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

NCT Number: NCT03420742

Protocol Approve Date: 13 May 2019

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

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

Sponsor:	ARIAD Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA		
Study Number:	Brigatinib-1001		
IND Number:	IND 110,935	**EudraCT Number:**	2018-001624-19
Compound:	Brigatinib (ALUNBRIG)		
Date:	13 May 2019	**Amendment Number**:	01
Version Number:	1.0		

Amendment History

Date	Amendment Number	Type	Region
14 November 2017	Initial protocol	Not applicable	Global
13 May 2019	01	Substantial	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 is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored 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 Section 3.1 and relevant guidelines provided 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 Council 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, as applicable) can be found on the signature page.

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

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, 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 Council 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 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

This document describes the changes to the protocol incorporating Amendment 01. The primary reason for this amendment is to update the dose modification table (Table 8.b Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events) for consistency with the Company Core Data Sheet (CCDS) for brigatinib and provide clarity on allowed dose levels.

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

For specific descriptions of text changes and where the changes are located, see Appendix E.

Changes in Amendment 01

1. Update Table 8.a (Recommended Brigatinib Dose Reduction Levels)
2. Update Table 8.b (Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events).
3. Update Excluded Concomitant Medications and Procedures (Section 8.3) to include moderate cytochrome P450 (CYP) 3A inhibitors in Part B of the study and to provide further guidance to investigators.
4. Add information regarding administration of brigatinib with certain concomitant medications to Precautions and Restrictions (Section 8.5).
5. Update adverse event (AE) definition (Section 10.1.2) to provide guidance on reporting of disease progression.
6. Update Schedule of Events (Appendix E) to include laboratory tests on Day 15 of Cycle 1.
7. Update Schedule of Events (Appendix E) to include laboratory tests on Day 15 of Cycles 2 to 3.

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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	
Title of Protocol: A Phase 1 Drug-Drug Interaction Study Between Brigatinib and the CYP3A Substrate Midazolam in Patients With *ALK*-Positive or *ROS1*-Positive Solid Tumors	IND No. 110,935	EudraCT No. 2018-001624-19
Study Number: Brigatinib-1001	**Phase:** 1	

Study Design:

This study will consist of 2 parts: Part A (Cycle 1: pharmacokinetics [PK] cycle) and Part B (Cycle 2 and beyond: treatment cycles). Part A of the study will use a fixed-sequence design over a single 28-day treatment cycle. Patients will receive a 3 mg oral dose of midazolam on Day 1 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the absence of brigatinib. Brigatinib 90 mg will then be orally administered once daily (QD) on Days 2 through 8. If the 90 mg QD brigatinib dose is tolerated by the patient, the brigatinib dose will be increased to 180 mg QD, starting on Day 9 and continuing through Day 28 (in accordance with the United States [US] prescribing information). For patients who have escalated to brigatinib 180 mg QD, a 3 mg oral dose of midazolam will be administered on Day 21 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the presence of brigatinib.

Any patients in Part A who are not PK evaluable will be replaced. Patients will be considered PK evaluable if they receive the protocol-specified dosing regimen during Part A (including the 180 mg QD brigatinib dose) without dose reductions or interruptions through the completion of PK sampling (Day 22); do not receive any excluded concomitant medications through the completion of PK sampling; and have sufficient midazolam concentration-time data to permit the reliable estimation of PK parameters by noncompartmental analysis methods.

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

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

Primary Objective: To characterize the effect of repeat-dose administration of brigatinib 180 mg QD on the single-dose PK of midazolam.

Other Objectives:

Safety: To assess the safety and tolerability of brigatinib in patients with *ALK*-positive or *ROS1*-positive solid tumors.

CCI [redacted]

Subject Population: Adult cancer patients with locally advanced or metastatic solid tumors who meet 1 of the following 4 criteria: 1) patients with locally advanced or metastatic *ALK*-positive NSCLC who have progressed on

<table>
<tr><td colspan="2">treatment with at least 1 other ALK inhibitor, 2) patients with ALK-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available, 3) patients with locally advanced or metastatic ROS1-positive NSCLC who have progressed with crizotinib therapy or are intolerant to crizotinib, or 4) patients with ROS1-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available.</td></tr>
<tr><td>Number of Subjects: approximately 20 enrolled patients to achieve 15 PK-evaluable patients</td><td>Number of Sites: Approximately 16 sites in Europe</td></tr>
<tr><td>Dose Level(s):
Brigatinib: 180, 120, 90, 60 mg
Midazolam: 3 mg (Part A only)</td><td>Route of Administration: oral</td></tr>
<tr><td>Duration of Treatment:
Part A:
Midazolam: 2 single 3 mg doses on Day 1 and Day 21.
Brigatinib: 90 mg QD×7 days, followed by 180 mg QD× 20 days.
Part B: Brigatinib at highest tolerated dose (180, 120, 90, or 60) QD×28 days per cycle. During Part B, patients may receive up to 23 months of treatment, or treatment until PD, intolerable toxicity, or another discontinuation criterion is met. If patients are still continuing to receive benefit at 23 months, they may have the option to continue brigatinib monotherapy at the same dose.</td><td>Period of Evaluation:
Part A: 28 days
Part B: up to 23 28-day cycles through the 30-day Follow-up period following EOT
(A maximum period of evaluation of 25 months)</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
• Adult patients with cancer aged 18 years and older.
• Patients with locally advanced or metastatic solid tumors who meet 1 of the following 4 criteria: 1) patients with locally advanced or metastatic ALK-positive NSCLC who have progressed on treatment with at least 1 other ALK inhibitor; 2) Patients with ALK-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available; 3) Patients with locally advanced or metastatic ROS1-positive NSCLC who have progressed with crizotinib therapy or are intolerant to crizotinib, or 4) patients with ROS1-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available. Note: ALK or ROS1 positivity does not need to be diagnosed by a US FDA-approved test.
• Total bilirubin ≤1.5 times the upper limit of the normal range.
• Estimated glomerular filtration rate ≥30 mL/minute/1.73 m^2.</td></tr>
<tr><td colspan="2">Main Criteria for Exclusion:
• Systemic treatment with strong or moderate cytochrome P450 3A inhibitors or inducers within 14 days before enrollment.
• Prior therapy with brigatinib.</td></tr>
<tr><td colspan="2">Endpoints and Assessments:
• Primary: Midazolam PK parameters in the presence and absence of brigatinib, including:
– Area under the concentration-time curve from time 0 to infinity (AUC_∞)
– Maximum observed concentration (C_{max})
– Time of first occurrence of C_{max} (t_{max}).
Other endpoints include safety and tolerability CCI [redacted], including confirmed objective response rate,</td></tr>
</table>

