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

NCT Number: NCT03535740

Protocol Approve Date: 24 September 2020

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

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

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

PROTOCOL

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

Sponsor: ARIAD Pharmaceuticals, Inc
a wholly owned subsidiary of Takeda
Pharmaceutical Company Limited
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Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000

Study Number: 2002

IND Number: IND 110,935 **EudraCT Number:** 2018-000635-27

Compound: Brigatinib (AP26113)

Date: 24 September 2020 Amendment 4

Version Number: 1.0

Amendment History

Date	Amendment Number	Type	Region
18 September 2020	4	Substantial	Global
27 September 2019	3	Substantial	Global
10 April 2019	2	Substantial	Global
11 December 2018	1 DE v1	Nonsubstantial	Germany
12 October 2018	1 SE v1	Nonsubstantial	Sweden
03 May 2018	1	Nonsubstantial	Global
22 February 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 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 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.

PPD

1.3 Protocol Amendment 4 Summary and Rationale

This section describes the changes in the protocol incorporating Amendment 4. The primary reasons for this amendment are to maintain patient safety, confidentiality, and study integrity in the context of healthcare challenges presented by the coronavirus disease 2019 (COVID-19) public health emergency. This amendment allows investigators and study personnel to conduct visits remotely, deliver study drug directly to patients, use local laboratory and imaging results if patients are unable to travel to the investigative site, and remotely access patient records for data monitoring as necessary during the COVID-19 public health emergency.

Secondly, the dose modification for Grade 3 and 4 creatine phosphokinase (CPK) elevations without concurrent muscular toxicity was deemed no longer warranted.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are also included.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location(s)	Description	Rationale
Section 8.1 Study Drug Administration	Added text: In extenuating circumstances, such as during the COVID-19 public health emergency, additional drug supply may be provided to the subjects to cover 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 (direct-to-patient [DTP] shipment) in agreement with Takeda processes and local health authorities. Before initiation of the DTP process, patients will agree to participate in this process. Patients will sign a separate acknowledgment of receipt form permitting this process and agree to share limited personal information with the delivery courier. The investigator and courier must ensure that no private patient information is shared with the sponsor or other CROs participating in the study. The local independent review board (IRB)/independent ethics	To maintain patient safety, confidentiality, and study integrity in the context of healthcare challenges presented by the COVID-19 public health emergency. This amendment allows investigators and study personnel to conduct visits remotely, deliver study drug directly to patients, and to use local laboratory and imaging results if patients are unable to travel to the investigative site.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location(s)	Description	Rationale
	committee (IEC) must be notified, as applicable per local requirements, that this process is being initiated, and sites must clearly document the chain of custody of any study drug dispensed directly to patients.	
Section 9.4 Study Procedures	Added text: Sites will make every effort to see patients in the clinic to complete all study-specified assessments as outlined in the Schedule of Events (SOE) (Appendix A). In unavoidable circumstances, such as during the COVID-19 public health emergency, exceptions can be made for alternative methods for conducting patient visits and performing laboratory and imaging assessments. Remote visits may be performed via telehealth or telemedicine as a safety check on subject well-being. Remote visits and telemedicine or telehealth must comply with Takeda processes and local health authorities. This will be recorded in the eCRF and in the study records. In extenuating circumstances, such as during the COVID-19 public health emergency, local laboratory results and imaging assessment may be used. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records. Missed clinic visits or subject withdrawals due to COVID-19 must be recorded in the protocol deviation report and eCRF, as applicable.	
Section 9.4.1 Informed Consent	Added text: Before initiation of the DTP process, patients will agree to participate in this process as described in Section 8.1.	
Section 9.8	Added text: In extenuating	

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Section(s) Affected by Change	**Description of Each Change and Rationale**	
Location(s)	Description	Rationale
Study Compliance	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 as described in Section 8.1.	
Section 12.1 eCRFs **Section 14.1 Study-Site Monitoring Visits**	In extenuating circumstances, such as during the COVID-19 public health emergency, direct, suitably controlled remote access to patients' electronic medical records may be used for data monitoring. Only pseudonymized documents may be shared through a cloud-based system. Videoconferencing may be used for remote site data verification, but copying or recording of the video and/or documents (eg, screen captures) is not permitted. These procedures will be documented in the Monitoring Plan.	
Table 8.b	Revised: ~~Grade 4 CPK elevation (greater than 10.0 × ULN) or recurrence of Grade 3 elevation~~ ~~• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume brigatinib at next-lower dose (Table 8.a).~~ ~~• If Grade 4 elevation of CPK recurs, permanently discontinue brigatinib.~~	The dose modifications for Grade 4 CPK elevation or recurrence of Grade 3 CPK elevation were changed to align with the Company Core Data Sheet. An analysis of data from Studies AP26113-13-301 and AP26113-13-201 suggested that CPK increases were associated with longer duration of treatment and did not seem to be associated with the frequency of muscular toxicity. In a review of individual patient data from these studies, only 1 patient reported a Grade 3 CPK elevation as well as a Grade 3 muscular toxicity (PT: muscular toxicity). Additionally, many of the 49 patients from these studies with a Grade ≥3 CPK elevation did not report a muscular toxicity event (any grade or Grade ≥3).

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 serious adverse events 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)

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2.0 STUDY SUMMARY

Name of Sponsor(s): ARIAD Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** Brigatinib (AP26113)	
Title of Protocol: Brigatinib in Patients With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non–Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib	**IND No.:** 110,935	**EudraCT No.:** 2018-000635-27
Study Number: 2002	**Phase:** 2	

Study Design:

A phase 2, open-label, single-arm, multicenter, international study in patients with ALK+ NSCLC whose disease has progressed on prior alectinib *or* ceritinib.

Primary Objective:

To determine the efficacy of brigatinib, as evidenced by confirmed objective response rate (ORR), in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib.

Secondary Objectives:

1. To characterize the durability of efficacy with brigatinib.
2. To assess intracranial efficacy of brigatinib.
3. To assess the overall survival (OS).
4. To assess the safety and tolerability of brigatinib.
5. To collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic analyses.
6. To assess patient-reported symptoms and health-related quality of life (HRQOL).

CCI [redacted]

Study Endpoints

Primary Endpoint:

The primary endpoint is confirmed ORR, as assessed by the IRC, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the full analysis set population.

Secondary Endpoints:

1. Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.
2. DOR as assessed by the investigator and IRC.
3. PFS as assessed by the investigator and IRC.
4. Disease control rate (DCR), defined as best overall response of complete response (CR), partial response (PR) or stable disease (SD) ≥6 weeks by RECIST version 1.1, as assessed by the investigator and IRC.
5. Time to response as assessed by the investigator and IRC.
6. Confirmed iORR in patients with brain metastases at baseline, as assessed by the IRC.
7. Duration of intracranial response in patients with brain metastases at baseline, as assessed by the IRC.
8. Intracranial progression-free survival (iPFS) in patients with brain metastases at baseline, as assessed by the IRC.
9. OS.

Note: The efficacy endpoints will be analyzed in the full analysis set and in a subgroup of patients who progressed on prior alectinib. Additional details about subgroup analyses will be provided in the statistical analysis plan (SAP).

1. Safety/tolerability (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03).
2. HRQOL assessed with the global health status/quality of life (QOL) and other function and symptom from EORTC QLQ-C30 (version 3.0), and EORTC QLQ-LC13.

CCI [redacted]

Subject Population: Adult patients with ALK+ NSCLC whose disease has progressed on prior alectinib or ceritinib (with or without prior crizotinib and no more than 3 different systemic regimens as treatment for locally advanced/metastatic disease).

Number of Subjects:	**Number of Sites:**
Approximately 103	The study is planned to be conducted internationally.
Dose Level(s): Brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD. Patients who progressed on brigatinib 180 mg QD dose, did not experience toxicity Grade >2, and signed a separate informed consent will be given the option to receive brigatinib at an increased dose of 240 mg QD.	**Route of Administration:** Oral
Duration of Treatment: Patients will continue to be treated with brigatinib until they experience objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, or intolerable toxicity. Upon radiological progression, at the discretion of the investigator, patients who were receiving brigatinib at a dose of 180 mg and have not experienced toxicity greater than Grade 2 during the treatment may elect to receive brigatinib at an increased dose of 240 mg QD, or continue study treatment at the current dose in case they are still benefiting from the treatment at this dose. In both scenarios, sponsor medical monitor will review and approve the case.	**Period of Evaluation:** Efficacy: Radiological tumor assessment to chest, abdomen, brain and any other tumor metastatic sites will be performed every 8 weeks for the 52 weeks (14 cycles) and every 12 weeks after, until the radiological disease progression is identified. Safety: Treatment-emergent adverse events will be collected from informed consent form signoff to 30 days after last dose. After this period, only study drug-related serious adverse events will be collected.

