pharmacologic failure, may be required to overcome resistance.

Recently, 2 other ALK inhibitors, ceritinib [23] and alectinib [24], have become available for patients with NSCLC with *ALK* rearrangements. Both drugs are effective in patients previously treated with crizotinib. Ceritinib demonstrated significantly improved progression-free survival (PFS) vs chemotherapy (hazard ratio [HR] 0.55) [25] whereas alectinib demonstrated significantly improved PFS vs crizotinib (HR 0.34-0.47) [26,27] in treatment naïve ALK+ advanced NSCLC.

ALK secondary mutations associated with clinical resistance to ceritinib and alectinib have also been identified, including L1152R and F1174C/V for ceritinib, I1171N/T/S for alectinib, and G1202R for both agents [17,26-29].

More recently, the investigational agent lorlatinib has been evaluated in a phase 1/2 study showing responses after ≥1 prior ALK tyrosine kinase inhibitor (TKI) (25% [11 of 44] objective response rate [ORR] in patients with 2 prior ALK TKI and 31% [4 of 13] ORR in patients with 3 prior ALK TKI). The most common treatment-related adverse events (AEs) were hypercholesterolemia (90%) and hypertriglyceridemia (72%) [28].

4.1.4 Unmet Medical Need

Significant progress has been made with incorporation of ALK TKIs for treatment of ALK+ NSCLC, but eventually almost all patients progress after crizotinib with over 50% of these patients developing brain metastases. The impact of progression is seen in the quality of life of patients as well as their survival. Despite 2 ALK inhibitors (ie, ceritinib and alectinib) being available for crizotinib failures, the majority of patients currently treated with ALK inhibitors in second-line therapy progress within 1 year. *ALK* secondary mutations associated with clinical resistance and treatment failure to crizotinib, ceritinib, and alectinib have been identified. The alternative treatments for these patients include chemotherapy and checkpoint inhibitors (PD-1 or PD-L1 antibody). The efficacy of platinum doublet chemotherapy is not impacted by prior TKI treatment; however, the benefits of doublet therapy are limited with response rates about 30% and median PFS about 4 months [29]. Checkpoint inhibitors have recently become available as treatment for NSCLC. These agents are particularly effective in patients whose tumors over-express PD-L1 and have less benefit in patients with *EGFR* mutation or *ALK* rearrangements [30], possibly related to the low mutation burden in this population. Of note, patients with ALK+ NSCLC are often nonsmokers, which may help to explain the low mutation burden [31].

Clinicians treating patients with ALK+ NSCLC with metastatic disease need to know the benefit, in months, of one next generation ALK inhibitor versus another in terms of PFS, time to intracranial progression without prior systemic progression (iPD), duration of response (DOR), and intracranial duration of response (iDOR). These measures represent time free of interventions such as radiotherapy or surgery. The likelihood of response as assessed by PFS as assessed by the investigator, ORR, and intracranial objective response rate (iORR) are also important factors in clinical decision making. Given that the majority of these patients will have had CNS metastases, the intracranial data obtained from this study will be of particular value in determining the best therapeutic option for that large subset of patients with brain metastases present at the initiation of therapy. This study (the primary analysis) will provide the CNS data to address this unmet medical need.

Brigatinib

Brigatinib (AP26113) is a novel, orally administered TKI discovered and developed by ARIAD Pharmaceuticals, Inc (ARIAD; Cambridge, Massachusetts), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Primary targets are activated, mutant forms of *ALK* and *ROS1*, which play important roles in NSCLC and other cancers.

A series of in vitro and in vivo studies demonstrated that brigatinib potently inhibited ALK activity and proliferation in ALK+ cell lines and exhibited >100-fold selectivity over ALK-negative lines.

In clinical studies, brigatinib has an acceptable safety profile at the recommended dose of 90 mg once daily (QD) for 7 days, then 180 mg QD, continuously (hereinafter mentioned as 90 mg QD →180 mg QD). Brigatinib at this dose level exhibited substantial efficacy in patients with ALK+ NSCLC who had progressed on crizotinib. In 110 patients, the confirmed response rate was 56.4% (62 of 110, 97.5% CI: 45.2, 67.0) by Independent Review Committee (IRC) assessment. The IRC assessed median DOR was 15.7 months (95% CI: 12.8, 21.8 event rate: 54.8%) and median PFS

was 16.7 months (95% CI: 11.6, 21.4, event rate: 49.1%). High IRC-assessed iORR (66.7%, 12/18, 95% CI: 41.0, 86.7) with a median 16.6 month (95% CI: 3.7, not reached) iDOR was also observed in patients with measurable baseline brain metastases by IRC (ALTA study, data cut-off: 29 September 2017, data on file). On 28 April 2017, the FDA granted accelerated approval to brigatinib for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant of crizotinib.

4.2 Rationale for the Proposed Study

Crizotinib has been approved by both the FDA and European Medicines Agency (EMA) for first-line treatment of advanced ALK+ NSCLC, after 2 phase 3 clinical studies demonstrated a significant PFS benefit over chemotherapy [32,33]. Since crizotinib was approved for first-line treatment of advanced ALK+ NSCLC, several newer ALK inhibitors with greater efficacy and tolerability have been developed and approved for this patient population.

The newer ALK inhibitors, ceritinib, alectinib, and brigatinib, have been shown to be of benefit in a postcrizotinib setting. Ceritinib received accelerated approval by the FDA in April 2014, and was approved in the EU in May 2015, in patients previously treated with crizotinib [34-36]. In a phase 2 study of ceritinib, patients who had progressed on crizotinib showed an ORR of 38.6% and a median PFS of 5.7 months [35]. In patients with intracranial brain metastases, the iORR was 33% [35]. Alectinib was granted accelerated approval in the US in December 2015 for patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib. In 2017, alectinib received conditional marketing authorization from the EMA in patients with ALK+ NSCLC previously treated with crizotinib. In 1 clinical studies, alectinib has been shown to be well tolerated by patients. The ORR based on IRC assessment was 38% and 44% in studies 1 and 2, respectively [37-39]. Median PFS was approximately 9 months [38]. In patients with intracranial CNS metastases (N = 51), the iORR was 61%, with a median duration of CNS response of 9.1 months [24]. Brigatinib received accelerated approval by the FDA in April 2017 for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant of crizotinib. Brigatinib's accelerated approval was based on efficacy seen in a 2-arm, open-label, multicenter trial (NCT02094573 [ALTA]). In this study, patients with ALK+ NSCLC who had progressed on crizotinib demonstrated an IRC assessed ORR of 51% in patients given 90 mg QD (Arm A; N = 112) and 55% in patients who were given 180 mg QD with a 7-day lead in at 90 mg QD (Arm B; N = 110). The IRC-assessed median DOR was 13.8 months in Arm A and 14.8 months in Arm B. IRC-assessed PFS was 9.2 months in Arm A and 16.7 months in Arm B. In patients with measurable brain metastases, the iORR was 50% (N = 26) in Arm A and 67% (N = 18) in Arm B, and median iDOR was not reached in Arm A and was 16.6 months in Arm B. Both doses were well tolerated in this study. Based on these results, the recommended dosing regimen of brigatinib is 180 mg QD with 7-day lead-in at 90 mg QD.

Both brigatinib and alectinib are being or have been compared directly with crizotinib as first line therapy in separate phase 3 open-label studies. Alectinib demonstrated a PFS advantage in previously untreated advanced ALK+ NSCLC; HR for disease progression or death, 0.47 [95% CI, 0.34 to 0.65]; p<0.001 [26]. Brigatinib is being compared with crizotinib in patients with advanced ALK+ NSCLC treated with 1or fewer lines of systemic chemotherapy in the phase 3 randomized

open-label ALTA-1L study. ALTA-1L completed enrollment in August 2017, with follow-up ongoing.

There is a need for a head-to-head comparison of the newer ALK inhibitors in this patient population. This study will provide a direct comparison of brigatinib with alectinib. This study will be conducted in the postcrizotinib setting rather than in the ALK inhibitor naïve setting, because the sample size required for a head-to-head study in the first-line setting would be prohibitive. Alectinib has been chosen as the comparator, because it is more widely prescribed than ceritinib or lorlatinib. Data also suggest alectinib has the best PFS in this setting; although at this time, lorlatinib data is still maturing.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to compare the efficacy of brigatinib to that of alectinib in patients with ALK+ locally advanced or metastatic NSCLC who have progressed on crizotinib as evidenced by PFS as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

5.1.2 Secondary Objectives

The secondary objectives are:

1. To compare the efficacy of brigatinib with that of alectinib as evidenced by overall survival (OS), PFS as assessed by the investigator, ORR, DOR, and time to response (all as assessed by RECIST v1.1).
2. To compare the efficacy of brigatinib in the CNS to that of alectinib as evidenced by iORR, iDOR, and time to iPD as assessed by modified RECIST criteria.
3. To assess the safety and tolerability of brigatinib in comparison with alectinib.
4. To collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic (PK) analyses.
5. To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (v3.0) and its Quality of Life Lung Cancer Module (QLQ-LC13), in patients treated with brigatinib compared with those treated with alectinib.

5.1.3 Exploratory Objectives

The exploratory objectives are:

1. To compare the efficacy in the CNS of brigatinib to that of alectinib as evidenced by iORR, iDOR, and time to iPD, per the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria.

2. To explore the molecular determinants of efficacy and safety with brigatinib and alectinib.
3. To evaluate health resource utilization.
4. To use patient reported outcomes to assess morbidity related to CNS symptoms.

5.2 Endpoints

5.2.1 Primary Endpoint

- The primary endpoint is PFS as assessed by the blinded Independent Review Committee (BIRC) per RECIST v1.1.

5.2.2 Secondary Endpoints

Key Secondary Endpoint:

- OS.

Other Secondary Endpoints:

1. PFS, as assessed by the investigator per RECIST v1.1.
2. ORR, as assessed by the investigator and BIRC per RECIST v1.1.
3. DOR, as assessed by the investigator and BIRC.
4. Time to response, as assessed by the investigator and BIRC.
5. iORR, as assessed by BIRC per modified RECIST v1.1 (as described in protocol and BIRC charter).
6. iDOR, as assessed by the BIRC per modified RECIST v1.1.
7. Time to iPD, as assessed by the BIRC per modified RECIST v1.1.
8. HRQoL assessed with the global health status/quality of life and other function and symptom domains from EORTC QLQ-C30 (v3.0) and EORTC QLQ-LC13.

5.2.3 Safety Endpoints

The safety endpoint assessments will include physical and laboratory examinations, vital signs, and electrocardiograms (ECGs). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

5.2.4 Exploratory Endpoints

The exploratory endpoints are:

1. CNS efficacy outcomes as assessed by the BIRC per RANO-BM criteria (iORR, iDOR, and time to iPD).
2. Molecular determinants of efficacy and safety with brigatinib and alectinib as uncovered by genetic alterations noted on tumor tissue DNA or plasma samples of circulating tumor DNA.

3. HRQoL measured by EuroQoL–5 Dimensions–5 Levels (EQ-5D-5L) questionnaires.
4. To evaluate healthcare resource utilization.
5. Items from the EORTC Quality of Life Brain Cancer Module (QLQ-BN20) used to assess morbidity related to CNS symptoms.

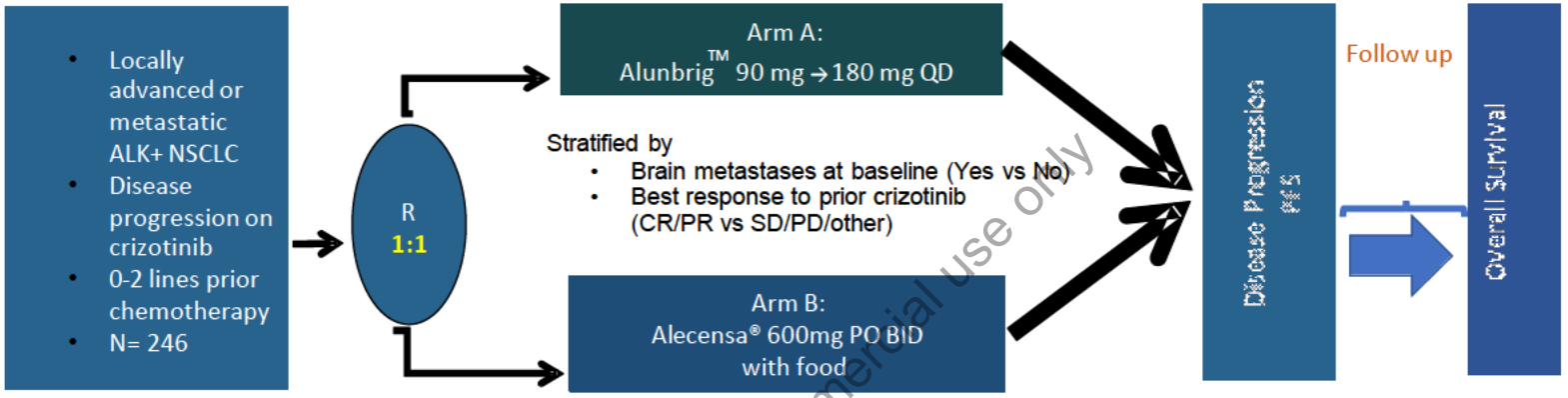
6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 3, randomized, open-label, comparative, multicenter, international study in which patients with ALK+ NSCLC who have progressed on crizotinib will be randomized in a 1:1 fashion to receive brigatinib in Arm A or alectinib in Arm B. Patients will be stratified by the presence of intracranial CNS metastases at baseline (Yes versus No) and best prior response to crizotinib therapy as assessed by the investigator (complete response [CR]/partial response [PR] vs any other response/status unknown).