duration of response, and progression-free survival in the 4 subgroups of patients.
Statistical Considerations: Midazolam PK parameters in the presence and absence of brigatinib will be summarized descriptively. For the estimation of the effect of brigatinib on midazolam PK, the ratios of geometric mean midazolam AUC_{∞} and C_{max} (with vs without brigatinib coadministration) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance using a mixed-effects analysis of variance. Analyses for Part A of the study will be performed when all patients have completed Cycle 1 (PK cycle) and will include analyses of PK and safety. Descriptive statistics will be presented for continuous safety variables (laboratory test values, vital signs, weight) by scheduled time point. Shift tables for laboratory parameters will be generated to show changes in National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, grade from Baseline to the worst post-Baseline value.
Sample Size Justification: It is anticipated that approximately 20 patients will be enrolled to obtain approximately 15 PK-evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC_{∞} means of midazolam in the absence and presence of brigatinib. The within-patient coefficient of variation for midazolam AUC_{∞} was estimated to be 28% on the basis of a pooled analysis of data from 5 drug-drug interaction studies with midazolam conducted in patients with cancer [1-5]. Assuming that the AUC_{∞} ratio for midazolam in the presence versus absence of brigatinib is 1, with a sample size of 15, the 90% CI for the AUC_{∞} ratio is expected to be 0.84 to 1.19 on the basis of the variance assumptions. If the AUC_{∞} ratio for midazolam in the presence versus absence of brigatinib is X, with a sample size of 15, the 90% CI for the AUC_{∞} ratio is expected to be 0.84X to 1.19X on the basis of the variance assumptions.

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 clinical study supplier list or equivalent. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

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

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

3.4 Corporate Identification

ARIAD	ARIAD Pharmaceuticals Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Americas	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

Lung cancer is the leading cause of cancer death in the United States (US) and Europe. Approximately 78% of patients have regional/distance metastases at diagnosis [6], and the 5-year survival rates are low (17.7% and 13.0%, respectively) [7]. In the United States, an estimated 222,500 new cases of lung and bronchial cancer will be diagnosed by the end of 2017, with an estimated 155,870 deaths occurring due to the disease [8].

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 [9,10], and includes a number of subtypes such as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, and bronchioloalveolar carcinoma [11]. In recent years, attention has turned to stratifying patients with lung cancer on the basis of molecular alterations. This is because 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 *EGFR*-mutant and *ALK*-rearranged NSCLC. NSCLC and other solid tumors that contain oncogenic rearrangements in the *ALK* gene and the *ROS1* gene are potential targets for brigatinib.

Brigatinib is an orally administered tyrosine kinase inhibitor whose primary targets are activated, mutant forms of *ALK* and *ROS1*, which play important roles in NSCLC and other solid tumors. *ALK* is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults [12]. A series of in vitro and in vivo studies to characterize the pharmacodynamic profile of brigatinib have demonstrated that brigatinib potently inhibits activated variants of *ALK*, such as *EML4-ALK*, and variants of *ALK*, including the L1196M gatekeeper mutation that confers resistance to crizotinib. No *ALK* mutations that confer resistance to brigatinib at clinically achievable concentrations have been identified in in vitro mutagenesis assays, and brigatinib has been shown to potently inhibit activated variants of *ROS1* kinase. Brigatinib also inhibits certain mutant variants of *EGFR* and *IGF1R* without affecting the insulin receptor.

Brigatinib (marketed as ALUNBRIG) was granted accelerated approval by the US Food and Drug Administration (FDA) on 28 April 2017 for the treatment of patients with metastatic *ALK*-positive NSCLC who have progressed on or are intolerant to the *ALK* inhibitor crizotinib. The recommended dose of brigatinib is 90 mg orally once daily (QD) for the first 7 days, and if tolerated, the dose is to be increased to 180 mg QD. Approval was based on the phase 2 Study AP26113-13-201, which compared the brigatinib 90 mg QD dosing regimen to the 90 mg→180 mg QD dosing regimen (90 mg QD for 7 days followed by escalation to 180 mg QD) in patients who had progressed on crizotinib. Brigatinib is designated an orphan drug for the treatment of *ALK*-positive, *ROS1*-positive, and *EGFR*-positive NSCLC.

In ongoing Study AP26113-13-201, patients were stratified for randomization by brain metastases at Baseline and best response to prior treatment with crizotinib. Based on data from a clinical database extraction date of 21 February 2017, brigatinib is highly effective in the

crizotinib-refractory, *ALK*-positive NSCLC population, with confirmed investigator-assessed objective response rates (ORRs) of 45.5% and 55.5% for the 90 mg QD and 90 mg→180 mg QD regimens, respectively, and investigator-assessed progression-free survival (PFS) of 9.2 months and 15.6 months, respectively. In patients with measurable brain metastases at Baseline, the IRC-assessed intracranial ORR was 50.0% and 66.7% for patients receiving the 90 mg QD and 90 mg→180 mg QD regimens, respectively.

In ongoing phase 1/2 Study AP26113-11-101, 2 of the 4 patients with *ROS1*-positive NSCLC who were enrolled had confirmed partial responses (PRs) to brigatinib, with durations of response (DORs) of 22.5 and 22.8 months; both patients were crizotinib naïve.

Also ongoing is the phase 3, randomized Study AP26113-13-301, which is evaluating brigatinib versus crizotinib in patients with locally advanced or metastatic *ALK*-positive NSCLC who have had no prior therapy with an *ALK* inhibitor.

4.2 Rationale for the Proposed Study

In vitro studies using human hepatocytes have indicated that brigatinib, at clinically relevant concentrations of 1 to 2.5 µM, caused an increase in CYP3A4 messenger RNA levels (see the Investigator's Brochure for further details). Therefore, brigatinib may have the potential for pharmacokinetic (PK) drug interactions with substrates of CYP3A through induction of expression of this enzyme, potentially leading to decreased systemic exposures of its substrates.