Main Criteria for Inclusion:

1. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for curative therapy) or stage IV NSCLC.
2. Must meet both of the following 2 criteria:
   a) Have documentation of ALK rearrangement by a positive result from any laboratory test approved by the Food and Drug Administration (FDA) (eg, the Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit or the Ventana ALK [D5F3] CDx [companion diagnostic] Assay or Foundation Medicine's FoundationOne CDx)

      or

      Have documented ALK rearrangement by a different test (non–FDA-approved local lab tests) and have provided tumor sample to the central laboratory (Note: Central laboratory ALK rearrangement testing results are not required to be obtained before randomization.)

   b) The patient had been treated with any 1 of the ALK tyrosine kinase inhibitors (TKIs) (alectinib, ceritinib, crizotinib) for at least 12 weeks before progression.
3. Had progressive disease while on alectinib or ceritinib (defined as no more than 1 month from last dose of alectinib or ceritinib to disease progression, as assessed by the investigator or treating physician). (Number of patients not previously treated with alectinib will be capped at 10 for every 30 patients enrolled.)
4. Had alectinib or ceritinib as the most recent ALK inhibitor therapy. Chemotherapy before or after progression on alectinib or ceritinib is allowed.
5. Have at least 1 measurable lesion per RECIST version 1.1 as assessed by the investigator.
6. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 Grade ≤1. (Note: Treatment-related alopecia or peripheral neuropathy that are Grade >1 are allowed if deemed irreversible.)
7. Have Eastern Cooperative Oncology Group performance status ≤1.
8. Have adequate organ and hematologic function.

Main Criteria for Exclusion:

1. Received any prior ALK-targeted TKI other than crizotinib, alectinib, or ceritinib.
2. Received both alectinib and ceritinib.
3. Received crizotinib, alectinib, or ceritinib within 7 days of the first dose of brigatinib.
4. Previously received more than 3 regimens of systemic anticancer therapy for locally advanced or metastatic disease.

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. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this (neo-)adjuvant therapy.

1. Have symptomatic brain metastasis (parenchymal or leptomeningeal). Patients with asymptomatic brain metastasis or who have stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the past 7 days before the first dose of brigatinib may be enrolled.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is confirmed ORR, as assessed by the independent review committee, per RECIST version 1.1 in full analysis set.

Statistical Considerations:

The purpose of this phase 2 study is to determine the confirmed ORR of orally administered brigatinib at current clinical doses (≤180 mg QD) in patients with ALK+ NSCLC whose disease progressed after therapy on alectinib or ceritinib. The sample size was determined so that it would allow for stating that the true ORR (expected response rate) is greater than the threshold response rate of 20% for patients previously treated by alectinib or ceritinib. A sample size of 103 patients will be enrolled. This sample size was calculated to provide at least 90% power to rule out an uninteresting ORR of 20%, assuming the true ORR is 35%. The calculation is based on an exact binomial test

with a one-sided alpha level of 0.025 at primary endpoint analysis, allowing for dropout.

The final analysis of the primary endpoint will be conducted approximately 6 months after the last patient is enrolled. ORR will be tested at a one-sided alpha of 0.025. If the primary endpoint is achieved in patients previously treated with alectinib or ceritinib, then a subgroup analysis of confirmed ORR in patients previously treated with alectinib will be performed and tested at a one-sided alpha of 0.025.

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, their 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
BCRP	breast cancer resistance protein
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P-450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
DTP	direct-to-patient
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOPE	early onset pulmonary event
EORTC	European Organization for Research and Treatment of Cancer
EQ VAS	European Quality of Life Scale 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
GI	gastrointestinal
HRQOL	health-related quality of life
HU	health resource utilization
IB	investigator's brochure
IEC	independent ethics committee
ICF	informed consent form
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
iORR	intracranial objective response rate

iPFS	intracranial progression-free survival
IRB	institutional review board
IRC	independent review committee
KD	kinase domain
LD	longest diameter(s)
MATE	multidrug and toxin extrusion protein
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
OCT1	organic cation transporter 1
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PTE	pretreatment event
QD	once daily
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameters
SOE	Schedule of Events
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States

3.4 Corporate Identification

ARIAD	ARIAD PHARMACEUTICALS INC, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

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), which was 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 end of 2018, and 154,050 deaths due to the disease are estimated to occur [3]. In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 and 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 (Center for Cancer Control and Information Services, National Cancer Center, 2017). Most lung cancer cases are diagnosed at advanced stages and about 78% of newly diagnosed patients have regional/distant disease [1] [5].

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 nearly 85% of all lung cancers [6,7], and includes a number of subtypes such as adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and bronchioloalveolar carcinoma [8]. In recent years, attention has turned to stratifying lung cancer patients 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, anaplastic lymphoma kinase-rearranged (ALK+), c-ros oncogene 1 (ROS1) rearranged, or BRAF V600E mutant NSCLC. The focus herein is on NSCLC that contains oncogenic rearrangements in the ALK gene, and the role of brigatinib, a novel small-molecule inhibitor, in the treatment of ALK+ NSCLC.

4.1.2 ALK+ NSCLC

ALK is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults [9]. The first genetic rearrangement of ALK seen in NSCLC involved a fusion between the *EML4* gene and the ALK tyrosine kinase domain (KD). EML4-ALK has the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts to induce tumor formation [10]. 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 [11,12].

Estimates of the frequency of ALK rearrangement in the overall population of NSCLC patients range from 2% to 7% [13,14], which represent, on the basis of proportionality of total populations in the US and EU, approximately 7000 to 25,000 ALK+ NSCLC patients in the US

and 5800 to 20,000 patients in the EU 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 Kirsten rat sarcoma virus oncogene [9].

4.1.3 Current Treatment for ALK+ NSCLC

While the standard treatment algorithm for unselected NSCLC patients 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 [15].

The efficacy of crizotinib has been confirmed in a randomized study of crizotinib versus chemotherapy [15,16].

ALK-dependent mechanisms of resistance, observed in approximately 30% of patients [17], 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 [18,19]. The central nervous system (CNS) is the first site of progression in approximately 50% of patients treated with crizotinib [20,21], 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 [22] and alectinib [23], have become available for NSCLC patients with ALK rearrangements. Both drugs are effective in patients previously treated with crizotinib. Ceritinib demonstrated significantly improved progression-free survival (PFS) versus chemotherapy (hazard ratio 0.55) [24] whereas alectinib demonstrated significantly improved PFS versus crizotinib (hazard ratio 0.34-0.47) [25,26] 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 [18,27-30].

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

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 on these TKIs. The alternative treatments for these patients include chemotherapy and checkpoint inhibitors (PD-1 or PD-L1 antibody). The efficacy of platinum doublet chemotherapy seems not to be impacted by prior TKI treatment, but the efficacy was limited with a response rate of about 30% and median PFS of about 4 months [32]. Checkpoint inhibitors have been introduced into the market recently 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 [33], possibly related to low mutation burden in this population characterized by nonsmoking status [34].

There is still high unmet medical need for these ALK+ NSCLC patients progressed on alectinib or ceritinib to have access to an efficacious targeted therapy (evidenced by higher ORR and durable responses) and adequate CNS penetration with robust intracranial responses. Such a new therapeutic option could prolong disease control and translate into improved long-term outcomes including longer PFS. These efficacy attributes of a new therapy, along with a favorable safety profile, are needed for this patient population.

4.2 Brigatinib

Brigatinib (AP26113) is a novel, orally administered (PO) 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 a greater than 100-fold selectivity over ALK-negative lines.

In clinical study, 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 presented 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 duration of response (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 intracranial objective response rate (iORR) (66.7%, 12 of 18, 95% CI: 41.0, 86.7) with a median 16.6 months (95% CI: 3.7, Not Reached) duration of intracranial response 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 (ALUNBRIG) for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant of crizotinib.

4.3 Rationale for the Proposed Study

Second-generation ALK TKIs, including alectinib and ceritinib, have shown efficacy, including durable response to intracranial lesions, and have an acceptable safety profile in both ALK TKI treatment-naïve and pretreated patients. Both alectinib and ceritinib were approved as first-line treatment for ALK+ advanced NSCLC in US and European countries. However, resistance to alectinib and ceritinib develops eventually, with emergence of secondary resistant mutations detected in approximately 50% of patients [33].

Brigatinib (AP26113) is a novel, synthetic, orally active ALK TKI. A pre-clinical study [35] revealed that assessed at concentrations relative to the level of exposure achieved in patients at the approved or recommended phase 2 doses, brigatinib was the most potent inhibitor compared with crizotinib, ceritinib, and alectinib. Brigatinib inhibits 17 clinically and preclinically observed crizotinib-, ceritinib- and/or alectinib-resistant ALK mutations. Compared with these 3 ALK TKIs, brigatinib also exhibited superior preclinical activity when in vitro potencies were related to steady-state plasma level of each drug achieved in patients at the approved dose. Among the 4 ALK TKIs tested, brigatinib was the only TKI to maintain substantial activity against the most recalcitrant G1202R mutant in vivo. Brigatinib also has activity in a mice orthotopic brain model metastasis.