Patients will be treated on each arm until they experience progressive disease (PD) assessed by the investigator or intolerable toxicity, or until any other discontinuation criterion is met. On each arm, treatment will be given continuously. For logistical convenience, every 28 days is defined as 1 cycle. Continuation of study drug beyond progression is permitted, if there is potential for continued clinical benefit (eg, absence of clinical symptoms or signs, indicating clinically significant disease progression requiring alternative systemic anticancer therapy; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [eg, 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).

Figure 6.a Study Design



Primary endpoint: PFS per RECIST v1.1 as assessed by BRIC
Key secondary endpoint: OS
Other secondary endpoint: PFS (RECIST v1.1), ORR by BRIC (RECIST v1.1), DOR by BRIC, timer to response by BRIC, iORR by BRIC (modified RECIST v1.1), iDOR by BRIC (modified RECIST v1.1), time to iPD by BRIC (modified RECIST v1.1), HRQoL by global health status/QoL and other function and symptom domains from EORTC QLQ-C30 (v3.0), and EORTC QLQ-LC13
Statistical considerations: ~246 total patients (164 events) to detect an improvement in median PFS from 9 to 15 months (HR=0.60)
IA for efficacy and futility at 70% of target PFS events

Abbreviations: ALK+, anaplastic lymphoma kinase-positive; BID, twice daily; BIRC, blinded Independent Review Committee; CR, complete response; DOR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; HRQoL, health-related quality of life; IA, interim analysis; iDOR, intracranial duration of response; iORR, intracranial objective response rate; iPD, intracranial progression without prior systemic progression; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral; PR, partial response; q8w, every 8 weeks; QD, once daily; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Lung Cancer Module; QoL, quality of Life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

The primary endpoint of the study is to compare the efficacy of brigatinib with that of alectinib in patients with ALK+ locally advanced or metastatic NSCLC who have progressed on crizotinib as evidenced by BIRC-assessed PFS. An interim analysis (IA) to assess the primary endpoint will be conducted once 70% of PFS events have been observed. It is expected that enrollment will be completed before reaching IA.

AEs will be assessed from the time a patient signs the informed consent form (ICF) until 30 days after last dose of the study drug a patient receives. Patients' signs and symptoms, laboratory values, vital signs, ECGs, and any other relevant special examinations as clinically indicated will be obtained to evaluate the safety and tolerability of brigatinib. **For patients randomized to the brigatinib arm of the study (Arm A),** sparse PK samples will be collected during the study to measure plasma concentrations of brigatinib as outlined in Appendix A, PK Sampling Schedule. Before randomization, ALK status must be confirmed with documentation from a pathology report of ALK+ tumor tissue. If the determination of ALK positivity was made by a non-FDA-approved test, tumor tissue (archival or new biopsy) must be submitted to a central laboratory for *ALK* rearrangement testing. Central laboratory results of *ALK* testing are not required to be available before randomization. Given that all patients are required to have received therapy with crizotinib, it is not deemed necessary that central laboratory tests be in agreement with local *ALK* tests (it is anticipated that the central laboratory will have an intrinsic false negative rate).

For patients for whom there is available formalin-fixed, paraffin-embedded (FFPE) tumor tissue that was acquired after progression on crizotinib, a sample will be requested for exploratory molecular genetic analysis. In patients without such tissue available, an optional biopsy for exploratory molecular genetic analysis may be obtained during screening if the patient has an amenable lesion. An optional biopsy will be obtained at the time of disease progression for patients who consent to the procedure and genetic testing of the sample. FFPE tumor tissue will be used for exploratory molecular genetic analysis. For all patients, blood samples will be obtained for exploratory biomarker studies, including molecular genetic analysis, according to the Schedule of Events (Appendix A).

Toxicity will be evaluated according to NCI CTCAE, Version 4.03, effective date 14 June 2010 [40].

6.2 Number of Patients

The expected number of patients is 246 enrolled at 100 to 120 sites globally (a patient is considered to be enrolled in the study once the ICF is signed, all screening evaluations are completed and the patient has been randomized).

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will continue to be treated with brigatinib or alectinib until they experience objective disease progression by the investigator's assessment per RECIST v1.1 or until any other discontinuation criterion is met. Continuation of brigatinib and alectinib beyond progression is

permitted, at the investigator's discretion, if there is evidence of continued clinical benefit (see Section 8.2).

The follow-up period for survival begins after a patient has permanently discontinued study drug and continues until that patient dies, is lost to follow-up, withdraws consent or the study ends, whichever comes first. Patients who discontinue the study drug for reasons other than radiological disease progression shall still be followed for tumor assessment according to the protocol until radiological disease progression is observed. All new systemic anticancer therapies initiated in the follow-up period should be reported.

An IA for efficacy and futility to assess the primary endpoint will be conducted once 70% of PFS events have been observed. This corresponds to 115 PFS events.

The primary analysis for the primary endpoint will be conducted when 164 events have been observed, which is approximately 30 months after the first patient has enrolled.

The final analysis for OS and HRQoL endpoints will occur approximately 5 years after the first patient has enrolled. The study will end after the final analysis has been performed. The sponsor may also terminate the study prematurely due to safety or administration reasons.

This study will begin to enroll patients in May 2019. The overall timeframe will depend upon the actual enrollment rate and event rate.

6.3.2 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Maximum Timeframe
Primary:	
PFS as assessed by the BIRC per RECIST v1.1.	Up to 5 years
Key Secondary:	
OS.	Up to 5 years
Other Secondary:	
1. PFS, as assessed by the investigator per RECIST v1.1.	Up to 5 years
2. ORR, as assessed by the BIRC per RECIST v1.1.	Up to 5 years
3. DOR, as assessed by the investigator and BIRC.	Up to 5 years
4. Time to response, as assessed by the investigator and BIRC.	Up to 5 years
5. iORR, as assessed by BIRC per modified RECIST v1.1 (as described in protocol and BIRC charter).	Up to 5 years
6. iDOR, as assessed by the BIRC per modified RECIST v1.1.	Up to 5 years
7. Time to iPD, as assessed by the BIRC per modified RECIST v1.1.	Up to 5 years
8. HRQoL assessed with the global health status/quality of life and other function and symptom domains from EORTC QLQ-C30 (v3.0), and EORTC QLQ-LC13.	Up to 5 years after FPI

Abbreviations: BIRC, blinded Independent Review Committee; EORTC, European Organization for Research and Treatment of Cancer; FPI, first patient in; HRQoL, health-related quality of life; iDOR, intracranial duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Lung Cancer Module; RECIST, Response Evaluation Criteria in Solid Tumors.

6.3.3 Total Study Duration

The time for completion of the clinical study report analyzing the primary and secondary endpoints will be approximately 5 years. The time for completion of the entire study (eg, completion of clinical study report reporting OS and HRQoL results) will be approximately 5 years.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be randomized:

1. Male or female, aged 18 years or older or of local legal adult age.
2. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
3. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent) or stage IV NSCLC.

4. Must meet one of the following criteria:
   a) Have documentation of *ALK* rearrangement by a positive result from the Vysis ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx.
   b) Have documented ALK rearrangement by a different test and be able to provide tumor sample to the central laboratory. (Note: central laboratory ALK rearrangement testing results are not required to be obtained before randomization.)
5. Had PD while on crizotinib, as assessed by the investigator or treating physician. (Note: crizotinib does not need to be the last therapy a patient received. The patient may have received chemotherapy as his/her last therapy.)
6. Treatment with crizotinib for at least 4 weeks before progression.
7. Have had no other ALK inhibitor other than crizotinib.
8. Have had no more than 2 prior regimens of systemic anticancer therapy (other than crizotinib) in the locally advanced or metastatic setting*.
   Note: a systemic anticancer therapy regimen will be counted if it is administered for at least 1 complete cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this neoadjuvant or adjuvant therapy.
   *Systemic therapy followed by maintenance therapy will be considered as one regimen if the maintenance therapy consists of a drug or drugs that were used in the regimen that immediately preceded maintenance.
9. Have at least 1 measurable (ie, target) lesion per RECIST v1.1.
10. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE v4.03 grade ≤1. (Note: treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed, if deemed irreversible.)
11. Have adequate organ function, as determined by:
    a) Total bilirubin ≤1.5 times the upper limit of normal (ULN).
    b) Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2, using the modification of diet in renal disease equation (Appendix F).
    c) Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 × ULN; ≤5 × ULN is acceptable if liver metastases are present.
    d) Serum lipase ≤1.5 × ULN.
    e) Platelet count ≥75 $\times 10^9$/L.
    f) Hemoglobin ≥9 g/dL.
    g) Absolute neutrophil count ≥1.5 × 10^9/L.

12. Suitable venous access for study-required blood sampling (ie, including PK and laboratory safety tests).
13. Have the willingness and ability to comply with scheduled visits and study procedures.
14. For female patients of childbearing potential, have a negative pregnancy test documented before randomization.
15. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use a highly effective **nonhormonal** form of contraception with their sexual partners during the dosing period and for a period of at least 120 days after the end of treatment with either brigatinib or alectinib (Section 8.6.1.1).
16. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus five half-lives) after the last dose of study drug, or
    b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
    c) Do not donate semen or sperm during treatment and for 90 days after the last dose of study therapy.
17. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

(Note: Given that, globally, the patient population who has received crizotinib as the sole ALK inhibitor is decreasing, Takeda reserves the right to amend the inclusion criteria to include crizotinib intolerant patients and/or patients who have progressed on or been found intolerant to ALK inhibitors other than crizotinib, brigatinib, or alectinib.)

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Participation in the control (crizotinib) arm of Study AP26113-13-301 (ALTA 1L).
2. Received crizotinib within 7 days before randomization.
3. Have a history or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
4. Have uncontrolled hypertension. Patients with hypertension should be under treatment for control of blood pressure upon study entry.

5. Received systemic treatment with strong cytochrome P-450 (CYP) 3A inhibitors, moderate CYP3A inhibitors, strong CYP3A inducers, or moderate CYP3A inducers within 14 days before randomization (refer to Section 8.5 for a list of example medications).
6. Treatment with any investigational systemic anticancer agents within 14 days or 5 half-lives, whichever is longer, before randomization.
7. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated nonmelanoma skin cancer or cervical cancer in situ; definitively treated nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
8. Received chemotherapy or radiation therapy within 14 days before randomization except for stereotactic radiosurgery (SRS) or stereotactic body radiation therapy.
9. Received antineoplastic monoclonal antibodies within 30 days of randomization.
10. Had major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed.
11. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening (patients with asymptomatic brain metastases or patients who have stable symptoms and did not require an increased dose of corticosteroids to control symptoms within 7 days before randomization will be enrolled). Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for at least 7 days before randomization.
12. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
13. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to the following:
    a) Myocardial infarction within 6 months before randomization.
    b) Unstable angina within 6 months before randomization.
    c) New York Heart Association Class III or IV heart failure within 6 months before randomization.
    d) History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician.
    e) Any history of clinically significant ventricular arrhythmia.
14. Had cerebrovascular accident or transient ischemic attack within 6 months before first dose of study drug.

15. Have malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug.
16. Have an ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics.
17. Have a known history of HIV infection. Testing is not required in the absence of history.
18. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection. Testing is not required in the absence of history.
19. Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to this protocol.
20. Have a known or suspected hypersensitivity to brigatinib or alectinib or their excipients.
21. Life-threatening illness unrelated to cancer.
22. Female patients who are lactating and breastfeeding.
23. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

8.0 STUDY DRUG

8.1 Study Drug Administration

Arm A: brigatinib 180 mg QD with 7-day lead-in at 90 mg QD. Brigatinib can be taken with or without food.