The primary purpose of this study (Brigatinib-1001) is to evaluate the effect of repeated doses of brigatinib on the single-dose PK of midazolam, a sensitive CYP3A probe substrate, to determine if brigatinib, at therapeutic doses, produces clinically meaningful CYP3A induction in vivo, and if so, to inform strategies for the management of potential drug-drug interactions (DDIs) between brigatinib and substrates of CYP3A. Midazolam is an established sensitive substrate of CYP3A that is commonly used in clinical DDI studies to assess the effect of a coadministered drug on CYP3A activity [13,14]. Oral doses of midazolam ranging from 2 to 7.5 mg have generally been used in clinical DDI studies [1,2,15-17]. A 3 mg oral dose of midazolam was selected for use in this study to allow for adequate PK characterization of midazolam after administration in both the absence (ie, baseline CYP3A expression levels) and presence (ie, possibly induced CYP3A expression levels) of brigatinib.

CCI [redacted] In addition to *ALK*-positive patients with NSCLC, patients with *ROS1*-positive NSCLC, and patients with *ALK*-positive or *ROS1*-positive nonlung solid tumors—all with locally advanced or metastatic disease—are eligible for enrollment, CCI [redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Safety Objective

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

CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

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

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

5.2.2 Secondary Endpoints

There are no secondary endpoints for this study.

5.2.3 Safety Endpoints

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

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

6.0 STUDY DESIGN

6.1 Overview of Study Design

This open-label, multicenter, phase 1 study will enroll approximately 20 patients with *ALK*-positive or *ROS1*-positive solid tumors, including NSCLC, and will consist of 2 parts: Part A (Cycle 1: PK cycle) and Part B (Cycle 2 and beyond: treatment cycles).

6.1.1 Part A

Part A will use a fixed-sequence design over a single 28-day treatment cycle (Figure 6.a). All patients will receive a 3 mg oral dose of midazolam on Day 1, with serial PK sampling performed over the 24 hours following dosing to characterize the PK of midazolam in the absence of brigatinib. Brigatinib 90 mg QD will then be orally administered on Days 2 through 8. If the 90 mg brigatinib dose is tolerated by the patient, the brigatinib dose will be increased to 180 mg QD, starting on Day 9 and continuing through Day 28 (in accordance with the US prescribing information). For patients escalating to brigatinib 180 mg QD, a 3 mg oral dose of midazolam will be administered on Day 21 of Part A, with serial PK sampling performed over the 24 hours following dosing to characterize the PK of midazolam in the presence of brigatinib.

Any patients in Part A who are not PK evaluable will be replaced. Patients will be considered PK evaluable if they receive the protocol-specified dosing regimen during Part A (including the 180 mg QD brigatinib dose) without dose reductions or interruptions through the completion of PK sampling (Day 22); do not receive any excluded concomitant medications through the completion of PK sampling; and have sufficient midazolam concentration-time data to permit the reliable estimation of PK parameters by noncompartmental analysis methods.

Serial blood samples for determination of plasma concentrations of midazolam will be obtained during Part A (Cycle 1: PK cycle) at prespecified time points up to 24 hours postdose, as described in Appendix A Table 1 and Appendix A Table 2. Predose blood samples will also be collected on Days 21 and 22 of Part A and on Day 1 of Cycle 2 (Part B) to measure trough plasma concentrations of brigatinib.

Figure 6.a Study Design for Part A (Cycle 1: PK Cycle)

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

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

6.1.2 Part B

After completion of Part A, patients may continue to Part B to receive the potential therapeutic benefits of brigatinib. Any patients who are replaced because they are not PK evaluable in Part A will also be eligible to continue into Part B. The starting dose of brigatinib in Part B will be the dose that was tolerated by the patient at the end of Part A. Part B of the study will include 28-day treatment cycles in which brigatinib will continue to be dosed QD at the highest tolerated dose (up to 180 mg QD) up to 23 cycles of treatment, or until PD, intolerable toxicity, or another discontinuation criterion is met.

Patients who cannot escalate to 180 mg QD in Part A will be maintained at 90 mg QD or 60 mg QD. The brigatinib daily oral doses administered during Part A and Part B may include 180 mg or lower. Doses of 120, 90, and 60 mg may be offered as options to allow patients to have their dose reduced in cases of intolerability.

Drug safety and tolerability will be evaluated during the study by AE monitoring, clinical laboratory tests, vital sign measurements, and physical examinations. An electrocardiogram (ECG) will be performed at Screening, Day 1 of Part B, and at the end of treatment (EOT). The study will include a 30-day follow-up period after EOT for reporting of AEs and subsequent therapy. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010 [18].

CCI

[redacted]

6.2 Number of Patients

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

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Following the single 28-day PK cycle in Part A of the study, patients may enter Part B and continue daily treatment with brigatinib in 28-day repeated cycles at their highest tolerated dose (up to 180 mg QD) for up to 23 months of treatment or until PD, intolerable toxicity, or another discontinuation criterion is met. All patients will be assessed for safety and subsequent therapy during the 30-day follow-up period after EOT.

The maximum duration of study participation for an individual patient will be approximately 26 months (which includes screening period, the Part A PK cycle, a maximum of 23 cycles in Part B, and the 30-day follow-up period after EOT).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion

The estimated time frame for primary completion of the study is 13 to 15 months, which includes an estimated 12- to 14-month enrollment period and Part A of the study. The clinical study report (CSR) analyses for the primary endpoint will be conducted after all PK-evaluable patients complete Part A of the study, and will include analyses of PK and safety.

Other Planned Analyses

A CSR addendum for safety [CCI] is planned for when all enrolled patients have completed Part B of the study (approximately 2 years after enrollment of the last patient).

Study Completion

The estimated time frame for overall study completion is approximately 3 years.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for the primary endpoint.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
The primary endpoints of this study are midazolam PK parameters in the presence and absence of brigatinib, including: • AUC_{∞}. • C_{max}. • t_{max}.	Midazolam AUC_{∞}, C_{max}, t_{max}	For an individual patient, from predose up to 24 hours postdose on Days 1 and 21, for a total time frame of 22 days.
There are no secondary endpoints for this study.		

6.3.4 Total Study Duration

Part A will consist of a single 28-day PK cycle. Part B will consist of repeated 28-day treatment cycles up to 23 months of treatment (24 months in total, including Part A), or until PD, intolerable toxicity, or discontinuation due to other reasons. The total duration of the study is anticipated to be up to approximately 3 years, including the enrollment period, Part A PK cycle, Part B treatment cycles, and follow-up period.