In the ALTA study, the 90 mg QD→180 mg QD treatment regimen was associated with a higher confirmed ORR and longer PFS, as well as improved intracranial efficacy, as compared with the 90 mg QD regimen. Therefore, there appears to be a relationship between dose/exposure and efficacy, which suggests that higher brigatinib doses may result in better efficacy. However, higher brigatinib doses/exposures were associated with some treatment-related Grade 3 or higher adverse events (AEs) (eg, increased creatine phosphokinase [CPK], skin and subcutaneous tissue disorders and rash) (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208772Orig1s000TOC.cfm). A 240 mg QD dose of brigatinib was determined to be the highest acceptably tolerated dose in Study AP26113-11-101. As a result, in the present study, patients who progress on brigatinib 180 mg QD will have the option to receive brigatinib at an increased dose of 240 mg QD in an effort to provide better mutational coverage. Patients will be allowed to receive only the 240 mg QD brigatinib dose postprogression if they have not experienced toxicities greater than Grade 2 after the 180 mg brigatinib dose.

The rationale for escalation to 240 mg QD at disease progression is to provide an opportunity at progression for treatment at higher exposures of brigatinib that may consequently provide clinical benefit through a greater degree of antitumor activity compared to 180 mg and/ or to attempt to overcome potential pharmacologic resistance at 180 mg QD brigatinib (ie, to increase brigatinib exposure in order to have better activity against a given ALK KD resistance mutation or for increased exposure in the CNS).

In study AP26113-11-101, 10 patients were enrolled to receive brigatinib 240 mg QD, of which 1 patient experienced a dose-limiting toxicity (DLT) of Grade 3 alanine aminotransferase (ALT) elevation. Treatment-emergent adverse events (TEAEs) leading to dose interruption, reduction, or discontinuation occurred at similar rates for patients dosed at 90 mg QD→180 mg QD (56.3%

[18 of 32], 18.8% [6 of 32], and 12.5% [4 of 32], respectively) and 240 mg QD brigatinib (50.0% [5 of 10], 20.0% [2 of 10], and 10.0% [1 of 10], respectively). Common TEAEs were similar for patients dosed at 90 mg QD→180 mg QD and 240 mg QD brigatinib and included gastrointestinal [GI], constitutional, and pulmonary events. Data from studies AP26113-11-101 and AP26113-13-201 indicate the incidence of early onset pulmonary events (EOPEs) is related to the initial dose of brigatinib, but EOPEs have not been observed upon dose escalation (ie, 90 mg QD→180 mg QD regimen). Therefore, it is expected that patients who tolerate brigatinib at 180 mg QD and then escalate to 240 mg QD will not have an increased risk of EOPEs after escalation.

In separate but similar studies, ALK+ patients taking brigatinib after progressing on crizotinib, had a longer median PFS as assessed by IRC (15.6 months, 95% CI: 11.1, 21.0, ALTA study, data cut: 29 September 2017) than those taking alectinib (8.9 months, [36] and 7.1 months, [37], both by IRC assessment) or ceritinib (5.7 months, by investigator assessment, [38]).

On the basis of nonclinical and clinical data, brigatinib may be efficacious in patients who developed resistant mutations to alectinib or ceritinib or those who do not respond to alectinib or ceritinib because of pharmacologic resistance. This phase 2 study is designed to assess the clinical efficacy and safety of brigatinib in ALK+ advanced NSCLC patients who have progressed on alectinib or ceritinib.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of the study is to determine the efficacy of brigatinib, as evidenced by confirmed ORR, in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib.

5.1.2 Secondary Objectives

The secondary objectives are:

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

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is confirmed ORR, as assessed by the IRC, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the full analysis set (see Section 13.1.1.1).

5.2.2 Secondary Endpoints

The secondary endpoints are:

1. Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.
2. DOR as assessed by the investigator and IRC.
3. PFS as assessed by the investigator and IRC.
4. Disease control rate (DCR), defined as best overall response of complete response (CR), partial response (PR) or stable disease (SD) ≥6 weeks by RECIST version 1.1, as assessed by the investigator and IRC.
5. Time to response as assessed by the investigator and IRC.
6. Confirmed iORR in patients with brain metastases at baseline, as assessed by the IRC.
7. Duration of intracranial response in patients with brain metastases at baseline, as assessed by the IRC.
8. Intracranial progression-free survival (iPFS) in patients with brain metastases at baseline, as assessed by the IRC.
9. OS.

   Note: The efficacy endpoints will be analyzed in full analysis set and in a subgroup of patients who progressed on prior alectinib treatment (see Section 13.1.5). Additional details about subgroup analyses will be provided in the statistical analysis plan (SAP).
10. Safety/tolerability (CTCAE version 4.03).
11. HRQOL assessed with the global health status/quality of life (QOL) and other function and symptom from EORTC QLQ-C30 (version 3.0), and EORTC QLQ-LC13.

CCI

[redacted]

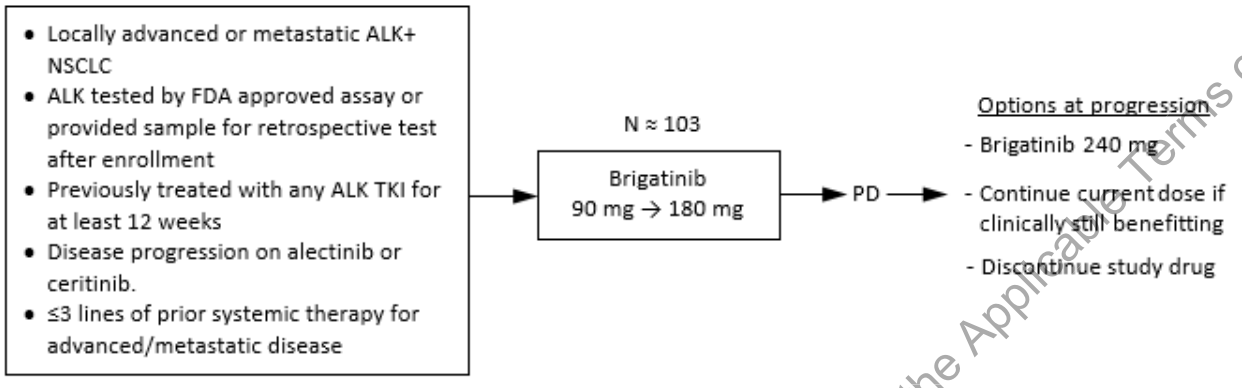
6.0 STUDY DESIGN

6.1 Overview of Study Design

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

It is expected that approximately 103 patients will enroll in this study initially. Once enrolled, patients will be treated with brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD. The study scheme is outlined in Figure 6.a.

Figure 6.a Study Design



Abbreviations: ALK+, anaplastic lymphoma kinase positive; NSCLC, non–small-cell lung cancer; FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitor, PD, progressive disease.

ALK+ by central laboratory is not required before enrollment.

Strongly encourage (but not mandate) re-biopsy at screening and at progression. Plasma sample to be collected at screening, Cycle 3 Day 1 and Cycle 5 Day 1 and at progression.

CCI [redacted]

Patients will continue to be treated with brigatinib until they experience objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity. Upon radiological progression, at the discretion of the investigator, patients who are receiving brigatinib 180 mg QD and have experienced toxicities no greater than Grade 2 during treatment may elect to increase the brigatinib dose to 240 mg QD, or continue study treatment at their current dose if they are still benefiting from treatment at this dose (eg, absence of clinical symptoms or signs indicating clinically significant disease progression requiring alternative systemic anti-cancer therapy; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [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 both scenarios (increase dose or continue at same dose), the medical monitor shall review and approve the case.

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

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

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective 14 June 2010 [39].

6.2 Number of Patients

The total number of patients is approximately 103.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will continue to be treated with brigatinib until they experience objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity. With medical monitor approval, treatment may be continued at 180 mg QD or may be escalated to 240 mg QD after initial progression if there is still potential for clinical benefit.

The follow-up period for survival begins after the patient has permanently discontinued study drug and continues until 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. For patients who qualify and elect to receive brigatinib 240 mg QD, the survival follow-up begins after they have discontinued study drug.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will end when either all patients die or 3 years have passed since the last patient started study treatment, whichever comes first.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

The study will start enrollment in 2018 and the overall timeframe will be pending on final sample size.

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

Table 6.a Secondary Endpoints for Disclosure

Endpoint
Primary: Confirmed ORR, as assessed by the IRC.
Secondary:
1. Confirmed ORR, as assessed by the investigator (per RECIST version 1.1).
2. DOR, as assessed by the investigator and IRC.
3. PFS as assessed by the investigator and IRC.
4. DCR as assessed by the investigator and IRC.
5. Time to response as assessed by the investigator and IRC.
6. Confirmed intracranial ORR in patients with brain metastases at baseline, as assessed by the IRC.
7. Intracranial DOR in patients with brain metastases at baseline, as assessed by the IRC.
8. Intracranial PFS in patients with brain metastases at baseline, as assessed by the IRC.
9. Overall survival.
10. Safety/tolerability (per CTCAE version 4.03).
11. HRQOL assessed with the global health status/quality of life and other function and symptom (per EORTC QLQ-C30 version 3.0, and EORTC QLQ-LC13).