Arm B: alectinib 600 mg orally twice daily with food.

The dose regimens are described fully in Section 8.3.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded (see Schedule of Events [Appendix A] for site staff review of diary card). Complete instructions for completing the diary card will be provided with the study manual.

8.2 Treatment With Study Drug Beyond Radiological Disease Progression

When radiological disease progression assessed by the investigator is identified, patients may continue to receive study drug at the current dose, if they are still benefiting from it as determined by the investigator (eg, absence of clinical symptoms or signs indicating clinically significant disease progression requiring alternative systemic anticancer therapy; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [eg, 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 this scenario, the medical monitor delegated by the sponsor shall review and approve the case and an informed consent shall be obtained from the patient.

Missed Doses of Either Brigatinib or Alectinib

A missed dose is defined as a dose not taken within 6 hours of the intended scheduled administration. Missed doses should be recorded in an appropriate source record (eg, clinic chart, patient diary card) and study drug administration electronic case report form (eCRF). If a dose of study drug is missed or vomiting occurs after taking a dose, do not administer an additional dose. The patient shall take the next dose of study drug at the scheduled time.

8.3 Recommended Dosing and Dose Modification Guidelines

BRIGATINIB RECOMMENDED DOSING

Brigatinib will be administered orally at a dose of 90 mg QD for the first 7 days. Patients who have tolerated the 90 mg starting dose on Days 1 through 7 of Cycle 1 will be expected to increase their dose to 180 mg QD continuously, beginning on Day 8. Brigatinib may be taken with or without food at approximately the same time every day, and patients will take their prescribed dose with water (recommended 240 mL).

The patient's daily dose of brigatinib should not be increased to 180 mg if any of the following AEs are experienced during treatment at 90 mg QD:

- Interstitial lung disease/pneumonitis (any grade).
- Symptomatic bradycardia (Grade 2 or greater).
- Grade 2 or higher visual disturbance.
- Any other Grade 3 or higher adverse reaction.

Once the decision not to increase the dose to 180 mg QD is made, it should not be increased in the future even if the AE has resolved.

The investigator should carefully evaluate the safety of the patients before making the decision to escalate the dose to 180 mg QD.

Brigatinib Dose Modifications for Adverse Reactions

The allowable daily doses of brigatinib in this study are 180 mg, 120 mg, 90 mg, and 60 mg. In cases where patients are intolerant of their current dose, they will have the option to reduce their dose, in accordance with the dose-reduction scheme shown in Table 8.a.

Table 8.a Recommended Brigatinib Dose Reduction Levels

Dose	Dose Reduction Levels			
	First	**Second**	**Third**	**Fourth**
90 mg QD	60 mg QD	Permanently discontinue	Not applicable	Not applicable
180 mg QD	120 mg QD	90 mg QD	60 mg QD	Permanently discontinue

Abbreviation: QD, once daily.

Guidelines for dose modification of brigatinib treatment-related AEs are outlined in Table 8.b. Unless otherwise noted, reduce dose as below, if one or more dose reductions are necessary because of AEs of Grade 3 or 4 severity, as defined by NCI CTCAE v4.03.

Table 8.b Brigatinib Dose Modification Recommendations for Treatment-Related AEs

Adverse Reaction	Severity [a]	Dose Modification
ILD/pneumonitis	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue brigatinib
	Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline. Resume at next lower dose (Table 8.a) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose. • If new ILD/pneumonitis recurs, permanently discontinue brigatinib
	Grade 3 or 4	Permanently discontinue brigatinib for ILD/pneumonitis.

Table 8.b Brigatinib Dose Modification Recommendations for Treatment-Related AEs

Adverse Reaction	Severity [a]	Dose Modification
Hypertension	Grade 3 hypertension (SBP greater than or equal to 160 mm Hg or DBP greater than or equal to 100 mm Hg, medical intervention indicated, more than 1 antihypertensive drug, or more intensive therapy than previously used indicated)	• Withhold brigatinib until hypertension has recovered to baseline or SBP less than 140 mm Hg and DBP less than 90 mm Hg, then resume brigatinib at same dose (Table 8.a) • Recurrence: withhold brigatinib until recovery to Grade 1 or less, and resume at next lower dose (Table 8.a) or permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold brigatinib until recovery to Grade 1 (or SBP less than 140 mm Hg and DBP less than 90 mm Hg), and resume at next lower dose (Table 8.a) or permanently discontinue treatment. • Recurrence of Grade 4 hypertension: permanently discontinue brigatinib.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	• Withhold brigatinib until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume brigatinib at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume brigatinib at next lower dose (Table 8.a) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• Permanently discontinue brigatinib if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume brigatinib at next lower dose (Table 8.a) upon recovery to asymptomatic bradycardia or to a resting HR of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue brigatinib.
Visual disturbance	Grade 2 or 3 visual disturbance	Withhold brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 8.a)
	Grade 4 visual disturbance	Permanently discontinue brigatinib

Table 8.b Brigatinib Dose Modification Recommendations for Treatment-Related AEs

Adverse Reaction	Severity [a]	Dose Modification
CPK elevation	Grade 3 or 4 CPK elevation (greater than 5.0 × ULN) with Grade ≥2 muscle pain or weakness	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume brigatinib at same dose. • If Grade 3 or 4 elevation of CPK recurs with Grade ≥2 muscle pain or weakness, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume at the next lower dose level per Table 8.a.
Lipase/amylase elevation	Grade 3 lipase or amylase elevation (greater than 2.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at same dose. • If Grade 3 elevation of lipase and amylase recurs, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume at the next lower dose level per Table 8.a.
	Grade 4 lipase or amylase elevation (greater than 5.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at next lower dose (Table 8.a). • If Grade 4 elevation of lipase/amylase recurs, permanently discontinue brigatinib.
Hyperglycemia	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next lower dose (Table 8.a) or permanently discontinue brigatinib.
Other	Grade 3	• Withhold brigatinib until recovery to baseline, then resume at same dose. • Recurrence: withhold brigatinib until recovery to baseline, then resume at next lower dose or discontinue brigatinib (Table 8.a).
	Grade 4	• First occurrence: either withhold brigatinib until recovery to baseline and resume at next lower dose (Table 8.a) or permanently discontinue. • Permanently discontinue brigatinib for recurrence.

Abbreviations: bpm, beats per minute; CPK, creatine phosphokinase; DBP, diastolic blood pressure; HR, heart rate; ILD, interstitial lung disease; SBP, systolic blood pressure; ULN, upper limit of normal.
[a] Graded per NCI CTCAE v4.03.

Comprehensive assessments of any study drug-related AEs (ie, adverse drug reactions) experienced by the patient will be performed throughout the course of the study. The severity of the event, as well as clinical judgment, will be used to determine appropriate management of the patient for any AE experienced while participating in this study.

Any medication, including those administered for therapy of symptoms considered associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF.

Reintroducing Brigatinib After Dose Interruption

If brigatinib treatment interruption lasts ≥14 days, and prior dose was >90 mg QD, patients should resume treatment at 90 mg QD for 7 days, before escalating dose back to their previous treatment dose, 120 mg QD or 180 mg QD. The dose should not be escalated higher than the prior dose level before treatment interruption. If an AE does not resolve to baseline after dose interruption for more than 28 days, the sponsor's medical monitor must be contacted before the study drug can be resumed.

Re-escalation of Brigatinib After Dose Reduction

Re-escalation after dose modification for AEs is discouraged. However, if in the opinion of the treating investigator re-escalation is warranted, this must be undertaken after consultation with the sponsor. To be a candidate for re-escalation, the AE that led to dose modification must not have recurred, and no other AEs of Grade 3 or 4 must have been observed during the preceding 28 days.

Pulmonary Adverse Reactions and Other AEs

During early clinical development of brigatinib, moderate and severe pulmonary AEs (eg, dyspnea, hypoxia, cough, pneumonia, and pneumonitis) were observed shortly after initiation of the drug in a subset of patients. These events were termed early onset pulmonary events (EOPE).

In the ALTA study (AP26113-13-201) for brigatinib, as of 21 February 2017, of 219 treated patients, there were 14 cases of EOPE (6.4%). All cases occurred at a dose of 90 mg QD. No EOPEs were identified after escalation to 180 mg QD in the 90 mg QD→180 mg QD dose group, or after re-initiation following study treatment interruption. Median time of onset of EOPE was Day 2 (range: 1-9). Eleven of these 14 cases were reported as SAEs. Seven patients had events that were Grade ≥3, all of whom permanently discontinued brigatinib because of these events. One patient had an EOPE that was Grade 5 (pneumonia).

Pulmonary events occurring within the first 7 days of treatment, including, but not limited to, dyspnea, hypoxia, dry cough, chest tightness, and presumptive lung infection (pneumonia) should be monitored and reported. To reiterate, some events occur after a single dose of brigatinib, and physicians should be aware of this possibility and discuss it with patients. Newly developed or worsening of pulmonary symptoms in the first week of study drug administration, specifically with hypoxia and ground glass opacity on radiographic imaging indicative of interstitial lung disease or pneumonitis, could suggest a relationship to brigatinib after other etiologies, including pulmonary embolism, rapid disease progression, and infectious pneumonia are ruled out. If no evidence of other etiology is identified, a causal relationship to brigatinib may be considered.

The management of new or worsening pulmonary symptoms within the first 7 days of brigatinib treatment should include drug interruption, monitoring of oxygen saturation, radiographic evaluation of the chest, and appropriate work up for infectious or other etiology, with high dose corticosteroids, supplemental oxygen therapy, and empiric antibiotics as indicated. After drug

interruption and workup of symptoms, if ILD/pneumonitis is suspected, dose modification should be accomplished according to the recommendations in Table 8.b.

See Section 6 of the current version of the investigator's brochure for detailed information on EOPE, late onset pneumonitis and other AEs, including bradycardia, hypertension, vision impairment, blood creatine kinase increased, pancreatic enzymes elevation, hyperglycemia, and other adverse drug reactions observed in the clinical studies with brigatinib.

ALECTINIB RECOMMENDED DOSING

Alectinib should be taken 600 mg orally twice daily with food at approximately the same time every day. If a dose of alectinib is missed or vomiting occurs after taking a dose of alectinib, take the next dose at the scheduled time.

Alectinib Dose Modifications for Adverse Reactions

The allowable daily doses of alectinib in this study are 600 mg taken orally twice daily, 450 mg taken orally twice daily, and 300 mg taken orally twice daily. Treatment needs to be discontinued if patients are unable to tolerate the 300 mg twice daily dose. In cases where the patient is intolerant of their current dose, they will have the option to reduce their dose, in accordance with the dose-reduction scheme shown in Table 8.c.

Table 8.c Alectinib Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting dose	600 mg taken orally twice daily
First dose reduction	450 mg taken orally twice daily
Second dose reduction	300 mg taken orally twice daily

Guidelines for dose modification of alectinib treatment-related AEs are outlined in Table 8.d. Unless otherwise noted, reduce dose as below, if one or more dose reductions are necessary because of adverse reactions of Grade 3 or 4 severity, as defined by NCI CTCAE v4.03.

Table 8.d Alectinib Dose Modification Recommendations for Treatment-Related AEs

NCI CTCAE Grade	Alectinib Treatment
ILD/pneumonitis of any severity grade	Immediately interrupt and permanently discontinue alectinib if no other potential causes of ILD/pneumonitis have been identified.
ALT or AST elevation of Grade ≥3 (>5 × ULN) with total bilirubin in ≤2 times ULN	Temporarily withhold until recovery to baseline or ≤Grade 1 (≤3 × ULN), then resume at reduced dose (see Table 8.c)
ALT or AST elevation of Grade ≥2 (>3 × ULN) with total bilirubin elevation >2 × ULN in the absence of cholestasis or haemolysis	Permanently discontinue alectinib
Bradycardia [a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as antihypertensive medicinal products. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥60 bpm. If no contributing concomitant medicinal products is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose (see Table 8.c) upon recovery to ≤Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥60 bpm.
Bradycardia [a] Grade 4 (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 8.c) upon recovery to ≤Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥60 bpm, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
CPK elevation >5 × ULN	Temporarily withhold until recovery to baseline or to ≤2.5 × ULN, then resume at the same dose.
CPK elevation >10 × ULN or second occurrence of CPK elevation of >5 × ULN	Temporarily withhold until recovery to baseline or to ≤2.5 × ULN, then resume at reduced dose as per Table 8.c.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; CPK, creatine phosphokinase; ILD, interstitial lung disease; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ULN, upper limit of normal.

[a] Heart rate less than 60 bpm.