6.3.5 Posttrial Access

Currently, there is no posttrial access (PTA) protocol available in the brigatinib development program. If an open-label, rollover, PTA study should become an option, and the investigator and sponsor agree that a patient would derive benefit from continued treatment or would be harmed

without continued access to brigatinib, the patient may be given the opportunity to enter the rollover study and continue receiving brigatinib.

In the event of a rollover PTA study, continued access to brigatinib for study participants will be terminated for those individuals who no longer benefit from treatment (eg, they have completed the recommended course of therapy or their disease has improved or resolved), the benefit-risk profile no longer favors the individual, or an appropriate alternative therapy becomes available. If patients are placed in a rollover PTA study, they will be considered to have completed Study Brigatinib-1001. PTA may be terminated in a country or geographical region where the development of brigatinib has been suspended or stopped by the sponsor or brigatinib can no longer be supplied.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Adult patients with cancer aged 18 years and older.
2. Patients with locally advanced or metastatic solid tumors who meet 1 of the following 4 criteria: 1) patients with locally advanced or metastatic *ALK*-positive NSCLC who have progressed on or are intolerant to treatment with at least 1 other *ALK* inhibitor, 2) patients with *ALK*-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available, 3) patients with locally advanced or metastatic *ROS1*-positive NSCLC who have progressed on crizotinib therapy or are intolerant to crizotinib, or 4) patients with *ROS1*-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available. *Note:* ALK *or* ROS1 *positivity does not need to be diagnosed by a US FDA-approved test.*
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Have at least 1 target lesion per RECIST version 1.1.
5. Have recovered from toxicities related to prior anticancer therapy to NCI CTCAE version 4.03 Grade ≤1. *Note: Treatment-related alopecia and peripheral neuropathy that are Grade >1 are allowed, if deemed irreversible.*
6. Adequate organ function as determined by:
   - Total bilirubin ≤1.5 times the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5×ULN; ≤5×ULN is acceptable if liver metastases are present.
   - Estimated glomerular filtration rate (eGFR) ≥30 mL/minute/1.73 m^2, calculated using the Modification of Diet in Renal Disease equation:

     eGFR (mL/min/1.73 m^2)=175×(serum creatinine in mg/dL)$^{-1.154}$×(age in years)$^{-0.203}$×(0.742 if female)×(1.212 if African American).
   - Serum lipase/amylase ≤1.5×ULN.
   - Absolute neutrophil count (ANC) ≥1.5×10^9/L.
   - Platelet count ≥75×10^9/L.
   - Hemoglobin ≥10 g/dL.
7. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, or
   - Are surgically sterile, or

- If they are of childbearing potential, agree to practice 1 highly effective *nonhormonal* method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
- Agree to practice true abstinence during the entire study treatment period through 4 months after the last dose of study drug, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8. Male patients, even if surgically sterilized (ie, postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period through 4 months after the last dose of study drug, or
   - Agree to practice true abstinence during the entire study treatment period through 4 months after the last dose of study drug, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
9. Suitable venous access for study-required blood sampling (ie, including PK and laboratory safety tests).
10. Have the willingness and ability to comply with scheduled visits and study procedures.
11. Provide 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. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

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

1. Systemic treatment with strong or moderate CYP3A inhibitors or inducers within 14 days before enrollment. (See Section 8.3 for lists of strong and moderate CYP3A inhibitors and inducers.)
2. Prior therapy with brigatinib.
3. Received prior *ALK*-inhibitor therapy within 7 days before the first dose of study drug.
4. Treatment with any investigational systemic anticancer agents within 14 days or 5 half-lives, whichever is longer, before the first dose of study drug.
5. Received chemotherapy or radiation therapy within 14 days before the first dose of study drug, except for stereotactic radiosurgery (SRS) or stereotactic body radiation therapy.

6. Received antineoplastic monoclonal antibodies within 30 days before the first dose of study drug.
7. Had major surgery within 30 days before the first dose of study drug. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed.
8. Have symptomatic central nervous system (CNS) metastases (parenchymal or leptomeningeal) at Screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days before study enrollment. *Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days before study enrollment.*
9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
10. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
    - Myocardial infarction within 6 months before the first dose of study drug.
    - Unstable angina within 6 months before the first dose of study drug.
    - Congestive heart failure (ie, New York Heart Association Class III or IV) within 6 months before the first dose of study drug.
    - History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician.
    - Any history of ventricular arrhythmia.
    - Cerebrovascular accident or transient ischemic attack within 6 months before the first dose of study drug.
11. Have uncontrolled hypertension. Patients with hypertension should be under treatment for control of blood pressure upon study entry.
12. Female patients who are pregnant, planning a pregnancy, or breastfeeding.
13. Have a history or presence at Baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
14. Have an ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics.
15. Have a known history of HIV infection. Testing is not required in the absence of history.
16. Have a known or suspected hypersensitivity to brigatinib or midazolam or their excipients.
17. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of midazolam or brigatinib, including difficulty swallowing or diarrhea Grade >1, despite supportive therapy.

18. Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to this protocol.
19. Life-threatening illness unrelated to cancer.
20. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
21. Known hepatitis B surface antigen positive, or known or suspected active hepatitis C infection.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before study drug administration. Study drug will be dispensed only to eligible patients under the supervision of the investigators or identified subinvestigators.

On Day 1 of Part A (Cycle 1: PK cycle), all enrolled patients will report to the clinic and receive a 3 mg oral solution dose of midazolam on an empty stomach (ie, at least 1 hour before or at least 2 hours after food). Immediately after administration of the oral midazolam dose, patients will consume approximately 8 ounces (240 mL) of water. Following collection of the 24-hour midazolam PK sample on Day 2 of Part A, patients will be dispensed brigatinib for administration of 90 mg QD on Days 2 through 8. Patients will return to the clinic on Day 9 for a study visit, and if the 90 mg QD brigatinib dose was tolerated on Days 2 through 8, the brigatinib dose will be increased to 180 mg QD. Patients will be instructed to administer each brigatinib dose at approximately the same time each day, approximately 24 hours apart, and as close as possible to the anticipated time of midazolam administration on Day 21 (ie, in the morning). Brigatinib may be taken with or without food on Days 2 through 20 of Part A. Patients will take the prescribed dose of brigatinib with approximately 8 ounces (240 mL) of water. On Days 21 and 22 of Part A, the 180 mg QD brigatinib dose will be administered in the clinic as described below.