Abbreviations: CNS: central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; HRQOL, health-related quality of life; IRC, independent review committee; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

6.3.4 Total Study Duration

The study will end around 5 years after enrollment starts, taking into consideration enrollment and follow-up.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for curative therapy) or stage IV NSCLC.
2. Must meet both of the following 2 criteria:

a) Have documentation of ALK rearrangement by a positive result from any laboratory test approved by the FDA (eg, 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).

or

Have documented ALK rearrangement by a different test (non–FDA-approved local lab tests) and have provided tumor sample to the central laboratory. (Note: Central laboratory ALK rearrangement testing results are not required to be obtained before randomization.)

b) The patient had been on any one of the ALK TKIs (alectinib, ceritinib, crizotinib) for at least 12 weeks before progression.

3. Had progressive disease (PD) while on alectinib or ceritinib (defined as no more than 1 month from last dose of alectinib or ceritinib to disease progression, as assessed by the investigator or treating physician). (Number of patients not previously treated with alectinib will be capped at 10 for every 30 patients enrolled.)
4. Had alectinib or ceritinib as the most recent ALK inhibitor therapy. Chemotherapy before or after progression on alectinib or ceritinib is allowed.
5. Have at least 1 measurable lesion per RECIST version 1.1 as assessed by the investigator.
6. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE, version 4.03, Grade ≤1. (Note: Treatment-related alopecia or peripheral neuropathy that are Grade >1 are allowed if deemed irreversible.)
7. Male or female, 18 years or older or of local legal adult age.
8. Have a life expectancy of ≥3 months.
9. Have adequate organ and hematologic function as determined by:
   a) ALT/aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present.
   b) Total serum bilirubin ≤1.5 × ULN (<3.0 × ULN for patients with Gilbert syndrome).
   c) Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, using the modification of diet in renal disease (MDRD) equation (Appendix F).
   d) Serum lipase ≤1.5 × ULN.
   e) Absolute neutrophil count ≥1.5 × 10^9/L.
   f) Platelet count ≥75 × 10^9/L.
   g) Hemoglobin ≥9 g/dL.
   h) Have Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
10. For female patients of childbearing potential, have a negative pregnancy test documented ≤7 days before start of study medication.
11. 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 4 months after the end of treatment (Section 8.8.1).

12. Have the willingness and ability to comply with scheduled visit and study procedures and provide a signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Received any prior ALK-targeted TKI other than crizotinib, alectinib, or ceritinib.
2. Received both alectinib and ceritinib.
3. Received crizotinib, alectinib, or ceritinib within 7 days of the first dose of brigatinib.
4. Previously received more than 3 regimens of systemic anticancer therapy for locally advanced or metastatic disease.

   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. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this (neo-)adjuvant therapy.
5. Received chemotherapy or radiation within 14 days of first dose of brigatinib, except for stereotactic radiosurgery (SRS) or stereotactic body radiation therapy.
6. Received anticancer monoclonal antibodies within 30 days of the first dose of brigatinib.
7. Had major surgery within 30 days of the first dose of brigatinib. Minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed.
8. 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.
9. Have symptomatic brain metastasis (parenchymal or leptomeningeal). Patients with asymptomatic brain metastasis or who have stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the past 7 days before the first dose of brigatinib may be enrolled.
10. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
11. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    a) Myocardial infarction within 6 months before the first dose of brigatinib.
    b) Unstable angina within 6 months before first dose of brigatinib.

c) Congestive heart failure within 6 months before first dose of brigatinib.

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.

12. Had a cerebrovascular accident or transient ischemic attack within 6 months before first dose of brigatinib.
13. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
14. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
15. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous antibiotics.
16. Have a known history of HIV infection. Testing is not required in the absence of history.
17. Have malabsorption syndrome or other GI illness that could affect oral absorption of brigatinib.
18. Have a known or suspected hypersensitivity to brigatinib or its excipients.
19. Are pregnant, planning a pregnancy, or breastfeeding.
20. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of brigatinib.
21. 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 enrollment (refer to Section 8.6 for a list of example medications).

8.0 STUDY DRUG

8.1 Study Drug Administration

In extenuating circumstances, such as during the COVID-19 public health emergency, additional drug supply may be provided to the subjects to cover 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 (direct-to-patient [DTP] shipment) in agreement with Takeda processes and local health authorities.

Before initiation of the DTP process, patients will agree to participate in this process. Patients will sign a separate acknowledgment of receipt form permitting this process and agree to share limited personal information with the delivery courier. The investigator and courier must ensure that no private patient information is shared with the sponsor or other CROs participating in the study. The local institutional review board (IRB)/independent ethics committee (IEC) must be

notified, as applicable per local requirements, that this process is being initiated, and sites must clearly document the chain of custody of any study drug dispensed directly to patients.

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 will be expected to increase their dose to 180 mg QD beginning on Day 8 and continuously every day, with a 28-day study procedure execution cycle. The study drug shall be taken approximately at the same time of the day each day. It may be taken with or without food. Patients shall be instructed to swallow the tablets whole and not crush or chew them. Patients will take the dose with water (recommended 240 mL). If a dose of brigatinib is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of brigatinib at the scheduled time.

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

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

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 and take the next dose of study drug at the scheduled time.

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).

8.2 Reference/Control Therapy

Not applicable.

8.3 Treatment Beyond Radiological Disease Progression

Until radiological disease progression is identified, patients may continue to receive brigatinib at current dose, if they are still benefiting from it as determined by 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). Patients will be required to provide consent to receive treatment beyond progression.

Patients who have progressed on brigatinib 180 mg QD and have had no greater than Grade 2 brigatinib-related toxicity will be given the option to increase the dose to 240 mg QD until radiological disease progression per RECIST, using the tumor assessment before dose escalation as the new baseline, is observed or intolerance. Patients will be required to provide consent to receive this increased dose of brigatinib.

In either scenario, medical monitor delegated by the sponsor shall review and approve the case and an informed consent shall be obtained from the patient. The patient shall continue to receive the efficacy, safety, patient report outcome and health resource utilization assessments as in the main study treatment phase.

8.4 Dose Modification Guidelines

The following sections provide recommended dose-modification guidelines for treatment-related AEs observed with brigatinib administration.

The allowable daily doses of brigatinib in this study are 240 mg (applicable only for patients eligible to increase to 240 mg after disease progression), 180 mg, 120 mg, 90 mg, and 60 mg. When 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.

Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs, upon clinical judgment of the investigator. Study drug administration may be delayed for up to 28 days to allow for improvement or resolution of the event. Patients may have an interruption in therapy for 14 days should emergency surgery be clinically indicated.

NOTE: 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 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 Grade 1 or less after dose interruption for more than 28 days, the sponsor's medical monitor must be contacted.

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.

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 utilized 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.

8.4.1 Dose Modification for Brigatinib-Related Adverse Events

The minimum dose for brigatinib is 60 mg QD. If a patient cannot tolerate study drug at this dose level, the study drug shall be permanently discontinued. The dose reduction levels of brigatinib are listed in Table 8.a.

Table 8.a Recommended Brigatinib Dose Reduction Levels

	Dose Reduction Levels				
Starting Dose	**First**	**Second**	**Third**	**Fourth**	**Fifth**
90 mg QD	60 mg QD	Permanently discontinue	Not applicable	Not applicable	Not applicable
180 mg QD	120 mg QD	90 mg QD	60 mg QD	Permanently discontinue	Not applicable
240 mg QD [a]	180 mg QD	120 mg QD	90 mg QD	60 mg QD	Permanently discontinue

Abbreviation: QD, once daily.
[a] For patients who tolerated 180 mg dose and had increased dose to 240 mg QD at disease progression.

8.4.1.1 General TRAEs

Guidelines for dose modification of brigatinib treatment-related AEs are outlined in Table 8.b and are based on the Company Core Data Sheet (CCDS) for brigatinib. Unless otherwise noted, reduce dose as shown in Table 8.b if 1 or more dose reduction is necessary because of adverse reactions of Grade 3 or 4 severity, as defined by NCI CTCAE version 4.03.

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

Adverse Reaction	Severity*	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.
Hypertension	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one antihypertensive drug, or more intensive therapy than previously used indicated).	• Withhold brigatinib until hypertension has recovered to baseline or SBP less than 140 mmHg and DBP less than 90 mmHg, 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 (SBP less than 140 mmHg and DBP less

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

Adverse Reaction	Severity*	Dose Modification
		than 90 mmHG), 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 heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: Permanently discontinue brigatinib.

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

Adverse Reaction	Severity*	Dose Modification
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.
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 (≤2.5 × ULN) CPK elevation or to baseline, then resume brigatinib at same dose. • If a 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 (≤2.5 × ULN) or to baseline, then resume at the next lower dose level per Table 8.a.
Lipase/amylase elevation	Grade 3 (>2.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (≤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 (≤1.5 × ULN) or to baseline, then resume at the next lower dose level per Table 8.a.
	Grade 4 (>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/mL 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-

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

Adverse Reaction	Severity*	Dose Modification
		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; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SBP, systolic blood pressure; ULN, upper limit of normal.
*Graded per NCI CTCAE, version 4.03.

8.4.2 Pulmonary Adverse Reactions and Other Adverse Events

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 EOPEs.