For Grade 3 toxicities (both hematologic and nonhematologic toxicities) not listed in Table 8.d:

- First occurrence: withhold alectinib until recovery to baseline, then resume at same dose.

- Recurrence: withhold alectinib until recovery to baseline, then resume at next lower dose (Table 8.c) or discontinue alectinib.

For Grade 4 toxicities (both hematologic and nonhematologic toxicities) not listed in Table 8.d:

- First occurrence: either withhold alectinib until recovery to baseline and resume at next lower dose (Table 8.c) or permanently discontinue.
- Permanently discontinue alectinib for recurrence.

Re-escalation of Alectinib After Dose Reduction

Re-escalation of alectinib after dose modification for AEs is discouraged; however, if in the opinion of the treating investigator, re-escalation is warranted, this must be undertaken after consultation with the sponsor.

In order for a patient to be a candidate for dose re-escalation, the AE that led to dose modification must not have reoccurred after alectinib was resumed at the decreased dose, and the patient must have had no other Grade 3/4 AEs in the past 28 days.

Reintroducing Alectinib After Dose Interruption

Alectinib may be resumed at the same dose if alectinib was held for reasons other than an adverse reaction. If an AE does not resolve to baseline after dose interruption for more than 28 days, the sponsor's medical monitor must be contacted before the study drug can be resumed.

8.4 Permitted Concomitant Medications and Procedures

Any medication, given for any reason, during any time period from the time a patient signs the ICF up to 30 days after the final treatment with study drug will be considered a concomitant medication. Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. This may include blood and blood products and growth factors as clinically needed.

8.5 Excluded Concomitant Medications and Procedures

Systemic treatment with the following medications should be avoided during the study for patients taking brigatinib due to the risk of drug-drug interactions:

- Strong CYP3A inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit-containing products including grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. If concomitant use of a strong CYP3A inhibitor cannot be avoided during the study, reduce the brigatinib QD dose by approximately 50% (ie, from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the brigatinib dose that was tolerated before initiating the strong CYP3A inhibitor.
- Moderate CYP3A inhibitors: aprepitant, cimetidine, ciprofloxacin, clotrimazole, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil. If concomitant use of a moderate CYP3A inhibitor cannot be avoided during the

study, reduce the brigatinib QD dose by approximately 40% (ie, from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a moderate CYP3A inhibitor, resume the brigatinib dose that was tolerated before initiating the moderate CYP3A inhibitor.

- Strong CYP3A inducers: carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, primidone, rifampin, rifapentine, rifabutin, and St. John's wort.
- Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil, and nafcillin. If concomitant use of a moderate CYP3A inducer cannot be avoided and after discussion with the Takeda medical monitor/designee, the dose of brigatinib may be increased in 30 mg increments after 7 days of treatment with the current brigatinib dose as tolerated, up to a maximum of twice the brigatinib dose that was tolerated before initiation of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, brigatinib should be resumed at the dose that was tolerated before initiation of the moderate CYP3A inducer.

As the above lists are not exhaustive, the investigator should consult the prescribing information for any medication under consideration for use to assess if it is a strong CYP3A inhibitor, moderate CYP3A inhibitor, strong CYP3A inducer, or moderate CYP3A inducer.

Refer to the local prescribing information for drug-drug interaction information for alectinib.

- The following medications and procedures are also prohibited before radiological disease progression is observed:
  - Any other systemic anticancer therapy including, but not limited to: chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator).
  - Use of any other investigational drug or device.
- Any illicit substance. (Note: medical use of cannabis is allowed if it is legal where the patient resides and no alternative treatment is available. The case must be reviewed and agreed to by the medical monitor. Nonmedicinal use of cannabis if legal is discouraged).
- Use of alternative or herbal therapy must be approved by the sponsor in advance and be documented.

8.6 Precautions and Restrictions

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Coadministration of brigatinib with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates. Brigatinib may also induce other enzymes and transporters (eg, CYP2C, P-glycoprotein [P-gp]) via the same mechanism responsible for induction of CYP3A (eg, pregnane X receptor activation). Therefore, additional monitoring should be considered for patients receiving substrates of these enzymes and transporters with a narrow therapeutic index during treatment with brigatinib as their effectiveness may be reduced.

Brigatinib is an in vitro inhibitor of P-gp, breast cancer resistance protein (BCRP), organic cation transporter 1 (OCT1), multidrug and toxin extrusion protein 1 (MATE1) and 2K (MATE2K). Patients should be closely monitored when brigatinib is coadministered with substrates of these transporters with a narrow therapeutic index (eg, digoxin, dabigatran, methotrexate) as their plasma concentrations may be increased.

Photosensitivity to sunlight has occurred in patients treated with brigatinib. Patients should be advised to avoid prolonged sun exposure while taking brigatinib, and for at least 5 days after discontinuation of treatment. When outdoors, patients should be advised to wear a hat and protective clothing, and to use a broad-spectrum ultraviolet A (UVA)/ultraviolet B (UVB) sunscreen and lip balm (SPF [sun protection factor] 30) to help protect against potential sunburn. For severe photosensitivity reactions (Grade ≥3), brigatinib should be withheld until recovery to baseline. The dose should be modified accordingly (see the "other" AE in the dose modification guidelines in Table 8.b).

8.6.1 Pregnancy, Breastfeeding, and Contraception

8.6.1.1 Brigatinib

It is not known what effects brigatinib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, female patients should not breastfeed during treatment with brigatinib and for 1 week following the final dose.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, *or*
- Surgically sterile, *or*
- If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method (see list below) and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through at least 120 days after the last dose of study drug, *or*
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing of the ICF through at least 120 days after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with brigatinib and after the final dose for the duration specified in the protocol.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception from the time of signing of the ICF through at least 120 days after the last dose of study drug, *or*
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing of the ICF through at least 120 days after the last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Highly effective nonhormonal contraceptive methods suitable for patients taking brigatinib include:

- intrauterine device.
- bilateral tubal occlusion.
- vasectomised partner.

8.6.1.2 Alectinib

Refer to the current local prescribing information for alectinib for full details regarding pregnancy, breastfeeding, and contraception.

Female Patients

Based on animal studies and its mechanism of action, alectinib can cause fetal harm when administered to a pregnant woman. There are no available data on alectinib use in pregnant women. Female patients of reproductive potential should use effective contraception during treatment with alectinib and for 1 week after the final dose.

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from alectinib, advise a lactating woman not to breastfeed during treatment with alectinib and for 1 week after the final dose.

Male Patients

Based on genotoxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment with alectinib and for 3 months following the final dose.

8.6.2 Additional Precautions and Restrictions for Alectinib

Refer to the local prescribing information for alectinib for full details regarding precautions/ restrictions for its use. If local prescribing information is not available, the latest edition of the alectinib Summary of Product Characteristics should be consulted.

8.7 Blinding and Unblinding

This is an open-label study. A double-blind design was not implemented due to lack of feasibility based on the following considerations:

- Brigatinib is given once daily with no food restriction while alectinib is given twice daily with food.
- Brigatinib is provided in tablet form whereas alectinib is provided in capsule form that leads to easy identification.
- Different safety profiles between the 2 drugs would likely unblind patients/investigators to treatment assignments.

It should be noted that of the multiple randomized phase 3 studies completed with ALK inhibitors to date, not one has utilized a double blind design.

Of note, primary and several secondary efficacy endpoints will be assessed by the BIRC (Section 11.2).

8.8 Description of Investigational Agents

Brigatinib drug product is supplied as film-coated tablets, which may contain 30 mg, 90 mg, or 180 mg of brigatinib active pharmaceutical ingredient. Other ingredients will include typical pharmaceutical excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate). The tablet coating is composed of typical pharmaceutical grade coating components (talc, propylene glycol, polyvinyl alcohol, and titanium dioxide). The drug product is manufactured under Current Good Manufacturing Practice in accordance with approved procedures.

Alectinib drug product will be supplied as hard capsules containing 150 mg of alectinib active pharmaceutical ingredient.

8.9 Packaging and Labeling

Brigatinib will be supplied in white high-density polyethylene bottles with induction sealed caps or blister packs. Bottle or blister pack labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

Alectinib will be supplied in the commercial package, the carton labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

8.10 Storage, Handling, and Accountability

Brigatinib is to be stored at controlled room temperature of 20°C to 25°C, with excursions permitted between 15°C to 30°C. Do not refrigerate or freeze.

Alectinib will be stored per local prescribing instructions. If local prescribing instructions do not exist or do not address storage, then alectinib will be stored as advised in the latest version of the Summary of Product Characteristics.

The investigator is responsible for ensuring that the study drug provided to the patient and returned from the patient are reconciled and noted in source documentation.

All used bottles or blister packs of study drug must be returned to the study sponsor or destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

During the study and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

No other use of brigatinib or alectinib intended for use in this study is authorized by the sponsor. The principal investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug. Each site is responsible for proper and careful destruction of study drug returned by patients.

Periodically, throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug must be destroyed on site per the standard operating procedures of the investigative site or returned to the study sponsor if this is not possible. Please refer to the study manual for additional details regarding storage, handling, and disposal of study drug.

8.11 Preparation and Dispensing

The study pharmacist or designee at the site will be responsible for handling and dispensing brigatinib and alectinib and completing associated documentary paperwork. Supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute used by the site. Each time study medication is dispensed for a patient, the following information must be recorded: the patient's initials, the patient's study number, drug product strength (eg, 120 mg), quantity dispensed with the corresponding lot number, date of dispensation, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the sponsor.

In extenuating circumstances, such as during the COVID-19 public health emergency, additional drug supply may be provided to the subjects to cover extended periods between on-site visits. Additional study drug may be dispensed during a scheduled study visit or study drug may be

shipped directly from investigational sites to participants' residences by a contracted logistics provider or distributor (DTP shipment) in compliance with national laws or temporary national emergency measures and Takeda processes. The details of the instructions are provided in the Direct to Patient Shipment of Clinical Trial Material document.

8.12 Other Protocol-Specified Materials

Details are provided in the study manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and any additional vendors may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC).

9.3 Treatment Group Assignments

This is an open-label study. Patients will be randomized in a 1:1 fashion to receive either brigatinib in Arm A or alectinib in Arm B. Patients will be stratified by:

- The presence of intracranial CNS metastases at baseline (Yes vs No).
- Best prior response to crizotinib therapy as assessed by the investigator (CR/PR vs any other response/status unknown).

Patients will be treated on each arm until they experience PD as assessed by the investigator or intolerable toxicity, or until any other discontinuation criterion is met.

Study Procedures

Refer to the Schedule of Events (Appendix A) for timing of assessments immediately after randomization. Additional details are provided as necessary in the sections that follow.

9.3.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patient Demographics

The date of birth (outside European Economic Area) or age (in European Economic Area), race, ethnicity (optional depending on country), and sex of the patient are to be recorded during screening.

9.3.2 Screening

Screening assessments must be performed no more than 28 days before Cycle 1 Day 1, with the exception of tumor imaging assessment, where the allowable window is 21 days before first dose of study drug (Cycle 1, Day 1) and pregnancy testing which must be completed within 7 days of Cycle 1 Day 1. However, whenever feasible, baseline imaging should be performed as close as possible to Cycle 1, Day 1. Tumor radiological imaging generated for the purpose of regular medical practice before patients sign the ICF can be used as baseline disease assessment provided the imaging meets the quality and time window required for this study.

Vital signs should be repeated on Cycle 1, Day 1 before the first dose, regardless of the time from screening. Physical examination, ECOG performance status assessments, hematology, chemistry, insulin, and pregnancy tests do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days before Cycle 1, Day 1 and, in the opinion of the investigator, there is no reason to believe they have substantially changed. The pregnancy test may be repeated at any time during the study if the patient or the investigator has cause to believe that the patient may be pregnant. If screening laboratory assessments need to be repeated on Cycle 1, Day 1, the result should be obtained before the treatment is started.

Any patient who is re-screened after screen failure must, in addition to the failed test, repeat only those screening tests that have fallen outside the specified screening period, as outlined in the SOE (Appendix A).

9.3.3 Visit Windows

The day the first dose of brigatinib or alectinib is administered is defined as Day 1. Following visits may be arranged ±3 days from the Day 1 of each cycle, with the exception of disease assessment, which can be arranged with a ±7-day window. Mid cycle day 15 visits also have a ±3 day window. There is no window for Cycle 1 Day 8. Once radiological disease progression is observed or patients have started a new systemic anticancer therapy, the survival follow-up shall be arranged with a ±14-day window.

9.3.4 Enrollment

A patient is considered to be enrolled in the study once the ICF is signed, all screening evaluations are completed, and the patient has been randomized.