On Day 21 of Part A, patients receiving the 180 mg daily dose of brigatinib will return to the clinic. Following collection of the Day 21 midazolam and brigatinib predose PK samples, patients will take 180 mg of brigatinib in the clinic together with 3 mg of oral midazolam on an empty stomach (ie, at least 1 hour before or at least 2 hours after food). The 3 mg oral solution dose of midazolam should be administered first, immediately followed by administration of the 180 mg dose of brigatinib with approximately 8 ounces (240 mL) of water.

Following collection of the PK samples on Day 22 (ie, 24-hour midazolam PK sample and predose brigatinib PK sample), QD administration of brigatinib will continue on Days 22 through 28 of Part A. Patients will continue on their highest tolerated dose of brigatinib (up to 180 mg QD) through Day 28 of Part A. Patients will be instructed to take brigatinib doses with or without food at approximately the same time each day and approximately 24 hours apart. Patients will take the prescribed dose of brigatinib with approximately 8 ounces (240 mL) of water.

Patients continuing into Part B of the study will visit the clinic on Day 1 of Cycle 2. The Cycle 2 Day 1 brigatinib dose will be administered in the clinic after collection of a predose brigatinib PK sample. Patients will continue into Part B at the brigatinib dose that they were receiving (and tolerating) at the end of Part A (180, 120, 90, or 60 mg) and will continue treatment until PD, unacceptable toxicity, or another discontinuation criterion is met. Brigatinib doses during Part B may be taken with or without food and should be taken at approximately the same time each day (ie, approximately 24 hours apart). Patients will take the prescribed dose of brigatinib with approximately 8 ounces (240 mL) of water.

During Part A, the date and time of brigatinib administration should be recorded in the patient's dosing diary. A diary will not be used in Part B of the study. If a patient fails to take the brigatinib

dose within the time frame specified (ie, within ±4 hours of the initial dosing time), that dose should be omitted and considered a missed dose. The patient should record any missed doses in the dosing diary. If emesis occurs after study drug administration, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled dosing time with the prescribed dosage. The timing of emesis relative to study drug administration should be recorded. Patients should not repeat a dose, try to make up a dose, or "double up" doses. In the case of a missed dose or emesis in Part A, patients may be considered not PK evaluable and may be replaced.

8.2 Dose Modification Guidelines

8.2.1 Recommended Dosing

In Part A, patients who have tolerated the 90 mg starting dose on Days 2 through 8 of Cycle 1 will be expected to increase their daily dose to 180 mg, beginning on Day 9 and continuing through Day 28. The patient's daily dose of brigatinib should **not** be increased to 180 mg if any of the following adverse drug reactions are experienced during treatment with 90 mg QD:

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

If a patient did not experience any of the above adverse drug reactions, but dose escalation did not occur during Part A, dose escalation may be permitted during Part B following approval from the medical monitor. The brigatinib daily dose must not exceed 180 mg daily.

8.2.2 Dose Modifications for Treatment-Related AEs

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

Table 8.a Recommended Brigatinib Dose Reduction Levels

Dose	Dose Reduction Levels			
	First	Second	Third	Fourth
90 mg QD (first week of treatment)	60 mg QD	Permanently discontinue	Not applicable	Not applicable
180 mg QD	120 mg QD	90 mg QD	60 mg QD	Permanently discontinue

Recommendations for dose modification of brigatinib for the management of treatment-related AEs are provided in Table 8.b and are based on the CCDS for brigatinib (ALUNBRIG). Unless

otherwise noted, reduce the dose as indicated in Table 8.b if 1 or more dose reductions are necessary because of Grade 3/4 treatment-related AEs (as defined by NCI CTCAE version 4.03).

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

AE	Severity (a)	Dose Modification
ILD/ pneumonitis	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue brigatinib.
	Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline. Resume at next lower dose (Table 8.a) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 8.a); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue brigatinib.
	Grade 3 or 4	Permanently discontinue brigatinib for ILD/pneumonitis.
Hypertension	Grade 3 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg, medical intervention indicated, more than 1 antihypertensive drug, or more intensive therapy than previously used indicated)	• Withhold brigatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume brigatinib at same dose. • Recurrence: Withhold brigatinib until recovery to Grade 1 or less, then resume at next lower dose or permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold brigatinib until recovery to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume at next lower dose (Table 8.a) or permanently discontinue treatment. • Recurrence: Permanently discontinue brigatinib for recurrence of Grade 4 hypertension.

Footnotes are on last table page.

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

AE	Severity (a)	Dose Modification
Bradycardia (HR <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 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 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.
Visual disturbance	Grade 2 or 3 visual disturbance	Withhold brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose
	Grade 4 visual disturbance	Permanently discontinue brigatinib.
CPK elevation	Grade 3 CPK elevation (>5.0×ULN)	• Withhold brigatinib until recovery to Grade 1 or less (≤2.5×ULN) or to baseline, then resume brigatinib at same dose. • If Grade 3 elevation of CPK recurs, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 2.5 x ULN) or to baseline, then resume at the next lower dose level per Table 8.a.
	Grade 4 CPK elevation (>10.0×ULN)	• Withhold brigatinib until recovery to Grade 1 or less (≤2.5×ULN) or to baseline, then resume brigatinib at next lower dose. • If Grade 4 elevation of CPK recurs, permanently discontinue brigatinib.
Lipase/amylase elevation	Grade 3 lipase or amylase elevation (>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 witheld until recovery to Grade 1 or less (less than or equal to 1.5×ULN) or to baseline, then resume at the next lower dose level per Table 8.a.

AE	Severity (a)	Dose Modification
	Grade 4 lipase or amylase elevation (>5.0×ULN)	• Withhold brigatinib until recovery to Grade 1 or less (≤1.5×ULN) or to baseline, then resume brigatinib at next lower dose • If Grade 4 elevation of lipase/amylase recurs, permanently discontinue brigatinib.
Hyper-glycemia	Grade 3 (>250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next lower dose **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.
	Grade 4	• First occurrence: either withhold brigatinib until recovery to baseline and resume at next lower dose or permanently discontinue. • Permanently discontinue brigatinib for recurrence.

Source: US prescribing information, April 2017.
Bpm=beats per minute, CPK=creatine phosphokinase, DBP=diastolic blood pressure, HR=heart rate, SBP=systolic blood pressure.
(a) Graded per NCI CTCAE version 4.03.