In the ALTA study (Study AP26113-11-201) for brigatinib, as of 21 February 2017, of 219 treated patients, there were 14 cases of EOPE (total 6.4%, 14 of 219). 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 EOPE onset was Day 2 (range: 1-9). Eleven of these 14 cases were reported as serious adverse events (SAEs). Seven patients had events that were Grade ≥3, all of whom permanently discontinued brigatinib because of these events. One patient had a Grade 5 EOPE (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 ILD or pneumonitis could suggest a relationship to brigatinib. Other etiologies, including pulmonary embolism and infectious pneumonia, should be ruled out. If no evidence of other etiology is identified, a causal relationship to brigatinib should 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 workup 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 (IB) for detailed information on EOPE, late-onset pneumonitis and other AEs, including bradycardia, hypertension, vision impairment, blood CPK increased, pancreatic enzymes elevation, hyperglycemia and other adverse drug reactions observed in the clinical studies with brigatinib.

8.5 Prior and Concomitant Therapies

Anticancer Therapy

History of prior cancer therapy will be recorded at screening, and concomitant cancer therapy will be recorded during the study on the appropriate eCRF for each patient. Reasonable efforts will be made to collect information on all prior cancer therapy received by the patient (eg, surgeries, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the patient's original source medical document (eg, medical chart for in-hospital care and medical record for outpatient clinic care) and recorded on the appropriate eCRF.

Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Patients with brain lesions requiring local radiotherapy such as SRS are allowed to continue study drug after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have PD.

New anticancer therapy initiated after radiological PD is observed shall also be collected in eCRF. The information to be collected may including name of the therapy, start and end dates, best response, and reason for discontinuation.

Other Therapy

Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least the 30 days after last dose, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

8.6 Excluded Concomitant Medications and Procedures

Systemic treatment with the following medications should be avoided during the study:

- 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 once daily 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.

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.

The following medications and procedures are also prohibited before radiological disease progression is observed:

- Any illicit substance. Medical use of cannabis is allowed if it is legal where the patient resides and no alternative treatment is available, on the base of case-by-case review and agreement by the medical monitor.
- 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.

8.7 Permitted Concomitant Medications and Procedures

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.

8.8 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, Pgp) 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-glycoprotein (Pgp), 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.

8.8.1 Pregnancy, Breastfeeding, and Contraception

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 group 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 nonhormonal method (see list below) and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through at least 4 months 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 4 months 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.

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 4 months 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 4 months 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.)

8.9 Blinding and Unblinding

This is an open-label study.

8.10 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. Brigatinib drug product is recommended for storage below 30°C. Do not refrigerate or freeze.

8.11 Packaging and Labeling

Brigatinib drug product will be supplied as film-coated tablets, containing 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. 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.

8.12 Storage, Handling, and Accountability

The recommended storage condition for brigatinib is under 30°C. Do not refrigerate or freeze.

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 redispensed.

No other use of brigatinib 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.

8.13 Other Protocol-Specified Materials

Details are provided in 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 IRB/IEC.

9.3 Treatment Group Assignments

This is a single arm study. All patients will be assigned to receive the same treatment.

9.4 Study Procedures

Refer to the Schedules of Events (Appendix A) for timing of assessments, including those for all patients, and for patients receive 240 mg brigatinib. Additional details are provided as necessary in the sections that follow.

Sites will make every effort to see patients in the clinic to complete all study-specified assessments as outlined in the Schedule of Events (SOE) (Appendix A).

In unavoidable circumstances, such as during the COVID-19 public health emergency, exceptions can be made for alternative methods for conducting patient visits and performing laboratory and imaging assessments. Remote visits may be performed via telehealth or telemedicine as a safety check on subject well-being. Remote visits and telemedicine or telehealth must comply with Takeda processes and local health authorities. This will be recorded in the eCRF and in the study records.

In extenuating circumstances, such as during the COVID-19 public health emergency, local laboratory results and imaging assessment may be used. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records. Missed clinic visits or subject withdrawals due to COVID-19 must be recorded in the protocol deviation report and eCRF, as applicable.

9.4.1 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.

Before initiation of the DTP process, patients will agree to participate in this process as described in Section 8.1.

9.4.2 Patient Demographics

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

9.4.3 Screening

Screening assessments must be performed no more than 14 days before Day 1 (the day of the first dose). 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.

Visit Window

The day the first dose of brigatinib is administered is defined as Day 1. Following visit 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. 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.

Vital signs should be repeated on Cycle 1 Day 1 before first dose, regardless of the time from screening. Insulin, testosterone (male patients) and pregnancy tests (for female with child-bearing potential) do not need to be repeated on Day 1 if they were performed for screening within 7 days before Day 1, and in the opinion of the investigator, there is no reason to believe they have substantially changed. Physical examination, ECOG performance status assessments, hematology, and chemistry assessments do not need to be repeated on Day 1 if they were performed for screening within 3 days before 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, they should be obtained before starting treatment.

9.4.4 Enrollment

Patients are considered enrolled once the ICF is signed. Patients who signed ICF but did not start study treatment will be counted as screening failure. The reason for screening failure shall be documented clearly in the source document and the eCRF. Procedures for completion of the enrollment information are described in the study manual.

9.4.5 Medical History

A complete medical history, including cancerous and noncancerous disease, will be collected at the 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 that ALK+ status was tested shall also be recorded.

Diagnosis and Cancer History

The initial cancer diagnosis, risk factors (such as tobacco and alcohol intake), and the current cancer stage at the time of screening, along with tumor histology and all sites of disease, should be recorded. The American Joint Committee on Cancer) 7th edition staging

(https://www.sciencedirect.com/science/article/pii/S1359634907700186) will be utilized for clinical stage at study entry. 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, neo-adjuvant, 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.

Patients entering the study must either have a history of a positive results from FDA-approved tests. Otherwise, they must have a 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 a central laboratory is not required before enrollment. Specifications regarding handling and processing of tissue for this test are described in Section 9.4.18.2 and in the study manual.

In addition, concomitant medications will be recorded as specified in Section 9.4.9.

9.4.6 Physical Examination

A complete physical examination must be performed at screening, the extent of which should be consistent with medical history and the patients' underlying disease. Subsequent physical examinations as described in the Schedules of Events (Appendix A) may be directed to relevant findings. Of note, because of 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.

The end-of-treatment physical examination should be a complete physical examination. The 30-days-after-last-dose physical examination may be directed to any relevant findings.

9.4.7 Patient Height and Weight

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

9.4.8 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 first dose, regardless of the time from screening. Vital signs will also be assessed per the Schedules of Events (Appendix A).

9.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time informed consent is signed through 30 days after last dose. See Section 8.6 and Section 8.7 for a list of medications and therapies that are prohibited and/or allowed during the study treatment.

After 30 days from last dose, follow-up anticancer treatment for the ALK+ NSCLC shall be collected during the survival follow-up stage, with the exception of study drug brigatinib being used beyond radiological progression. Study drug brigatinib used in these cases, at original or increased dose, shall continue to be reported in study medication section in the eCRF.

In case brigatinib is prescribed again for regular medical practice after study drug brigatinib is permanently discontinued, this prescribed brigatinib shall be recorded as follow-up anticancer treatment.

9.4.10 AEs

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

9.4.11 ECG

A 12-lead ECG will be administered at the time points specified in the Schedules of Events (Appendix A).

All ECGs must be 12-lead ECGs and will be assessed per the Schedules of Events throughout the study. The Cycle 1 Day 1 ECG should be performed before the first dose of brigatinib.

Additional ECGs may be performed at the investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has, during the study, been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval (other than medications explicitly prohibited). For consistency, the Fridericia correction (QTcF = QT interval/(RR)1/3 interval) method must be used for all calculations of heart rate-corrected QT (calculated) intervals.

9.4.12 Clinical Laboratory Evaluations

Clinical laboratory testing for safety 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 Schedules 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 brigatinib 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 brigatinib. If the screening blood sample for hematology and chemistry was collected within 3 days of the first dose and, in the opinion of the investigator, there is no reason to believe that there may be substantial changes, these tests do not need to be repeated on Day 1. If the insulin, testosterone (for males only), and pregnancy test (for females with child-bearing potential) were performed within 7 days before Day 1 and, in the opinion of the investigator, there is no reason to believe that there may be substantial changes or that the patient could be pregnant, these assessments do not need to be repeated on Day 1. If the tests need to be repeated, the investigator should review the results before instructing the patients to take the first dose of brigatinib.

Table 9.a Clinical Chemistry and Hematology Tests

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

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

9.4.13 Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin test, and either urine or serum can be used. 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 the first dose of brigatinib (Cycle 1 Day 1). Women of childbearing potential at study start must also complete the pregnancy test once every 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.

9.4.14 Disease Assessment

Tumor response assessments will be determined per RECIST version 1.1 by the investigator and an independent radiological review.