9.3.5 Medical History

A complete medical history, including cancerous and noncancerous disease, will be collected at screening. The type (systemic, surgery, radiotherapy) and intent (neoadjuvant, adjuvant, palliative) of prior anticancer therapy to the ALK+ NSCLC, and particularly, the drugs used for prior systemic anticancer therapy, the start and end date of each of them and the best response, shall be captured in the eCRF. The method by which ALK+ status was determined shall also be recorded.

Diagnosis and Cancer History

The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology and all sites of disease, should be recorded per The American Joint Committee on Cancer (AJCC), 8th edition (http://www.cancerstaging.com). Any previously identified mutations other than *ALK*, and the dates of identification, must be recorded.

Prior Cancer Therapy

Prior cancer therapy history will be taken at screening and includes cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative and palliative, as well as diagnostic procedures (eg, biopsy). Radiation will include both definitive and palliative treatment. Systemic therapy should include all regimens given, type of regimen (eg, neoadjuvant, adjuvant, for advanced or metastatic disease), number of cycles administered for each regimen, each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation. Experimental or investigational therapy for cancer must also be recorded.

ALK Mutation Status

Regarding current and past *ALK* mutation history, any previously identified mutations, and the dates of identification, must be recorded at screening. This includes *ALK* rearrangements by FISH and other methods including immunohistochemistry, and *ALK* rearrangements and point mutations by next generation sequencing.

In addition, concomitant medications will be recorded as specified in Section 9.3.11.

9.3.6 Tumor Tissue Samples

Mandatory Tumor Tissue at Screening From Those Patients Without a Prior ALK+ Result From an FDA-Approved Test

Patients entering the study must have a history of a positive results from a FDA approved test. Otherwise, they must have history of ALK-positivity by another test and submit tissue samples for central laboratory analysis using an FDA-approved test, although confirmed ALK-positivity by central laboratory is not required before enrollment. Specifications regarding handling and processing of tissue for central laboratory analysis are described below in Tumor Tissue Samples and in the study manual.

Optional Tumor Tissue at Screening From All Patients

For all patients enrolled on the study, collection of FFPE tumor tissue obtained after progression on crizotinib is highly encouraged. These samples will be used for exploratory biomarker studies. Tissue can be obtained as part of Standard of Care or as an optional screening biopsy in this study.

Optional Tumor Tissue at Time of Disease Progression

For patients who consent, a fresh biopsy will be performed at the time of progression on brigatinib or alectinib. Biopsies are requested, but not mandatory, at progression. Formalin fixed tumor tissues should be sent to the central laboratory. This tumor tissue will be used for exploratory molecular genetic analysis.

9.3.7 Physical Examination

A complete physical examination must be performed at screening and at the end-of-treatment visit, the extent of which should be consistent with medical history and the patients' underlying disease. Subsequent physical examinations, including the 30 days after last dose physical examination may be directed to relevant findings described in the Schedule of Events (Appendix A). Of note:

- Assessment for early pulmonary symptoms must be performed during the visit on Day 8 before receiving study drug. If new pulmonary or worsening pulmonary symptoms are detected, conditions leading to worsening pulmonary function should be ruled out (eg, pneumonia, pulmonary embolism, congestive heart failure, worsening NSCLC) before attributing the pulmonary symptoms to study drug.
- Due to adverse reactions reported during treatment with brigatinib, investigators are cautioned to monitor patients for signs of vision dysfunction. For new or worsening severe vision disorders, an ophthalmological evaluation should be performed.

9.3.8 ECOG Performance Status

The ECOG Performance Status will be assessed at screening and with every physical examination as outlined in the Schedule of Events (Appendix A).

9.3.9 Patient Height and Weight

Height will be measured only during screening. Weight will be measured during screening and at every scheduled visit.

9.3.10 Vital Signs

Vital signs will include temperature, pulse, respiratory rate, and blood pressure (when patient is seated). Vital signs should be repeated on Cycle 1, Day 1, before the first dose, regardless of the time from screening. Vital signs will also be assessed per the Schedule of Events (Appendix A).

9.3.11 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the date of informed consent up to 30 days after the last dose of study drug. See Sections 8.4 and 8.5 for a list of medications and therapies that are prohibited and/or allowed during the study. Concomitant medications will be recorded through 30 days after the last dose of last study drug.

9.3.12 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

9.3.13 ECG

A 12-lead ECG will be administered at Screening and at the end-of-treatment visit. Additional ECGs may be performed at the investigator's discretion to ensure patient safety.

9.3.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally whenever possible; an external laboratory may be used if necessary. Clinical laboratory evaluations will be performed as outlined in Table 9.a. The frequency of the laboratory test are defined in the Schedule of Events (Appendix A). The results shall be recorded in eCRF. The attending physicians may order additional tests as clinically indicated to follow up on AEs observed during the study. These additional results shall also be captured in the eCRF. However, other tests for the purpose of regular clinical practice outside of the scope of safety surveillance for study drug will not be required to enter in the eCRF. The blood sample for Cycle 1, Day 1 clinical laboratory assessments should be drawn before the first dose of study drug. Hematology laboratory are listed in Table 9.a.

Serum chemistry tests are listed in Table 9.a and include amylase, lipase, magnesium, creatine kinase and insulin in addition to other electrolytes and liver function tests.

Day 15 Liver Function Testing

For Cycles 1, 2 and 3, the Day 15 chemistry serum testing will include only AST, ALT, and total bilirubin (see the Schedule of Events, Appendix A for details).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Chloride
Hemoglobin	ALP	Glucose
Leukocytes with differential	ALT and AST	LDH
Neutrophils (ANC)	Amylase	Lipase
Platelet (count)	Bilirubin (total)	Magnesium
	Blood urea nitrogen	Phosphate
	Calcium	Potassium
	CPK	Sodium
	Creatinine	**Insulin**

Abbreviations: ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

9.3.15 Pregnancy Test

Women who are not of childbearing potential (status posthysterectomy, status post–bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) and men do not need to have the test performed.

The test must be known to be negative before the study drug administration and be performed within 7 days before first study drug administration (Cycle 1, Day 1).

The pregnancy tests must be a beta-human chorionic gonadotropin test, and either urine or serum can be used. Women of childbearing potential at study start must also complete the pregnancy test once every 12 weeks (3 cycles) thereafter and at the end-of-treatment visit. Additional pregnancy testing should be performed if recommended or required per local guidelines or regulations.

9.3.16 Disease Assessment

Tumor response assessments will be determined per RECIST v.1.1 by the investigator and an independent radiological review committee. Patients must have at least 1 measurable lesion per RECIST v1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may be used as target lesions provided they are ≥10 mm and have not been: 1) previously treated with whole brain radiation therapy within 3 months, or 2) previously treated by SRS or surgical resection.

At screening, disease assessment must include imaging of the chest and abdomen (including adrenal glands), using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [MRI] with contrast, unless contrast media is contraindicated). Contrast-enhanced MRI of the brain (such as gadolinium) is required at screening for all patients, unless medically contraindicated. If contrast for MRI is contraindicated, use CT with contrast. All radiographic images (eg, CT scan, MRI) performed during the study will be submitted to the imaging core laboratory for central review. Imaging of chest, abdomen, and brain will occur at

each assessment for all patients. Disease assessment by CT and MRI scans will be performed at screening (this may be up to 21 days before Cycle 1, Day 1) and at 8-week intervals thereafter using C1D1 as the starting point (on Day 28 [±7 days] of every even-numbered cycle), through Cycle 12 after the initial dose of study drug, and every 3 cycles thereafter until end of treatment. More frequent imaging is recommended at any time if clinically indicated; confirmation of CR or PR should be performed at least 4 weeks after initial response. If confirmatory imaging occurs 4 weeks after the initial response it is preferred, but not required. that regular imaging resume at the original schedule (eg, on Day 28 of every even cycle or Day 28 of each original 3-cycle block). Imaging assessment will also be performed at end of treatment if more than 4 weeks have passed since the last imaging assessment. The same imaging modality at the same institution should be used at each assessment, if possible.

For patients who discontinue the study drug because of a reason other than PD by investigator's assessment, additional tumor assessment should be documented, if available, until disease progression or start of subsequent systemic anticancer therapy.

9.3.17 Confirmation of ALK Positivity

All patients are required to have documentation of *ALK* rearrangement before randomization. If the documentation is a positive result from either the Vysis ALK Break-Apart FISH Probe Kit or the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx, then confirmation by a central laboratory is not required.

If the patient has documented *ALK* rearrangement by a different test (other than 1 of the 2 listed above), the patient must provide a tumor sample to the central laboratory before randomization. A pathologist should assess the tissue sample to ensure adequate tumor tissue is available based on the minimum requirements described in the study manual. (Note: central laboratory *ALK* rearrangement testing results are not required to be obtained before randomization.)

9.3.18 PK Measurements

Patients randomized to the brigatinib arm of the study (Arm A) must provide blood samples (approximately 3 mL per sample) for measurement of plasma concentrations of brigatinib. Patients must be instructed not to take the day's dose of brigatinib until after the predose blood sample is collected. Predose samples should be collected as close as possible to 24 hours after the prior brigatinib dose. The administration date and time of the prior 2 brigatinib doses must be recorded. On the PK sampling day, the collection time of the predose PK sample along with time of brigatinib dosing should be recorded. Blood samples for the determination of plasma concentrations of brigatinib will be collected as indicated in Appendix A, PK Sampling Schedule. The exact date and time of each PK sample collection should be recorded.

Plasma concentrations of brigatinib will be measured using a validated liquid chromatography tandem-mass spectrometry assay. Details regarding the preparation, handling, and shipping of the PK samples are provided in the study manual.

For patients randomized to the alectinib arm of the study (Arm B), no PK samples will be collected at any time point during the study.

9.3.19 Circulating DNA Measurements

Circulating tumor DNA will be obtained at 3 time points for all patients: (1) Screening and (2) Cycle 3, Day 1, and at (3) the end-of-treatment visit. A blood sample (approximately 60 mL in total) will be collected for exploratory biomarker studies, including molecular genetic analysis of *ALK* and other genes implicated in tumor biology.

9.3.19.1 Biomarker Sample Retention

Biomarker samples will be stored at Takeda-designated laboratories for up to 15 years after the date of study completion as identified in the clinical study report, and then will be discarded. Tumor tissue samples will be stored at refrigeration temperature, and other samples will be stored at -70°C. If patients withdraw consent, the samples will be discarded.

9.3.20 Dosing Diary

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded. Complete instructions will be provided with the study manual. The schedule for when the diary card will be reviewed with site staff is presented in the Schedule of Events (Appendix A).

The dosing diary will be reviewed as per the Schedule of Events.

9.3.21 Quality of Life Assessment: Cancer (EORTC QLQ-C30, QLQ-LC13, and QLQ-BN20)

The HRQL assessments (EORTC QLQ-C30, QLQ-LC13, and QLQ-BN20) will be completed by the patient as specified in the Schedule of Events (Appendix A). The EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The lung cancer specific module QLQ-LC13 comprises 13 questions assessing lung cancer associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and use of pain medication. This will be administered subsequent to the EORTC QLQ-C30.

To reduce the clinical site and respondent burden, 5 items from the brain cancer module QLQ-BN20 will be used to assess morbidity related to CNS symptoms, including headaches (item 4), coordination (item 15), and communication deficit (items 11, 12, and 13). This will be administered subsequent to the EORTC QLQ-C30 and QLQ-LC13.

The time recall period for the instruments is 1 week (the week immediately preceding the assessment). These are reliable and valid measures of HRQoL in patients with cancer and take about 15 minutes to administer. The instruments have been validated and used in many countries.

The patient-reported outcomes (PRO) questionnaires (EORTC QLQ-C30, QLQ-LC13, and QLQ-BN20) will be administered at specified scheduled visits and at the visit 30 days after the last

dose of study drug. The PRO questionnaire should be administered to patients when they arrive for their scheduled visits, before other assessments are performed before any clinical measurements, assessments, evaluations, or study drug is taken procedures being performed.

9.3.22 Quality of Life Assessment: EQ-5D-5L Measurement

The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated on 5 levels. The EQ VAS records the respondent's self-rated health on a 20-cm, vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-5L will be administered as specified in the Schedule of Events (Appendix A); at time points when a clinic visit is not required, the EQ-5D-5L questionnaire may be administered for at least 1 or more complete cycles over the telephone, and site staff may enter the data from the patient.

9.3.23 Health Resource Utilization Data Collection

During the treatment and follow-up periods indicated in the Schedule of Events (Appendix A), all medical care encounters since the previous collection will be collected from all patients, regardless of the reason for the medical care encounter at the scheduled visit of each cycle, during the end-of-treatment visit, and the 30 days after last dose visit. Examples of data to be collected are number and duration of medical care encounters, such as inpatient/outpatient admissions, homecare, and time of work loss.