Grade 3 nonhematologic toxicities attributed to brigatinib that do not require dose reduction include:

- Grade 3 or greater nausea and/or emesis in the absence of optimal antiemetic prophylaxis. *(Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)*
- Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy.
- Grade 3 fatigue.

8.2.3 Reescalation After Dose Reduction

Reescalation of brigatinib after dose modification for AEs is discouraged; however, if in the opinion of the treating investigator, reescalation is warranted, this must be undertaken after consultation with the sponsor.

For a patient to be a candidate for dose reescalation, the AE that led to dose modification must **not** have reoccurred, and the patient must have had no other Grade 3/4 AEs in the past 28 days.

8.2.4 Reintroducing Brigatinib After Dose Interruption

If brigatinib treatment is interrupted for less than 14 days, patients may resume treatment at the current dose, provided the patient does not meet any of the criteria to reduce their dose by 1 dose level (as indicated in Table 8.b).

If brigatinib treatment is interrupted for 14 days or more, with the interrupted dose being greater than 90 mg QD, patients should resume brigatinib treatment at 90 mg QD for 7 days before escalating the dose to 120 mg QD or 180 mg QD; however, the dose should not be escalated higher than the dose level before treatment was interrupted.

8.3 Excluded Concomitant Medications and Procedures

Systemic treatment with the following medications is prohibited for 14 days before study enrollment and during Part A (Cycle 1: PK cycle) of 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.
- Moderate CYP3A inhibitors: amprenavir, aprepitant, atazanavir, ceritinib, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, diltiazem, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, and verapamil.
- 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.

Systemic treatment with the following medications should be avoided during Part B of 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 in Part B of the study, reduce the brigatinib QD dose by approximately 50% (ie, from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the brigatinib dose that was tolerated before the strong CYP3A inhibitor was initiated.
- Moderate CYP3A inhibitors: amprenavir, aprepitant, atazanavir, ceritinib, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, diltiazem, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, 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 the moderate CYP3A inhibitor was initiated.

- 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.

Because 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 prohibited during the study:

- Any investigational agent other than brigatinib, including agents that are commercially available for indications other than *ALK*-positive or *ROS1*-positive NSCLC and other solid tumors that are under investigation for the treatment of NSCLC and other solid tumors.
- 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.

8.4 Permitted Concomitant Medications and Procedures

During Part A of the study, no new concomitant therapy is allowed unless approved by the medical monitor, with the exception of concomitant medications found necessary by the investigator to treat severe or life-threatening conditions. Patients will be allowed to continue concomitant medications that they were taking during study screening, as long as the medications are not strong or moderate CYP3A inhibitors or inducers or other excluded medications, as described in Section 8.3.

During Part B, palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment. Patients with CNS 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, these patients will be considered to have PD.

Concomitant medications for all ongoing medical history conditions or AEs, as well as prophylactic treatments and supplements, must be reported from the date the informed consent is signed through the 30-day follow-up period after EOT. All concomitant medications related to serious or study-drug–related toxicities must be reported until the medication is no longer taken or until patient contact ceases.

Radiation therapy for the disease under study is allowed but will be considered evidence of PD; therefore, such patients will be considered to have PD at or before the initiation of radiation therapy.

8.5 Precautions and Restrictions

8.5.1 Brigatinib

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

Brigatinib is an in vitro inhibitor of P-gp, breast cancer resistance protein, organic cation transporter 1, multidrug and toxin extrusion protein 1 and 2K. 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.

If a patient experiences a brigatinib-related side effect, the investigator will advise the patient of any precautions or restrictions.

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

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 and 1 additional effective (barrier) method of contraception from the time of signing the informed consent form through 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 subject during the dosing period through 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.)

Male patients with female partners of reproductive potential, even if surgically sterilized (ie, postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 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 subject, from the time of signing the informed consent form through 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.)

8.5.2 Midazolam

Midazolam is a short-acting benzodiazepine that depresses activity of the CNS and has been associated with respiratory depression, most often when used concomitantly with other CNS depressants (eg, opioids and other benzodiazepines). Therefore, all patients will be closely monitored for respiratory and cardiac function (ie, pulse oximetry) after administration of midazolam on Days 1 and 21 of Part A of the study. Immediate availability of reversal agents (eg, flumazenil), resuscitative drugs, equipment for ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured. Please refer to the midazolam prescribing information for full details regarding the use of midazolam.

Midazolam causes sedation. Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination after receiving midazolam on Day 1 and Day 21 of Part A of the study.

8.6 Management of Selected Treatment-Related Clinical Events

8.6.1 Nausea and/or Vomiting

Although this study will not initially employ prophylactic antiemetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-HT_3 receptor antagonists and corticosteroids should be tried first.

8.6.2 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. Management of diarrhea will be at the discretion of the investigator. Fluid intake should be maintained to avoid dehydration.

8.6.3 Pneumonitis

Pneumonitis and ILD are known side effects of tyrosine kinase inhibitors used in NSCLC, generally occurring later in the course of therapy. Drug-related pneumonitis may be associated with signs and symptoms such as dyspnea, hypoxia, cough, hemoptysis, and fever, and radiologic evidence of parenchymal or interstitial changes.

The diagnosis of pneumonitis and determination of causal relationship to the drug is often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors, such as lung infection and radiation effects due to nonspecific signs and symptoms, and similar radiological appearance. Pneumonitis should be suspected when such signs and symptoms

develop, or in asymptomatic patients when a new ground glass opacity or interstitial infiltration is noted in imaging studies. If a patient is considered to have the potential diagnosis of drug-related pneumonitis, physical examination, assessment of oxygen saturation, evaluation for infectious etiologies, and thoracentesis, bronchoscopy, or open-lung biopsy should be considered to reach a diagnosis. If the causality is at least possibly related to the study drug, management of pneumonitis, including dose interruption and potential discontinuation, is required (see Table 8.b).

8.6.4 Hypertension

Blood pressure should be monitored and recorded at each visit. Hypertension detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE, version 4.03, which defines hypertension as a disorder characterized by a pathological increase in blood pressure: a repeated elevation in blood pressure exceeding 140 mmHg for systolic blood pressure (SBP) and 90 mmHg for diastolic blood pressure (DBP). For patients who either develop hypertension or experience worsening hypertension during treatment with study drug, antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study drug. If hypertension is persistent despite adequate antihypertensive therapy—including titration of antihypertensive medication or introduction of additional antihypertensive medications—or if Grade 4 hypertension develops, dose interruption and reduction is recommended (see Table 8.b).