At screening, disease assessment must include imaging of the chest and abdomen (covering adrenal glands) using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [MRI] with contrast medium, unless contraindicated). MRI of the brain enhanced by contrast medium (eg, gadolinium) is required at screening for all patients. If such medium for MRI is contraindicated, use CT with contrast medium. All radiographic images (eg, CT, MRI) performed during the study will be submitted to the imaging core laboratory for central review. Patients must have at least 1 measurable lesion per RECIST version 1.1. 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.

Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±7 days] of every even-numbered cycle) through 14 cycles after the initial dose of brigatinib, and every 3 cycles (12 weeks) thereafter until radiological disease progression is observed. Imaging of *chest, abdomen,* and *brain* will occur at each assessment for *all* patients. Additional tumor assessment can be performed at any time, if clinically indicated; confirmation of CR or PR shall be performed at least 4 weeks after initial response is observed. The same imaging modality at the same institution should be used at each assessment, if possible.

For patients who continue study treatment at the same dose beyond documented PD per RECIST version 1.1, at the investigator's discretion and with the sponsor's medical monitor approval, the sponsor does not require further tumor assessment to be collected. The tumor evaluation shall be managed according to local medical practice.

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.

For patients who continue the study treatment at 240 mg QD beyond documented PD per RECIST version 1.1, at the investigator's discretion and with the sponsor's medical monitor approval, imaging will continue with the same assessment schedule (Appendix A). If the patient experiences symptomatic deterioration in the absence of radiologic progression, it is strongly recommended that additional imaging studies be performed to confirm PD.

The disease assessment that documents progression will serve as the new baseline for the dose escalation to 240 mg QD portion of the study. The investigator will reevaluate the patient for target and nontarget lesions, according to RECIST criteria, on the basis of the disease assessment scans showing the initial progression. The patient need not repeat imaging assessments before dose escalation unless the disease assessment is incomplete or occurred >21 days before the first dose of brigatinib 240 mg QD, in which case disease assessments must be repeated and will serve as the new baseline. If the disease assessment is incomplete, the site will obtain any missing radiographic imaging (eg, MRI of the brain) before dose escalation to 240 mg QD.

Disease assessment by CT and MRI scans will be performed at 8-week intervals thereafter (on Day 28 [±7 days] of every even-numbered cycle) for 14 cycles after the initial dose of brigatinib

at 240 mg QD, and every 3 cycles (12 weeks, ±7 days) thereafter until radiological disease progression is observed, according to the new baseline. The same imaging modality at the same institution should be used at each assessment.

All patients will be followed for radiological disease progression. For patients who discontinue the study drug for a reason other than objective disease progression, additional tumor assessment should be documented, if available, until disease progression or start of another systemic anticancer therapy.

9.4.15 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, insulin and testosterone for males), as outlined in Table 9.a. ECGs 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. For patients who discontinued the study drug before having radiological progression, tumor assessments shall be continued according to the schedule in Appendix A until radiological progression is observed.

9.4.16 Thirty-Days-After-Last-Dose Visit

The 30-days-after-last-dose assessments must be performed 30 days (±7 days) after the last dose of study drug. Physical examinations, laboratory tests (hematology, chemistry, insulin and testosterone), and ECG 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 of last dose is more than 30 days before the decision to permanently discontinue from study treatment is made, the end-of-treatment visit and 30 days after last dose visit can be combined as one visit. If patients permanently discontinued study treatment before radiological disease progression is observed, this visit may occur before the end-of-treatment visit.

9.4.17 Follow-up Period

The follow-up period for a patient begins after disease progression or patient starts another systemic anticancer therapy and continues until patient contact ceases. If a patient discontinues study drug for reasons other than disease progression and has not yet started another systemic anticancer therapy, the patient shall continue to be followed for radiological tumor assessment and only enters follow-up phase once the radiological tumor progression is observed or another systemic anticancer therapy is started. The follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks (±14 days) after the end of treatment for the last study drug administered. The allowable window for follow-up assessments is 14 days. All new anticancer therapies should be reported. CCI [redacted].

9.4.18 Biomarker, Pharmacodynamic, and PK Samples

9.4.18.1 Primary Specimen Collection

The Primary Specimen Collection is shown in Table 9.b.

Table 9.b Primary Specimen Collection

Number	Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
1	Archival (banked) tumor tissue sample	FFPE block FFPE slides	DNA RNA Protein		Biomarker measurements	Mandatory if patient's ALK test results are from non-FDA approved test methods
2	Fresh tumor tissue biopsy sample	Fresh tumor tissue	FFPE block FFPE slides	DNA RNA Protein	Biomarker measurements	Optional, but highly desirable if patients have biopsiable lesions
3	Fresh tumor tissue biopsy sample at PD	Fresh tumor tissue	FFPE block FFPE slides	DNA	Biomarker measurements	Optional, but highly desirable if patients have biopsiable lesions
4	Plasma sample for ctDNA	Plasma	ctDNA		Biomarker measurements	Mandatory
5	Plasma sample for brigatinib PK	Plasma			PK measurements	Mandatory

Abbreviations: ALK, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; PD, progressive disease; PK, pharmacokinetics.

CCI

[redacted]

CCI

[redacted]

9.4.19 Pharmacokinetic Measurements

All patients 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 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 the time of the brigatinib dosing should be recorded. Blood samples for the determination of plasma concentrations of brigatinib will be collected as indicated in the PK Sampling Schedule (Appendix A).

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.

The exact date and time of each PK sample collection should be recorded.

9.4.20 QOL Assessment: EORTC QLQ-C30 and QLQ-LC13

The HRQOL assessments (EORTC QLQ-C30 and QLQ-LC13, will be completed by the patient as specified in the Schedules 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 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.

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 and QLQ-LC13) will be administered at specified scheduled visits and at the visit 30 days after the last dose of brigatinib. The PRO questionnaire should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed. For patients who continue treatment with brigatinib at 240 mg QD after progression, these PRO questionnaires will be administered with the same assessment schedule as described above with the baseline reset at the disease progression.

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9.4.22 Health Utilization Data Collection

During the treatment and follow-up periods indicated in the Schedules 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 schedule visit of each cycle during study treatment, end-of-treatment visit, and 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.

9.5 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 brigatinib because of disease progression, intolerance, investigator discretion, or death 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 patient has the last dose equals or more than 30 days before the decision of permanent discontinuation from study treatment is made, the end-of-treatment visit and 30-days-after-last-dose visit can be combined as 1 visit.

9.6 Completion of Study (for Individual Patients)

All patients who discontinued study drug shall be followed for survival, regardless of the reason for discontinuation. The survival follow-up will continue until patients die or study ends. Patients will be considered to have completed the study if they died before or were alive at the time of data cut. Patients lost to follow-up or who withdraw consent before study completion are not counted in the number of patients who completed the study.

9.7 Discontinuation of Treatment With Study Drug

Study drug must be permanently discontinued for:

- Intolerable toxicity as determined by the investigator.
- Progression of disease requiring an alternative therapy, in the opinion of the investigator.

Note: At the discretion of the investigator, treatment of patients with brigatinib may be continued at the recommended dose of 180 mg QD, despite investigator-assessed progression per RECIST version 1.1, if there is still potential for clinical benefit. Treatment of patients with brigatinib may be escalated to 240 mg QD, despite investigator-assessed progression per RECIST version 1.1, at the discretion of the investigator and if there is still potential for clinical benefit. Treatment beyond progression or escalation to 240 mg brigatinib dose is allowed. In both scenarios, the sponsor's medical monitor shall be contacted to approve these cases. Patients shall sign an additional ICF before the treatment continues or increases.

- Requested by the patient. Note: In cases where patients request to discontinue the study drug, the investigator should assess whether this request is due to study drug–related toxicity. This election is applicable only if the patients are not having intolerable toxicity in the 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 in the study.

- Lost to follow-up.
- Per investigator discretion, it is in the best interest of the patient to discontinue. If the investigator's determination is made on the basis of intolerable toxicity, the reason of discontinuation shall be recorded as intolerable toxicity. In cases where it is reported that patient discontinuation is due to investigator discretion, the situation shall be clearly documented in the source document and sponsor medical monitor shall be contacted to discuss alternative solutions before the discontinuation decision is made.
- Significant protocol deviations that will jeopardize safety surveillance and pose a significant threat to the safety of the patient.

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

9.8 Study Compliance

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.

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 as described in Section 8.1.

9.9 Overall Survival

After disease progression or starting another systemic anticancer therapy, all patients will be followed for OS till death or study termination. The survival follow-up can be conducted by remote method (eg, telephone call, etc). At each visit, survival status and information about subsequent anticancer therapy (eg, 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.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

A pretreatment event (PTE) 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 should be reported as AEs in the appropriate section of the eCRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

10.1.3 AE Severity

The severity of AEs will be assessed according to the CTCAE version 4.03 (see the study manual). If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE on the basis of 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.

10.1.4 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**. (Refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it 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 lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [39]. 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 (fax) of the completed Takeda paper-based SAE form will be sent. 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 PTEs, 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 lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [39]. 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.
- SAEs.
- Serious PTEs 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 SAEs suspected by the investigator to be related to the study treatment 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 email 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 email addresses provided below.