9.3.24 End-of-Treatment Visit

The end-of-treatment visit should be performed within 2 weeks (14 days) of the patient's last dose of study drug or the patient/investigator decision to discontinue study drug, whichever occurs later. Physical examinations, laboratory tests (hematology, chemistry, and insulin), and ECG may be omitted if they had been previously performed within 2 weeks since the last assessments and if, in the investigator's judgment, significant change is unlikely.

9.3.25 30 Days After Last Dose

The 30 days after last dose assessments must be performed 30 days (±7 days) after the last dose of study drug. Physical examinations and laboratory tests (hematology, chemistry, and insulin) can be omitted if the visit occurs within 10 days of the end-of-treatment assessment and there have been no clinically significant findings. Any new systemic anticancer therapies that the patient has begun receiving since the end of treatment should be reported at this visit. For both the end-of-treatment and 30 days after last dose assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care. If the day the patient has the last dose equals or is more than 30 days before the decision of permanent discontinuation from study treatment, the end-of-treatment visit and 30 days after last dose visit can be combined as 1 visit. If patients permanently discontinued study treatment before radiological disease progression is observed, this visit may occur before the end-of-treatment visit.

9.3.26 Follow-up Period

The follow-up period for a patient begins after end of treatment (ie, when all study drug has been discontinued) and continues until patient contact ceases. The follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the last dose of the study treatment. The allowable window for follow-up assessments is 14 days. All new systemic anticancer therapies should be reported. Also, the EQ-5D-5L will be obtained in this period every 12 weeks (±14 days) (the questionnaires should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed).

9.4 Completion of Study Treatment (for Individual Patients)

For the purpose of analysis, patients will be considered to have completed study treatment once they have permanently discontinued study drug (either brigatinib or alectinib) because of disease progression by the investigator's assessment, intolerance, investigator discretion, or if they die while on study treatment.

For visit purposes, the end-of-treatment visit occurs at the last dose of study drug or when the investigator or the patient decide the patient will receive no further study drug, whichever occurs later.

At 30 days after last dose of study drug, the patient shall complete all posttreatment discontinuation assessments. If the date the patient has the last dose equals or is 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 1 visit.

9.5 Completion of Study (for Individual Patients)

All patients who have discontinued study drug(s) shall be followed for survival, regardless of the reason of discontinuation. The survival follow-up will continue until the patient dies or the study ends. Patients will be considered to have completed the study if they died before the time of data cut. Patients lost to follow-up or who have withdrawn consent before study completion are not counted in number of patients completing this study.

9.6 Discontinuation of Treatment With Study Drug

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- PD assessed by the investigator as defined by RECIST v1.1.
  - Note: Treatment of patients with brigatinib or alectinib may be continued, despite progression by RECIST v1.1, at the discretion of the investigator, if there is still evidence of clinical benefit. In this scenario, the medical monitor shall be contacted to approve these cases. Patients shall sign an additional ICF before the treatment continues.
- Intolerable toxicity as determined by the investigator.

Treatment with study drug may also be discontinued for any of the following reasons:

- Significant protocol deviations that will jeopardize safety surveillance and pose a significant threat to the safety of the patient.
- Study terminated by sponsor.
- Withdrawal by subject.

  In cases in which patients request to discontinue the study drug, the investigator should assess if this is due to study drug related toxicity. This election is only applicable if the patients are not having intolerable toxicity by investigators' medical judgment. Patients who request to permanently discontinue the study treatment shall continue to be followed for tumor assessment and survival, unless patients withdraw consent to participate the study.
- By investigator discretion it is in the best interests of the patient to discontinue.

  If investigator discretion is based on intolerable toxicity, the reason of discontinuation shall be recorded as due to intolerable toxicity. Before discontinuing a patient because it is in the best interests of the patient the investigator should contact the study sponsor to discuss the matter.
- Lost to follow-up.
- Pregnancy.
- Other.

Once study drug has been discontinued, all study procedures outlined for the end-of-treatment visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded in the eCRF.

9.7 Study Compliance

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded. Complete instructions will be provided with the study manual.

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.8 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

After end of treatment, all patients will be followed for OS until death or study end. The survival follow-up can be conducted by remote method (eg, telephone call). At each visit, the survival status and information about subsequent anticancer therapy, such as the name, starting and ending time and best-known response, will be collected.

If patients discontinue study treatment due to reasons other than disease progression, tumor assessment according to the protocol is strongly encouraged to be continued until radiological disease progression is observed.

If disease progression is already reported and the patient receives the study drug beyond initial disease progression, the tumor assessment will continue to occur at the same schedule; however, the sponsor does not require further tumor assessment data to be collected.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Worsening of signs and symptoms of the malignancy under study does not need to be reported as AEs.

AE Severity

The severity of AEs will be assessed according to the NCI CTCAE v4.03 (see the study manual). If the AE is not defined in the NCI CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- Mild (grade 1): The AE is noticeable to the patient but does not interfere with routine activity.
- Moderate (grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest.
- Severe (grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- Life-threatening (grade 4): The patient is at immediate risk of death.
- Death (grade 5): The patient dies as a direct result of the complication or condition induced by the AE.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

  In this study, severity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [40]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an

AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. In case of fax, site personnel need to confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [40]. The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: “Is there a reasonable possibility that the AE is associated with the study drug?”

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs that occur between the ICF and the first dose of study drug will be captured as pretreatment events or medical history.

- SAEs:
  - Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided below.

Product	Call center	Phone number	E-mail	Fax
Brigatinib	Dohmen Life Science Services, or DLSS (formerly known as MedComm)	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, the investigator must report the SAE through EDC (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Steering Committee

A steering committee comprised of external medical experts will be organized to provide scientific guidance to study design, conduction, and reporting. The details of the steering committee membership and responsibilities will be included in the steering committee charter.

11.2 IRC

A central BIRC with no knowledge of the patients' status on treatment will evaluate all images collected during the study for the primary endpoint of PFS per RECIST v1.1, as well as several secondary endpoints such as time to iPD, as per modified RECIST v1.1. An IRC charter defines the procedures used by the committee.

The central BIRC assessment may be terminated if the primary endpoint is met at the IA or primary analysis, or not met at the primary analysis. The tumor assessment of on-going patients will only be performed by investigators thereafter.

11.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) supported by an independent statistician will review safety and efficacy data at the planned primary analysis and IA for PFS. The IDMC will be composed of 3 medical oncologists with expertise in NSCLC and 2 statisticians. They will make recommendations on study conduct if needed. Study accrual will not be interrupted because of the scheduled safety reviews. The IDMC or Brigatinib-3001 study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs

(including all SAEs, treatment-related AEs, serious treatment-related AEs, and AEs requiring the discontinuation of study therapy) will be tabulated by system organ class, preferred term, and severity grade. Listings and/or narratives of on-study deaths and other serious and significant AEs, including any early withdrawals because of AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Takeda. Further details including frequency of IDMC meetings will be provided in the IDMC charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, pretreatment events, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

Full Analysis Set

The full analysis set is based on the intent-to-treat (ITT) principle and includes all patients randomized to each regimen regardless of whether they are ALK+ by the Vysis ALK Break Apart FISH Probe Kit or the Ventana ALK (D5F3) CDx Assay, Foundation Medicine's FoundationOneCDx or a local test other than FISH and immunohistochemistry, or whether they receive study drug or adhere to the assigned dose. The primary analyses of efficacy will be based on the full analysis set.

Safety Analysis Set

The safety analysis set for each regimen includes all patients receiving at least 1 dose of study drug. Safety will be analyzed using the safety analysis set.

Per-Protocol Analysis Set

The per-protocol analysis set will exclude all patients in the safety analysis set 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. Additional analyses may also be performed excluding patients who were not confirmed as ALK+ (locally or centrally) by an FDA approved test. Further criteria for the per-protocol population and the sensitivity analyses of the primary endpoint and selected secondary efficacy endpoints using this population will be detailed in the SAP.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics at the time of randomization will be summarized using descriptive statistics for the full analysis set according to the randomly assigned treatment. Continuous variables will be summarized by means, medians, standard deviations, and ranges; categorical variables will be summarized by counts and percentages. Other variables may also be included in this analysis by categorizing the continuous variables or re-categorizing existing categorical variables.

13.1.3 Efficacy Analysis

13.1.3.1 Definitions of Efficacy Endpoints

The primary endpoint, PFS assessed by BIRC, is defined as the time interval from the date of randomization until the first date at which disease progression is objectively documented via RECIST v1.1, or death due to any cause, whichever occurs first, in the full analysis set. PFS will be censored for patients without documented disease progression or death at the last valid tumor response assessment.

Secondary efficacy endpoints for this study are defined as follows (unless otherwise stated, secondary efficacy endpoints of response will use BIRC assessments with sensitivity analyses performed using the investigator assessments):

- OS is defined as the time interval from the date of randomization until death due to any cause in the full analysis set. It will be censored on the date of last contact for those patients who are alive.
- PFS as assessed by the investigator.
- ORR is defined as the proportion of the patients who have achieved CR or PR using RECIST v1.1 after the initiation of study treatment in the full analysis set.
- DOR is defined as the time interval from the time that the measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that the PD is objectively documented or death.

- Time to response is defined as the time interval from randomization until the initial observation of CR or PR. Time to response will be summarized using descriptive statistics in patients with objective response.
- iORR, as assessed by the BIRC, is defined as the proportion of the patients who have achieved CR or PR in the CNS per a modification RECIST v1.1 after the initiation of study treatment in patients with CNS metastases at baseline.
- iDOR, as assessed by the BIRC, is defined as the time interval from the time that the measurement criteria are first met for CR or PR in the CNS (whichever is first recorded) until the first date that the PD in the CNS is objectively documented or death.
- Time to iPD, as assessed by the BIRC, is defined as the time interval from the date of randomization until the first date at which intracranial disease progression is objectively documented via a modification of RECIST v1.1. Time to iPD will be censored for patients without documented intracranial disease progression at the last valid intracranial tumor response assessment.

Exploratory efficacy endpoints include CNS efficacy via RANO-BM on initial treatment, molecular determinants of efficacy and safety with brigatinib and alectinib, HRQoL endpoints and health resource utilization endpoints. Detailed definitions of these exploratory efficacy endpoints will be provided in the SAP.

13.1.3.2 Primary Efficacy Endpoint Analyses

The primary analysis of the primary endpoint will be performed using a 2-sided stratified log-rank test (stratification factors: presence of intracranial CNS metastases at baseline [yes vs no], and best prior response to crizotinib therapy as assessed by the investigator [CR/PR vs any other response/status unknown]) to compare the BIRC-assessed PFS of patients randomized to brigatinib with the BIRC-assessed PFS of patients randomized to alectinib. The overall (2-sided) type I error rate will be controlled at 0.05. The primary analysis will be based on the full analysis set. PFS will be estimated for each treatment arm using the Kaplan-Meier method [41]. Additionally, HRs will be estimated using the stratified Cox regression model with the stratification factors.

Sensitivity analyses of the primary endpoint of PFS will also be performed in the following populations:

- Per-protocol population, as assessed by the BIRC.
- FDA approved ALK test population, as assessed by the BIRC.

Subgroup analyses will be performed by baseline prognostic factors.

BIRC-assessed PFS will be tested at the IA after 115 PFS events have been observed. If the observed HR doesn't meet the prespecified stopping rules for efficacy or futility at the IA then a primary analysis will be conducted after 164 events are observed.

13.1.3.3 Secondary Efficacy Endpoint Analyses

OS, the key secondary endpoint, will be formally tested for statistical significance only once PFS per BIRC is statistically significant. OS will be assessed in the full analysis set.

PFS as assessed by the investigator and ORR will be assessed in the full analysis set. iORR will be assessed in patients in the full analysis set with measurable brain metastases. The percentage responding and the associated 2-sided 95% CI will be calculated. A Mantel-Haenszel (using the stratification factors) test will be performed to compare each endpoint between the 2 arms.

The analysis of time to iPD, as assessed by the BIRC, will be performed using a 2-sided stratified log-rank test (using the stratification factors) to compare the BIRC-assessed time to iPD of patients randomized to brigatinib with the BIRC-assessed time to iPD of patients randomized to alectinib. The analysis will be based on patients in the full analysis set. Time to iPD will be estimated for each treatment arm using the Kaplan-Meier method [41]. Additionally, HRs will be estimated using the stratified Cox regression model with the stratification factors. Additional analyses in patients with measurable brain metastases and in patients without brain metastases will also be performed in a similar manner.