8.6.5 Bradycardia

Heart rate should be monitored and recorded at each visit. Brigatinib should be avoided in combination with other agents known to cause bradycardia (eg, β-blockers, nondihydropyridine calcium-channel blockers, clonidine, and digoxin) to the extent possible. For symptomatic bradycardia, dose interruption and reduction is recommended (see Table 8.b).

8.6.6 Visual Disturbance

In patients with new onset or worsening severe (Grade ≥3) visual disturbance, ophthalmological evaluation should be performed. Visual disturbance should be managed as described in Table 8.b.

8.7 Blinding and Unblinding

As this is an open-label study, there will be no study drug blinding.

8.8 Description of Investigational Agents

Brigatinib will be supplied as film-coated tablets in the following strengths of active pharmaceutical ingredient: 30, 90, and 180 mg, with all strengths being dose to weight proportional. The inactive ingredients (excipients) will include lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide. Brigatinib is manufactured under current Good Manufacturing Practice in accordance with approved procedures.

Midazolam is a short-acting benzodiazepine that is a probe substrate of CYP3A. Midazolam oral syrup (2 mg/mL) will be obtained from commercial sources. The dose regimen for midazolam in this study is 3 mg orally on Day 1 and Day 21 of Part A (ie, 1.5 mL of the 2 mg/mL syrup). Midazolam will be administered on an empty stomach (ie, at least 1 hour before or at least 2 hours after food). The dose of midazolam should be administered using an oral syringe. Patients will consume approximately 8 ounces (240 mL) of water immediately after administration of midazolam. The precautions, warnings, contraindications, and AEs associated with midazolam therapy are included in the midazolam prescribing information.

8.9 Dispensation of Study Drug

Brigatinib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling it. Brigatinib will be supplied to the study sites as film-coated tablets (30, 90, and 180 mg) in high-density polyethylene (HDPE) bottles with child-resistant caps.

Midazolam hydrochloride oral syrup, at a concentration of 2 mg/mL, will be obtained commercially and administered to patients on Days 1 and 21 of Part A.

Additional details regarding study drug dispensation are provided in the study manual.

8.10 Packaging and Labeling

Brigatinib film-coated tablets will be supplied to the study sites in strengths of 30, 90, and 180 mg in white HDPE bottles with induction sealed, polypropylene child-resistant caps. Each bottle of brigatinib will be labeled with pertinent study information, country-specific requirements, and a caution statement. Brigatinib will be dispensed directly to the patients without repackaging.

8.11 Storage, Handling, and Accountability

Brigatinib tablets should be stored at controlled room temperature (20°C-25°C; 68°F-77°F), with excursions permitted from 15°C to 30°C (59°F-86°F); refrigeration or freezing is not permitted. Storage area temperature conditions must be monitored and recorded daily. All temperature excursions must be reported to the sponsor for assessment and determination for continued use.

Brigatinib tablets should remain in the original bottle provided to the study site for dispensation to patients. The drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients.

A record is to be kept at the study site documenting the amount of study drug received from the sponsor, the amount dispensed to individual patients, and the amount returned to the site by the patients.

Midazolam hydrochloride oral syrup, 2 mg/mL, will be obtained from commercial sources and should be stored in accordance with the product's prescribing information.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

Contact information for the project clinician, laboratory conducting the analysis of PK samples, coordinating investigator, interactive response technology (IRT) provider, and contract research organization (CRO) team may be found in the study manual. The list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

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

9.3 Study Procedures

During Part A of the study (Cycle 1: PK cycle), clinic visits will take place on Days 1, 2, 9, 15, 21, and 22. Blood sampling for midazolam PK characterization will take place over the 24-hour postdose period beginning on Days 1 and 21. Patients will be closely monitored for respiratory and cardiac function (ie, pulse oximetry) after administration of midazolam on Days 1 and 21.

During Part B, clinic visits will take place on Day 1 of each cycle (±3 days) for assessment of ECOG performance status, physical examination, weight and vital signs measurements. Laboratory tests will be conducted on Day 1 (± 3 days) and Day 15. Imaging assessments will be conducted on Day 28 (± 3 days) of every even-numbered cycle up to Cycle 14, and on Day 28 (±3 days) for every 3 cycles thereafter.

For the timing of assessments, please refer to the Schedules of Events in Appendix A (Table 1 for Part A and Table 3 for Part B). The timing of midazolam PK assessments is specified in Appendix A Table 2. Additional details are provided as necessary in the sections that follow.

9.3.1 Informed Consent

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

9.3.2 Enrollment

A patient is considered enrolled in the study once they sign the informed consent form for study participation.

Procedures for completing enrollment information are described in the study manual.

9.3.3 Patient Demographics

Patient demographic characteristics will be collected at Screening and will include date of birth, sex, race, and ethnicity.

9.3.4 Medical History

A complete medical history will be recorded for each patient during Screening. The history will describe the background, progress, and stage of the patient's malignancy, and will include a description of prior therapies. In addition, concomitant medications will be recorded, as specified in Section 9.3.10.

9.3.5 ECOG Performance Status

ECOG performance status will be assessed and recorded at Screening, on Day 1 of each cycle, and at EOT. See Appendix D for the ECOG scale.

9.3.6 Physical Examination

A physical examination will be completed in accordance with the study site's standard of care at the times specified in the Schedules of Events (Appendix A Table 1 and Table 3). Additional symptom-directed evaluations may be performed.

A complete physical examination must be performed at Screening, the extent of which should be consistent with the patient's medical history and underlying disease. Subsequent physical examinations may be directed to relevant findings. Of note, because of adverse reactions reported during treatment with crizotinib and brigatinib, investigators are cautioned to monitor patients for signs of vision dysfunction. For new or worsening severe vision disorders, ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography, and other evaluations should be performed.

The Part B EOT physical examination should be a complete physical examination. The physical examination at the end of the 30-day follow-up period may be directed to any relevant findings.

9.3.7 Patient Height and Weight

The patient's height will be measured during Screening (within 28 days before the first dose of study drug).

The patient's weight will be obtained on Day 1 of each cycle and at EOT.

9.3.8 Vital Signs

Vital sign measurements will be taken at each visit after 3 to 5 minutes in the supine position and will include measurements of DBP, SBP, heart rate, and body temperature.