Product	Call Center	Phone Number	Email	Fax
Brigatinib	Dohmen Life Science Services	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 European Medicines Agency, 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 composed 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 Independent Review Committee

A central blinded IRC with no knowledge of the patients' status on study will evaluate all images collected during the study for the primary endpoint of confirmed ORR as well as several secondary endpoints. An IRC charter defines the procedures used by the committee.

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, PTEs, 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 patient 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 (CRO) 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 patient'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.

In extenuating circumstances, such as during the COVID-19 public health emergency, direct, suitably controlled remote access to patients' electronic medical records may be used for data monitoring. Only pseudonymized documents may be shared through a cloud-based system. Videoconferencing may be used for remote site data verification, but copying or recording of the video and/or documents (eg, screen captures) is not permitted. These procedures will be documented in the Monitoring Plan.

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 patients, 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 patient'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 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.

The final analysis of the primary endpoint (confirmed ORR) will be conducted approximately 6 months after the last patient is enrolled. The confirmed ORR will be tested at a one-sided alpha of 0.025.

13.1.1 Analysis Sets

13.1.1.1 Full Analysis Set

All patients who receive at least one dose of brigatinib will be included in the full analysis set. Primary analyses of safety and efficacy will be performed using the full analysis set.

13.1.1.2 Per-Protocol Population

The per-protocol population will exclude all patients in the full 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. In particular, patients who have no history of an ALK rearrangement by an FDA approved test at study entry and whose protocol-mandated central test is negative for an ALK rearrangement will be excluded from the per-protocol analysis.

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 will be summarized using descriptive statistics. 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 recategorizing existing categorical variables.

13.1.3 Efficacy Analysis

13.1.3.1 Definitions of Efficacy Endpoints

The primary endpoint (confirmed ORR assessed by the IRC) is defined as the proportion of the patients who are confirmed to have achieved CR or PR, per RECIST version 1.1 (confirmed ≥4 weeks after initial response), out of all patients who have had at least one dose of study drug (the full analysis set).

Secondary efficacy endpoints for this study are defined as follows:

- Confirmed ORR assessed by the investigator is defined as the proportion of the patients who are confirmed to have achieved CR or PR per investigator using RECIST version 1.1 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/PR (whichever is first recorded) until the first date that the PD is objectively documented, or death in patients with a confirmed response.
- PFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which radiological disease progression is objectively documented, 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.

- Disease control rate is defined as the proportion of patients who have achieved CR, PR, or SD (in the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks) after the initiation of study treatment.
- Time to response is defined as the time interval from the date of the first dose of the study treatment until the initial observation of CR or PR.
- Confirmed iORR is defined as the proportion of the patients who have achieved CR or PR in the brain per a modification of RECIST version 1.1, after the initiation of study treatment, in patients with intracranial brain metastases at baseline. The criteria of intracranial efficacy assessment will be defined in more detail in the SAP.
- Duration of intracranial response is defined as the time interval from the time that the measurement criteria are first met for CR or PR in the brain (whichever is first recorded) until the first date that PD in the brain is objectively documented or death, in patients with intracranial metastases at baseline.
- iPFS is defined as the time interval from the date of the first dose of the study treatment until the first date at which intracranial brain disease progression is objectively documented, or death due to any cause, whichever occurs first, in patients with intracranial metastases at enrollment. iPFS will be censored for patients without documented intracranial disease progression or death.
- OS is defined as the time interval from the date of the first dose of the study treatment 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.

13.1.3.2 Primary Efficacy Endpoint Analyses

The best response (CR, PR, SD, or PD), according to RECIST version 1.1, will be derived for each eligible patient who receives at least 1 dose of study treatment. The ORR is calculated as the proportion of patients who are confirmed to have achieved CR or PR after the initiation of study treatment. Confirmed responses are those that persist on repeat imaging at least 4 weeks after initial response. At the final analysis, exact 2-sided 95% CIs for the ORR will be calculated on the basis of the binomial distribution. The primary analysis will be performed on ORR assessed by the IRC. Best target lesion response will be displayed using a "waterfall" plot. Supportive sensitivity analyses will be performed for ORR assessed by the IRC in the per-protocol population. Supportive sensitivity analyses will also be performed in patients confirmed to be ALK+ via central assessment and within subgroups defined by age, sex, race, geographic region, mutation status, prior anticancer therapies, and other prognostic factors. Continuous prognostic factors affecting the ORR may be explored using simple logistic regression models.

13.1.3.3 Secondary Efficacy Endpoint Analyses

Confirmed ORR assessed by the investigator in the full analysis set and the per-protocol population will be analyzed to assess the robustness of the primary analysis of the primary endpoint.

Disease control rate assessed by the investigator in the full analysis set and the per-protocol population and the exact 2-sided 95% binomial CIs will be calculated.

For time-to-event efficacy endpoints (PFS, DOR, OS), median values and 2-sided 95% CIs will be estimated using Kaplan-Meier method [40] in the full analysis set. The PFS rates and OS rates at 12 and 24 months and the associated 2-sided 95% CIs will be computed.

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

In patients with CNS metastases at enrollment, iORR assessed by a separate IRC and the exact 2-sided 95% binomial CIs will be calculated; median intracranial DOR and PFS will be estimated using the Kaplan-Meier method.

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

13.1.5 Subgroup Analysis in Patients Progressed on Alectinib

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

13.1.6 Analysis of Patient-Reported Outcomes and Health Resource Utilization Data

The analysis will be based on patients with baseline and at least 1 postbaseline measurement.

The actual value and change from baseline of the summary/subscale scores of EORTC QLQ-C30 and the subscale scores of EORTC QLQ-LC13 will be summarized using descriptive statistics over time. The number and percentage of patients with improved EORTC QLQ-C30 and EORTC QLQ-LC13 scores will also be summarized over time, where improvement will be defined on the basis of change from baseline scores and a published responder definition threshold of 10. Additionally, time to QOL deterioration based on EORTC QLQ-C30 and EORTC QLQ-LC13 scores will also be analyzed. Time to QOL deterioration will be defined from first dosing date to the date of the first occurrence of QOL scores deterioration of more than 10 from baseline.

Published manuals/guidance for the questionnaires will be used for scoring and handling missing data. Further investigation about missing data and subsequently sensitivity analysis for missing data may be conducted.

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Compliance for EORTC QLQ-C30, EORTC QLQ-LC13, CCI [redacted] will also be summarized over time.

HU as measured by hospitalizations, outpatient visits, and missed days of work or other activities by patients and caregivers will be summarized using descriptive statistics.

13.1.7 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 version 4.03.

All patients who receive at least 1 dose of study treatment will be evaluated for safety. The proportion of patients with at least 1 TEAE, TRAE, and serious treatment-emergent adverse event (SAE) 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 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.

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

13.2 Sample Size Justification

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

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 (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the IB, study medication, patient medical records, informed consent documentation, documentation of patient 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.

In extenuating circumstances, such as during the COVID-19 public health emergency, direct, suitably controlled remote access to patients' electronic medical records may be used for data monitoring. Only pseudonymized documents may be shared through a cloud-based system. Videoconferencing may be used for remote site data verification, but copying or recording of the video and/or documents (eg, screen captures) is not permitted. These procedures will be documented in the Monitoring Plan.

14.2 Protocol Deviations

The sponsor or sponsor delegates cannot grant waiver to the protocol requirement. The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. 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 patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

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, patients) 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 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 Benefit-Risk of the Study

The intended study population are patients with refractory disease and those who have limited treatment options.

The study drug brigatinib will be used at the standard 90 mg to 180 mg dose. The safety profile of brigatinib at this dose is well established from the previous studies (AP26113-11-101, AP26113-13-201, and AP26113-13-301). The safety surveillance procedures in this protocol are similar to those used in previous brigatinib studies and are reasonable to ensure proper monitoring of patients' safety. A detailed dose modification guideline is provided in this protocol in case treatment-related toxicity emerges. Only patients who tolerated previous doses well and have disease progression will be offered the opportunity to escalate to 240 mg, and an additional ICF will be provided before dose escalation. This dose level is still below the maximum dose studied in humans, and the MTD was not reached in a phase 1 study of brigatinib. Therefore, any toxicities are expected to be manageable.

The mandatory procedures required by this study are similar to the management that these patients will receive as part of clinical practice.

The data collection and reporting plan are standard for such studies. These will ensure the collection of high-quality data to report clinically meaningful outcomes.

Brigatinib may have antitumor effects in ALK+ metastatic NSCLC patients who have already progressed on alectinib or ceritinib according to nonclinical studies. Patients enrolled in this study may have clinical benefit from the study drug brigatinib. The efficacy and safety from this study will serve as important evidence to evaluate the use of brigatinib in this population and potentially benefit more patients in the future.

In summary, the benefit-risk of this study supports the protocol to be implemented.

15.2 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 IB, a copy of the ICF, and, if applicable, patient 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 ship drug/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 trial. Until the site receives [drug/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 patients, 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.

15.3 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 IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, 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, or the subject's legally acceptable representative, 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, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative 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 or the relevant subject's legally acceptable representative 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.

15.4 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 15.3).

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 [e]CRF).

15.5 Publication, Disclosure, and Clinical Trial Registration Policy

15.5.1 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.