DOR will be assessed among responders in the full analysis set. iDOR will be assessed among patients with brain metastases with an intracranial response in the full analysis set. For each time to event endpoint, values and 2-sided 95% CIs will be estimated using Kaplan-Meier method according to the initially assigned treatment. Stratified log-rank tests (using the stratification factors) will be performed to compare each endpoint between the 2 arms. Survival probabilities at 12 months and the associated 2-sided 95% CIs will be calculated.

Time to response will be summarized only for responders using descriptive statistics.

13.1.4 PK Analysis

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 plans for these analyses will be separately developed and the results reported separately.

13.1.5 Analysis of PRO and Health Resource Utilization Data

Analyses of PRO data will be performed using the PRO-ITT population, which will be defined as patients with baseline and at least 1 postbaseline measurement in the ITT population. The global health status/quality of life and functions from EORTC QLQ-C30 and symptoms measured by QLQ-LC13 will be of special interest.

The descriptive statistics of the actual value and change from baseline of the EORTC QLQ-C30, QLQ-LC13, and QLQ-BN20 scores will be summarized by treatment group over time. The change from baseline scores will be analyzed using linear mixed models to compare 2 treatment groups. The number and percentage of patients with improved, stable and worsened quality of life scores will be analyzed by treatment group over time. Time to quality of life worsening will also be summarized and compared by treatment group.

EQ-5D-5L scores will be summarized by treatment group over time using descriptive statistics. Details of scoring and initial handling of missing item scores are included in the EORTC QLQ-C30, QLQ-LC13, QLQ-BN20, and EQ-5D-5L scoring guidelines. Further investigation on patterns of missing data and subsequent sensitivity analysis may be conducted. EORTC QLQ-C30, QLQ-LC13, QLQ-BN20, and EQ-5D-5L questionnaires compliance will be summarized by treatment arm at each time point (and overall).

Health resource utilization will be summarized using descriptive statistics by treatment group in the ITT population.

More details will be described in the SAP.

13.1.6 Safety Analysis

AEs will be summarized using the safety analysis set. Safety assessments will include physical and laboratory examinations, vital signs, and ECGs. AEs will be graded according to the NCI CTCAE v4.03. All patients who receive at least 1 dose of either study treatment (alectinib or brigatinib) will be evaluated for safety. The proportion of patients with at least 1 treatment-emergent AE, treatment-related AEs, and treatment-emergent SAEs will be described, as identified with Preferred Terms and MedDRA System Organ Class. The frequency of occurrence of overall toxicity, categorized by the maximum toxicity grades (severity), will also be described. Listings of laboratory test results and NCI CTCAE grades will be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented.

Exploratory analyses will also be performed on other safety parameters, as deemed appropriate, and within subgroups defined by age, sex, race, mutation status, prior anticancer therapies, medical history, and other prognostic factors.

Exposure to study treatment over time will be summarized with time on treatment, total amount of administrated treatment, dose intensity, and relative dose intensity.

13.2 IA

One IA for efficacy and futility is planned after approximately 70% of the total expected events (progression or death) have been observed. An O'Brien-Fleming Lan-DeMets [42] alpha spending function will be used to control the overall alpha level at 0.05 2-sided. A gamma spending function [43] will be used for the futility stopping boundary. Futility is nonbinding. The IA is planned to be performed after the 115 events have been observed. If the observed HR doesn't meet the prespecified stopping rule for efficacy or futility at the IA then the primary analysis will be conducted after 164 events are observed. The efficacy and futility stopping boundaries used in the analysis will be adjusted based on the actual number of events observed at each analysis using the O'Brien-Fleming Lan-DeMets [42] alpha spending function and gamma spending function [43]. Details of the stopping boundaries will be described in the SAP.

13.3 Determination of Sample Size

For the purposes of this sample size calculation, the median PFS for alectinib is estimated as 9 months and the PFS for brigatinib is estimated to be 15 months on the basis of the outcomes observed in previous single-arm studies (AP26113-13-201 and AP26113-11-101). Approximately 246 patients will be randomized in a 1:1 fashion to receive brigatinib or alectinib. A total of 164 events (progression or death among the randomized patients) will provide 90% power to detect a 6-month improvement in PFS (HR=0.60). This power projection is based on a 2-sided log-rank test, and is controlled at the 2-sided 0.05 level, adjusting for the proposed IA plan. The number of events is fixed, but the enrollment number may change based on an assessment of the overall event rate pooled across treatment groups (before the close of enrollment).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches, such as remote source data verification or telephone contact, may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local health authority and permitted by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or

misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. Refer to the study manual for specific information on protocol deviations.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific

screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or EC.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and before the subject entering into the study. The

subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public

disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European Journal of Cancer 2013;49(6):1374-403.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69-90.
3. American Cancer Society. Cancer Facts & Figures. CA: A Cancer Journal for Clinicians 2018.
4. Francisci S, Minicozzi P, Pierannunzio D, Ardanaz E, Eberle A, Grimsrud TK, et al. Survival patterns in lung and pleural cancer in Europe 1999-2007: Results from the EUROCARE-5 study. Eur J Cancer 2015;51(15):2242-53.
5. Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Altekruse S, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute 2016.
6. Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Kosary C, et al. SEER Cancer Statistics Review, 1975-2014. Published April 2017.
7. Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute Myeloid Leukemia. Version 3.2017. National Comprehensive Cancer Network.
9. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83(5):584-94.
10. Camidge DR, Doebele RC. Treating ALK-positive lung cancer--early successes and future challenges. Nature Reviews Clinical Oncology 2012;9(5):268-77.
11. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448(7153):561-6.
12. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131(6):1190-203.
13. Takeuchi K, Choi YL, Togashi Y, Soda M, Hatano S, Inamura K, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009;15(9):3143-9.
14. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363(18):1693-703.

15. Wong H, Belvin M, Herter S, Hoeflich KP, Murray LJ, Wong L, et al. Pharmacodynamics of 2-[4-[(1E)-1-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl]-3-(pyridine-4-yl)-1H-pyrazol-1-yl] ethan-1-ol (GDC-0879), a potent and selective B-Raf kinase inhibitor: understanding relationships between systemic concentrations, phosphorylated mitogen-activated protein kinase kinase 1 inhibition, and efficacy. Journal of Pharmacology & Experimental Therapeutics 2009;329(1):360-7.
16. XALKORI (crizotinib) [prescribing information]. New York, NY, USA: Pfizer Labs, March 2016.
17. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371(23):2167-77.
18. Gainor JF, Varghese AM, Ou SH, Kabraji S, Awad MM, Katayama R, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res 2013;19(15):4273-81.
19. Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. Clin Cancer Res 2015;21(10):2227-35.
20. Toyokawa G, Seto T. Updated Evidence on the Mechanisms of Resistance to ALK Inhibitors and Strategies to Overcome Such Resistance: Clinical and Preclinical Data. Oncol Res Treat 2015;38(6):291-8.
21. Costa DB, Kobayashi S, Pandya SS, Yeo WL, Shen Z, Tan W, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. Journal of Clinical Oncology 2011;29(15):e443-5.
22. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA, Jr., et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2012;7(12):1807-14.
23. ZYKADIA (ceritinib). Prescribing Information. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 6/2017.
24. ALECENSA (alectinib). Prescribing Information. South San Francisco, CA: Genentech USA, Inc., November 2017.
25. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389(10072):917-29.
26. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017;377(9):829-38.
27. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390(10089):29-39.

28. Shaw A, Peters S, Mok T. Alectinib versus crizotinib in treatment-naive advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study. J Clin Oncol 2017;35(suppl; abstr 9006).

29. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017;376(7):629-40.

30. Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. Cancer Discov 2016;6(10):1118-33.

31. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376(25):2415-26.

32. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368(25):2385-94.

33. Mok T, Kim D, Wu Y, Solomon B, Nakagawa K, Mekhail T, et al. First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014). Journal of Clinical Oncology 2014;32(15_suppl):8002.

34. Felip E, Kim D, Mehra R, Tan D, Chow L, Camidge D, et al. Efficacy and safety of ceritinib in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC). Annals of Oncology 2014;25(suppl_4):iv426-70. 1295P.

35. Mok T, Spigel D, Felip E, deMarinis F, Ahn M-J, Groen H, et al. ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). 2015 ASCO Annual Meeting Abstract. J Clin Oncol 2015;33(suppl).

36. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370(13):1189-97.

37. Alecensa (alectinib). Prescribing Information. San Francisco, CA, US: Genentech USA, Inc., Revised November 2016.

38. Ou SH, Greenbowe J, Khan ZU, Azada MC, Ross JS, Stevens PJ, et al. I1171 missense mutation (particularly I1171N) is a common resistance mutation in ALK-positive NSCLC patients who have progressive disease while on alectinib and is sensitive to ceritinib. Lung Cancer 2015;88(2):231-4.

39. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17(2):234-42.

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

41. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958;53:457-81.

42. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13(13-14):1341-52; discussion 53-6.

43. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9(12):1439-45.

44. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

Appendix A Schedule of Events

Schedule of Events

Assessment	Screening Period	Treatment Through 30 Days After Last Dose									Follow-up Period
	Screening (Note: Tumor assessments must be 21 days before Day 1)	Cycle 1 [a]			Cycles 2 and 3		Day 1 of Every Cycle Starting C4D1	Every 2 Cycles	End-of-Treatment [b]	30 Days After Last Dose	Follow-up
Day	**D -28 to D0**	**D1**	**D8**	**D15**	**D1**	**D15**					
Informed consent (may be 28 days before D1)	X										
Demographics	X										
Medical/surgical history	X										
Diagnosis and cancer history [c]	X										
Prior cancer therapy	X										
Archival (banked) tumor tissue sample (patients with local non–FDA-approved *ALK* testing and patients who agree to optional genetic testing)	X										
Fresh FFPE tumor tissue biopsy sample [d]	X *(only if archival tumor tissue is not available)*								X [e, m] (optional at time of progression)		
Plasma sample for ctDNA *(DNA for NGS analysis including but not limited to ALK mutations)*	X				C3D1 only				X [m] (at time of progression)		
PE (screening and end-of-treatment will be complete PE, rest may be symptom directed) [f]	X	X	X [g]		X		X		X	X	
Height	X										
Weight	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	

Assessment	Screening Period	Treatment Through 30 Days After Last Dose									Follow-up Period
	Screening (Note: Tumor assessments must be 21 days before Day 1)	Cycle 1 [a]			Cycles 2 and 3		Day 1 of Every Cycle Starting C4D1	Every 2 Cycles	End-of-Treatment [b]	30 Days After Last Dose	Follow-up
Day	**D -28 to D0**	**D1**	**D8**	**D15**	**D1**	**D15**					
Hematology	X	X			X		X		X	X	
Chemistry	X	X		X [h]	X	X [h]	X		X	X	
Insulin (fasting, if possible)	X	X			X		X		X	X	
ECG	X								X		
Brigatinib (Arm A only)		ONCE DAILY ORAL DOSE									
Alectinib (Arm B only)		TWICE-DAILY ORAL DOSE (with food)									
AEs	Throughout study [g]										
Concomitant medications	Throughout study										
Pregnancy test [i] (must be within 7 days before D1)	X	X						X (every 12 weeks)	X		
Disease assessment (this may be 21 days before D1)	X							X (every 8 weeks through Cycle 12 then every 12 weeks thereafter)	X [n]		
Plasma sample for brigatinib PK (Arm A only)	Please refer to Appendix A, PK Sampling Schedule										
PRO assessment [j] and HRU	X	X			X		X		X	X	EQ-5D-5L only
Review patient diary with patient [k]		X [k]			X		X				
Subsequent anticancer therapy /survival [l]											X (every 12 weeks) [l]

For details regarding any item on the Schedule of Events, please refer to Section 9.3, Study Procedures, of this protocol.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; C, Cycle; ctDNA, circulating tumor DNA; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL–5 Dimensions–5 Levels; FDA, Food and Drug Administration; FFPE, formalin-fixed, paraffin-embedded; HRU, health resource utilization; NGS, Next Generation Sequencing; PE, physical examination; PK, pharmacokinetics; PRO, patient-reported outcomes; QD, once daily; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-LC13, Quality of Life Lung Cancer Module; QLQ-BN20, Quality of Life Brain Cancer Module.

[a] 1 cycle = 28 days. The allowed visit day window is ±3 days, starting from Cycle1 Day 15, with the exception of disease assessment. There is no window for C1D8.

[b] This visit shall be scheduled with a ±7-day window. If patient's last dose equals or is 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 1 visit.

[c] The medical history needs to include the detail of prior treatment, starting and ending time, and the best response to each treatment. The assay and sample type of prior *ALK* test will also be collected.

[d] Exploratory biomarker studies (including *ALK* mutation status) will be performed on tissue biopsy obtained after progression on crizotinib but before start of study treatment. Tissue can be obtained as part of standard of care or as an optional screening biopsy in this study. The collection of this tissue is not mandatory, but highly encouraged. An optional biopsy will also be taken at time of progression on brigatinib and alectinib for patients who consent to the procedure and test. FFPE tumor tissue will be used for exploratory molecular genetic analysis.

[e] Exploratory biomarker studies (including ALK mutation status) will be performed on tissue biopsy, taken at time of progression on brigatinib and alectinib for patients who consent to the procedure and test. FFPE tumor tissue will be used for exploratory molecular genetic analysis.

[f] Physical examination, ECOG performance status assessments, hematology, chemistry, insulin, and pregnancy tests do not need to be repeated on Cycle 1, Day 1 if they were performed for screening within 7 days before Cycle 1, Day 1 and, in the opinion of the investigator, there is no reason to believe they have substantially changed.

[g] Assessment for early pulmonary symptoms must be performed during the visit on Day 8 before receiving study drug.

[h] Only aspartate aminotransferase/alanine aminotransaminase and total bilirubin will be evaluated at this visit.

[i] Pregnancy tests will be performed for women of childbearing potential at screening. The test must be known to be negative before the study drug administration and be performed within 7 days before first study drug administration (Cycle 1, Day 1). The pregnancy tests must be a beta-human chorionic gonadotropin test, and either urine or serum can be used. Women of childbearing potential at study start must also complete the pregnancy test once every 12 weeks (3 cycles) ±7 days thereafter and at the end-of-treatment visit. Additional pregnancy testing should be performed if recommended or required per local guidelines or regulations.

[j] PRO assessments: EORTC QLQ-C30 (v3.0) and its lung cancer module, QLQ-LC13, items of QLQ-BN20, and EQ-5D-5L questionnaires will be administered at baseline, per the Schedule of Events throughout the study, and at the 30 days after last dose visit. The questionnaires should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed. The EQ-5D-5L will be administered in the follow-up period.

[k] On C1D1 site staff will explain to the patient how to complete the patient diary.

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

[m] If study treatment is stopped for a reason other than disease progression, the re-biopsy or plasma for ctDNA shall be collected after confirmed disease progression occurs.

[n] 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 continue to occur at the same schedule; however, the sponsor does not require further tumor assessment data to be collected.

PK Sampling Schedule (Arm A only)

The PK samples outlined in the schedule below are to be collected in all patients randomized to the brigatinib arm (Arm A) of the study. For patients randomized to the alectinib arm of the study (Arm B), no PK samples are to be collected at any time point during the study.

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 hours before dosing)		X	X	X	X	X
1 hour postdose (±15 minutes)	X	X	X			
4 hours postdose (±30 minutes)	X	X	X			

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. (This responsibility lies on the appropriate individual, designated by the site in Japan.)
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

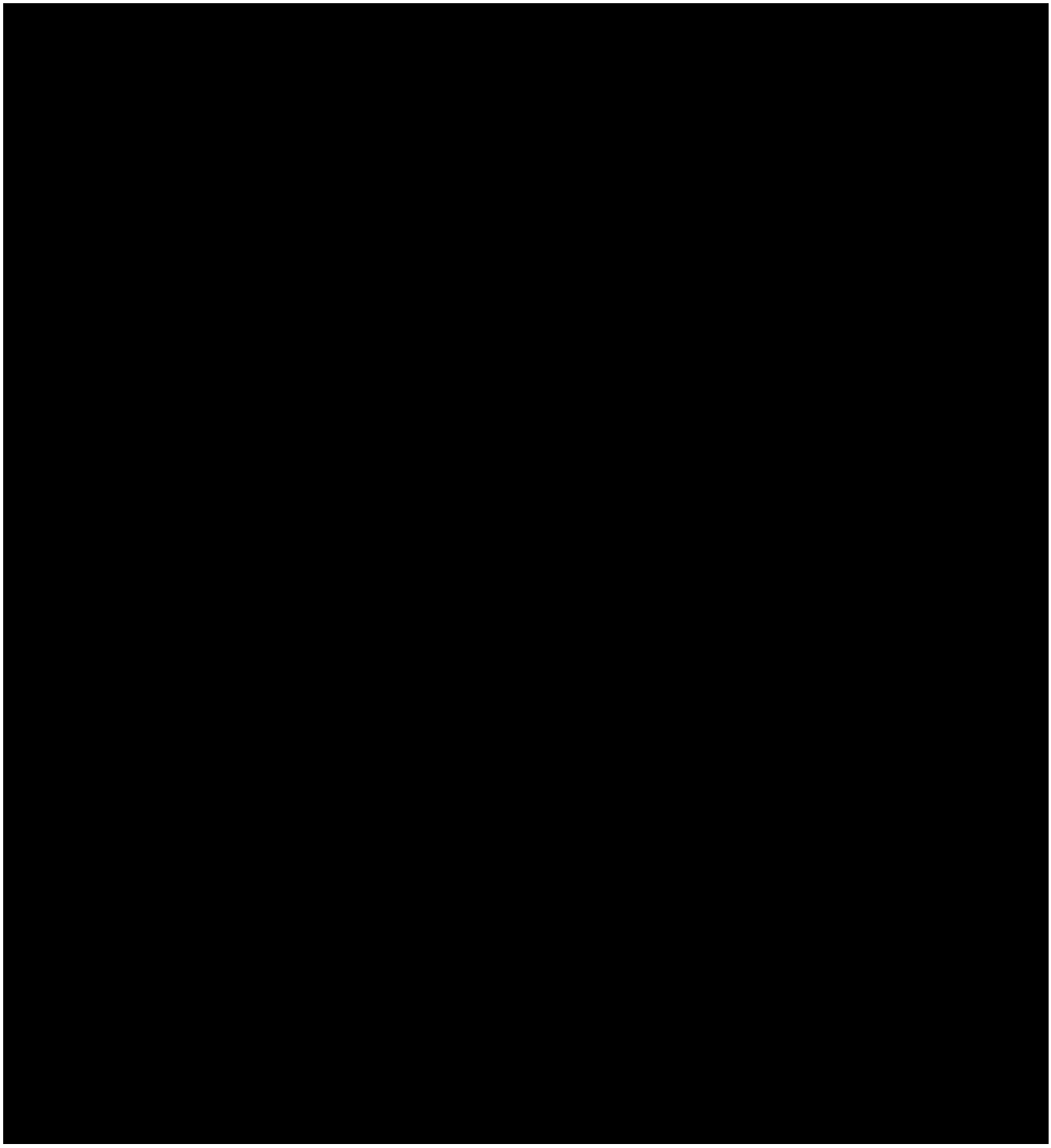
Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E RECIST (Version 1.1)

Note: These criteria are adapted from Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eu J Cancer 2009;45:228-247.



Appendix F Modification of Diet in Renal Disease Equation for Estimated Glomerular Filtration Rate

The following is the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) equation (for creatinine methods calibrated to an IDMS reference method):

GFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Abbreviations: GFR, glomerular filtration rate; Scr, serum creatinine.

Levey et al, 2006 [44].

Appendix G Protocol History

Date	Amendment Number	Amendment Type	Region
08 March 2021	4	Substantial	Global
09 March 2020	3	Substantial	Global
07 June 2019	2	Substantial	Global
11 January 2019	1	Nonsubstantial	Germany
15 May 2018	Initial Protocol	Not applicable	Global

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

- Change the legal entity of the sponsor and the name of study lead due to a company level change.
- Incorporate the recommendation from the United States (US) Food and Drug Administration (FDA) for the endpoint of "time to intracranial disease progression (iPD)," which will no longer be a key secondary endpoint and was removed from hierarchical testing. The ordering of secondary objectives and endpoints were revised to reflect this change.
- Provide clarification for some of the protocol language.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 3

The following is a summary of changes made in the amendment:

- Updated sponsor information from ARIAD Pharmaceuticals, Inc to Takeda Development Center Americas, Inc.
- Changed the clinical study lead to [redacted], MD, on signatory page.
- Removed "time to intracranial progressive disease (iPD)" from the key secondary endpoints and revised the order of other secondary endpoints. The order of secondary objectives was revised to match the order of key and other secondary endpoints.
- Clarified throughout the protocol that the treatment will continue until "progressive disease (PD) assessed by the investigator."
- Removed statements about "End of Study/Study Completion Definition, and Planned Reporting," "Primary Completion/Study Completion," and "Study Completion," and unified the terms in Section 6.3.1 for the definition of "End of Study" and "Primary Completion."
- Specified that timing for exclusion criteria 2 (crizotinib use) and 7 (chemotherapy or radiation therapy) was before randomization.

- Added new exclusion criterion 7 (other primary malignancies other than NSCLC) and renumbered subsequent criteria.
- Clarified that timing for exclusion criterion 11 (symptomatic central nervous system metastases; formerly exclusion criterion 10) was a minimum of 7 days.
- Clarified the required test to support protocol exclusion criteria 18 (formerly exclusion criterion 17) for an active hepatitis B virus/hepatitis C virus infection.
- Clarified requirement that both brigatinib and alectinib be administered at approximately the same time every day and added detail regarding dose-limiting AEs.
- Clarification for dose modification for AEs and clarifications that if the brigatinib dose cannot be escalated to 180 mg QD due to AE, 90 mg QD should be administered throughout the study.
- Clarification for pulmonary events occurring within the first 7 days of treatment regarding ruling out other etiologies including rapid disease progression for assessing relation to treatment.
- Clarification for alectinib dose discontinuation due to AEs.
- Provided additional information regarding the use of moderate CYP3A inducers and alternative or herbal therapy after consultation with and approval by the sponsor.
- Clarification for disease assessment in patients who discontinue study drug for reasons other than PD.
- Corrected total blood volume collection for DNA measurements.
- Added requirement for acknowledgment of receipt when reporting AEs and SAEs by facsimile.
- The secondary endpoint analyses were revised to reflect that iPD will no longer be a key secondary endpoint and was removed from hierarchical testing.
- Minor editorial revisions were made for clarification throughout the document.

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Change the current secondary endpoint for intracranial progression-free survival (iPFS) to time to intracranial progression (iPD) without prior systemic progression per advice from the United States Food and Drug Administration (US FDA).
- To clarify the dose modification table for treatment-related adverse events (Table 8.b) and provide consistency with the Company Core Data Sheet (CCDS) for brigatinib and to provide clarity on allowed dose levels.

- To add an additional week of testing of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin levels (Cycle 3 Week 15) to align with the latest Summary of Product Characteristics (SmPCs) for both brigatinib and alectinib.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification purposes only.

Changes in Amendment 2

- Update title to reflect brigatinib (Alunbrig®) registration.
- Changed the terminology from intracranial progression-free survival (iPFS) to time to intracranial progressive disease (iPD) without prior systemic progression or death.
- Updated the date that patient enrollment began.
- Updated inclusion criterion #1 to clarify gender and age eligibility requirements.
- Clarified inclusion criterion #8 regarding prior systemic anticancer therapy.
- Updated the guidance regarding female contraception.
- Updated Dose Modification Table 8.b.
- Updated Excluded Medications to include moderate CYP3A inhibitors and to provide further guidance to investigators.
- Added information regarding administration of brigatinib with certain concomitant medications.
- Provided explanation for not implementing double-blind design.
- Clarified screening procedures and visit windows.
- Provided additional guidance regarding clinical laboratory evaluations.
- Clarified procedures related to confirmatory imaging.
- Added Biomarker Sample Retention section.
- Clarified health-related quality of life assessment for follow-up period.
- Provided additional guidance regarding posttreatment follow-up assessments.
- Revised AE Definition section.
- Removed the term “confirmed” from references to the ORR endpoint and remove the term "median" from references to study endpoints to be estimated using the Kaplan-Meier method.
- Removed Japan-specific instructions.
- Corrected Schedule of Event Column Heading for Cycles 2 and 3 and Cycle 4.
- Added footnotes to Appendix A regarding biomarker sample collection and disease assessment after confirmed disease progression occurs.

- Added Appendix F Modification of Diet in Renal Disease Equation for Estimated Glomerular Filtration Rate.

Protocol Amendment 1 was a local amendment and is not applicable to the global protocol.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	09-Mar-2021 14:09 UTC
[redacted]	Clinical Approval	09-Mar-2021 15:00 UTC
[redacted]	Biostatistics Approval	09-Mar-2021 15:13 UTC
[redacted]	Clinical Pharmacology Approval	09-Mar-2021 15:23 UTC