15.5.2 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.

15.5.3 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.

15.6 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.

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Appendix A Schedules of Events

Schedule of Events: Study Assessments for All Patients

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

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

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

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

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

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

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

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

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

	Screening Period	Treatment Through 30 Days After Last Dose									Follow-up Period
Assessment	**Screening**	**Cycle 1 [a]**			**Every Cycle (Starting at Cycle 2)**	**Cycle 3 Day 1 and Cycle 5 Day 1**	**Every 2 Cycles (From Cycle 2 to Cycle 14)**	**Every 3 Cycles After Cycle 14**	**End of Treatment [b]**	**30 Days After Last Dose [b]**	**Follow-up [c]**
Day	**D -14 to D0**	**D1**	**D8**	**D15**	**D1**	**D1**	**D28**	**D28**			

[g] Glucose and insulin will be tested concurrently.

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

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

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

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

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

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

[redacted]

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

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

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

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

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

Assessment	Before Dose Escalation (14 Days) [a]	Treatment Through 30 Days After Last Dose								Follow-up Period
		Escalation Cycle 1 [b]		Every Escalation Cycle (Starting at Cycle 2)	Cycle 3 Day 1 and Cycle 5 Day 1	Every 2 Escalation Cycles [c] (From Escalation Cycle 2 to Cycle 14)	Every 3 Escalation Cycles after Escalation Cycle 14	End of Treatment	30 Days After Last Dose	Follow-up
Day	**D1** [d]	**D1**	**D15**	**D1**						
sample at disease progression										
PRO assessment	X	X		X				X	X	
HU assessment				X						
Subsequent anticancer therapy/survival										X

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

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

[b] 1 cycle = 28 days.

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

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

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

[f] Glucose and insulin will be tested concurrently.

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

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

[i] At disease progression.

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

PK Sampling Schedule

All Patients

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

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

PK, pharmacokinetics.

For Patients Receiving 240 mg Brigatinib Postprogression

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

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

PK, pharmacokinetics.

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

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 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.
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 Eastern Cooperative Oncology Group 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 Response Evaluation Criteria In Solid Tumors (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.

Choosing Target Lesions

- Select up to 5 lesions (up to 2 per organ).
- Select largest reproducibly measurable lesions.
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be.
- Add up longest diameters (LD) of non-nodal lesions (axial plane).
- Add short axis diameters of nodes.
- This is the sum of the longest diameters (SLD).

Nontarget Lesions

- All other sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions.
- It is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (eg, "multiple enlarged pelvic lymph nodes").

Determining Response

- Assess at baseline and on study with consistent modalities (CT, MRI, PET/CT).
  - Measure target lesions and calculate SLD.
  - Visually assess nontarget lesions.
  - Search for new lesions.
  - Combine these assessments into the overall response.

Target Lesion Response

Complete response (CR)	• Disappearance of all extranodal target lesions. • All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial response (PR)	• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest). • SLD must also demonstrate an absolute increase of at least 5 mm. (2 lesions increasing from, for example, 2 mm to 3 mm, does not qualify).
Stable disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Nonevaluable (NE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings).

SLD, sum of the longest diameters.

Nontarget Lesion Response

Complete response (CR)	• Disappearance of all extranodal nontarget lesions. • All lymph nodes must be nonpathological in size (<10 mm short axis). • Normalization of tumor marker level.
Non-CR/non-PD	• Persistence of 1 or more nontarget lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive disease (PD)	• Unequivocal progression of existing nontarget lesions (subjective judgment by experienced reader).
Unable to evaluate (UE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings).

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor (does not have to meet criteria to be "measurable").
- If a new lesion is equivocal, continue to next time point. If confirmed then, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new.
- New lesions on ultrasound should be confirmed on CT or MRI.

Evaluation of Overall Time Point Response for Patients With Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; NE, nonevaluable.

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)

GFR, glomerular filtration rate; S_{cr}, serum creatinine.
Levey et al, 2006 [41].

Appendix G Protocol History

Date	Amendment Number	Type	Region
24 September 2020	4	Substantial	Global
27 September 2019	3	Substantial	Global
10 April 2019	2	Substantial	Global
11 December 2018	1 DE v1	Nonsubstantial	Germany
12 October 2018	1 SE v1	Nonsubstantial	Sweden
03 May 2018	1	Nonsubstantial	Global
22 February 2018	Initial Protocol	Not applicable	Global

Amendment 3

Rationale for Amendment 3

The primary reason for this amendment is to remove the interim analysis.

Additional changes were made for consistency within the protocol and for clarity. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification purposes only.

Changes in Amendment 03

1. Removed interim analysis.
2. Clarified that the endpoint analyses will be performed using the full analysis set.

Amendment 2

Rationale for Amendment 2

The primary reason for this amendment is to update the following dose modification tables for consistency with the Company Core Data Sheet (CCDS) for brigatinib and provide clarity on allowed dose levels:

- Table 8.a Recommended Brigatinib Dose Reduction Levels.
- Table 8.b Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events.

Additional changes were made for consistency within the protocol and for clarity. Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification purposes only.

Changes in Amendment 2

1. Update primary objective in the Study Summary (Section 2.0) for consistency with primary objective in main protocol (Section 5.1.1).
2. Delete the redundant Sample Size Justification row from the Study Summary (Section 2.0).
3. Revise Study Design Figure 6.a to be consistent with the eligibility criteria.
4. Correct timing of AE assessments (Section 6.1).
5. Revise minimum age-related inclusion criterion and add clarification regarding patient sex (Section 7.1).
6. Clarify the definition of 1 cycle of prior systemic regimen and replace “antineoplastic” with “anticancer” (Section 7.2).
7. Update Table 8.a (Recommended Brigatinib Dose Reduction Levels).
8. Update Table 8.b (Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events).

9. Update Excluded Medications (Section 8.6) to include moderate CYP3A inhibitors and to provide further guidance to investigators.
10. Add information regarding administration of brigatinib with certain concomitant medications (Section 8.8).
11. Add list of acceptable highly effective non-hormonal methods of contraception (Section 8.8.1).
12. Correct timing for recording of concomitant medications (Section 9.4.9).
13. Provide additional guidance regarding clinical laboratory evaluations (Section 9.4.12).
14. Provide guidance regarding disease assessment of patients who continue study treatment at the same dose beyond documented PD (Section 9.4.14).
15. Remove buccal epithelial cell samples for DNA from Table 9.b (Section 9.4.18.1).
16. CCI [redacted]
17. CCI [redacted]
18. Clarify procedures for tumor assessment after study treatment discontinuation for reason other than disease progression (Section 9.9).
19. Clarify the primary endpoint analysis (Section 13.1).
20. Clarify definition of the full analysis set (Section 13.1.3.1).
21. Clarify sample size justification (Section 13.2).
22. Clarify conditional power for interim analysis (Section 13.3).
23. Add Risk-Benefit Section (Section 15.1).
24. Update SOE (Appendix A):
    - Buccal epithelial cells for DNA: remove from SOE.
    - Pregnancy test: Clarify footnote j regarding timing of test for screening.
    - Disease assessment: add footnote p regarding screening/baseline imaging and clarify footnote k regarding imaging during study treatment.
    - Archival tumor tissue sample: remove end of treatment sample and clarify footnote l related to screening sample.
    - Clarify optional tumor tissue biopsy as rebiopsy and add footnote q regarding optional tumor tissue and ctDNA at end of treatment.
25. Add Appendix F Modification of Diet in Renal Disease Equation for Estimated Glomerular Filtration Rate.

Amendment 1 DE v1

Rationale for Amendment 1 DE v 1

The primary reason for this amendment was to address requests about radiation exposure and minor technical editing from the Ethikkommission der Med. Fak. HD (Ethics Committee of the Medical Faculty of Heidelberg University) during initial assessment.

Changes in Amendment 1 DE v1

1. Clarification of inclusion criteria for brain imaging in Germany to be consistent with standard of care and recent changes to the Radiation Protection Act.
2. Clarification of statistical analysis used for the primary endpoint.
3. Clarification of sample size.
4. Clarification of statistical method used for interim analysis.

Amendment 1 SE v 1

Rationale for Amendment 1 SE v 1

The primary reasons for this amendment was to update the dose escalation schedule of events and to clarify that patient consent was required to receive treatment beyond progression.

Changes in Amendment 1 SE v 1

Patient consent was required before patients could receive treatment beyond progression. The dose escalation schedule was updated.

Amendment 1 (Global)

Rationale for Amendment 1

The primary reasons for this amendment were to update the dose escalation schedule of events and clarify that patient consent is required to receive treatment beyond progression.

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

Changes in Amendment 1

1. Patients are required to provide consent to receive an increased dose of brigatinib (240 mg QD).
2. Risk factors (such as tobacco and alcohol intake) will be captured during screening.
3. Updates to the schedule of events for treatment continuation at 240 mg QD after progression.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	25-Sep-2020 20:46 UTC
	Clinical Approval	25-Sep-2020 20:48 UTC
	Biostatistics Approval	26-Sep-2020 00:08 UTC