9.3.9 Pregnancy Test

A serum or urine pregnancy test will be performed for women of childbearing potential during Screening and within 7 days before the first dose of study drug on Day 1 of Cycle 1. The test results must be negative and available before the first dose of study drug is administered. Pregnancy testing must be conducted every 12 weeks thereafter and at EOT. Additional pregnancy testing may be required or recommended according to local guidelines and regulations.

9.3.10 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded in the electronic case report form (eCRF) from Screening through the 30-day follow-up period following EOT. See Section 8.3 for a description of prohibited medications and procedures, and Section 8.4 for a description of permitted medications and procedures during the study.

9.3.11 Adverse Events

AE monitoring will be conducted throughout the study as shown in the Schedules of Events in Appendix A Table 1 (for Part A) and Appendix A Table 3 (for Part B).

Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and serious adverse events (SAEs).

9.3.12 ECG

A 12-lead ECG will be performed at Screening (Part A), on Cycle 2 Day 1 (Part B), and at EOT (Part A or Part B). The ECGs will be performed at the sites and read locally.

9.3.13 Patient Dosing Diary

A patient dosing diary will be filled out only during Part A of the study. During Part A, patients are to bring unused brigatinib and the dosing diary with them to each clinic visit. The study center staff will check the diary and the patient's supply of brigatinib to assess adherence to the treatment regimen.

Refer to the study manual for complete instructions.

9.3.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations for safety will be performed locally, with reference ranges provided in the electronic data capture (EDC) system.

Instructions for handling and shipping clinical laboratory samples are provided in the study manual.

9.3.14.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a will be obtained as specified in the Schedules of Events for Part A (Appendix A Table 1) and Part B (Appendix A Table 3).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
• Hematocrit. • Hemoglobin. • WBC count with 5-part differential (lymphocytes, monocytes, neutrophils, eosinophils, basophils). • Platelet count.	• Albumin and total protein. • ALP. • ALT. • AST. • Amylase. • Bilirubin (total and direct/indirect). • BUN. • Calcium. • Bicarbonate (HCO_3; may be listed on chemistry panel as CO_2).	• Creatine kinase. • Creatinine. • Chloride. • Glucose. • LDH. • Lipase. • Phosphate. • Magnesium (a). • Potassium. • Sodium. • Urate (a).

ALP=alkaline phosphatase; BUN=blood urea nitrogen; LDH=lactate dehydrogenase; WBC=white blood cell.
(a) Analyzed only during Part A.

Urinalysis will be performed only during Part A of the study.

9.3.15 Disease Assessment

Patients will undergo CT and MRI scanning to monitor and assess disease progression using modified RECIST version 1.1.

Contrast CT scans of the chest, abdominal cavity, and pelvis will be obtained at Screening. For patients whose primary tumor or metastases are present in the head and neck or extremities, a CT scan of these regions is to be included. For patients with lung cancer and those with known brain metastases, MRI of the brain, with contrast, should be performed at Baseline (ie, during Screening) and repeated post-Baseline for patients with CNS metastases.

When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents.

Disease assessment by CT or MRI scan will be performed at Screening (ie, as close as possible to Day 1 of Cycle 1, but no more than 28 days before the first dose of brigatinib on Day 2 of Cycle 1), and at 8-week intervals thereafter (ie, on Day 28 [±3 days] of every even-numbered cycle) through 14 cycles after the initial dose of brigatinib, and every 3 cycles thereafter until PD (see Appendix A Table 3).

More frequent imaging is recommended at any time, if clinically indicated; confirmation of CR or PR may be performed at least 4 weeks after the initial response.

In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

9.3.16 PK Measurements

Plasma concentrations of midazolam and brigatinib will be measured using validated liquid chromatography-tandem mass spectrometry assays. Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual.

Blood samples for the determination of plasma concentrations of midazolam will be collected on Days 1, 2, 21, and 22 of Part A (Cycle 1: PK cycle) as described in Appendix A Table 2. Blood samples for the determination of trough plasma concentrations of brigatinib will be collected predose on Days 21 and 22 of Part A (Appendix A Table 1) and on Day 1 of Cycle 2 in Part B.

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

9.4 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they experience PD or intolerable toxicity despite dose reduction.

Patients may continue brigatinib treatment for up to 23 cycles during Part B.

9.5 Completion of Study (for Individual Patients)

A patient will be considered to have completed the study if they:

- Complete Part A; and
- Receive up to 23 cycles of brigatinib treatment during Part B; or
- Are withdrawn from treatment because of PD or intolerable toxicity, despite dose reduction; and
- Complete the 30-day follow-up period after EOT.

9.6 Discontinuation of Treatment With Study Drug and Withdrawal From the Study

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

- Intolerable toxicity, as determined by the investigator.
- PD requiring an alternate therapy.
- Entry into another therapeutic clinical study or start of new anticancer therapy.
- Significant deviation from the protocol or eligibility criteria, in the opinion of the investigator or the sponsor's medical monitor.
- Noncompliance with the study or follow-up procedures.

- Pregnancy.
- Patient withdrawal of consent or decision to discontinue study participation.
- Termination of the study by the sponsor.
- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study.
- Lost to follow-up.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedules of Events (Appendix A Table 1 for Part A; Appendix A Table 3 for Part B). The patient will be followed for 30 days after the EOT visit for drug safety and subsequent therapy. The primary reason for study drug discontinuation will be recorded in the eCRF.

9.7 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. Patients should be encouraged to administer their brigatinib dose at approximately the same time each day.

During Part A of the study, each patient will be required to complete a patient diary detailing the dates and times of each dose of brigatinib. In addition to recording their daily doses in the diary, patients in Part A will be required to return unused brigatinib to the clinic for assessment of compliance.

During Part B, patients will be required to return unused brigatinib to the clinic at each visit (ie, beginning of each cycle) for assessment of compliance. Any patient who receives <80% or >120% of their prescribed doses will be considered noncompliant.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed the informed consent to participate in a study, but which occurs 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 or subject 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 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when,

based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [18]. 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 decrease in 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 EDC SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. 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.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial 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.

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 [18]. 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 (EOT) and recorded in the eCRFs.

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

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by transmitting a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. 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 transmitting a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. 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.

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

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or Independent Ethics Committees, 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, investigators, and IRBs. 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 in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who receives study drug.

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, 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 subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6

(Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan 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.

A data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

13.1.1.1 Safety Population

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

13.1.1.2 PK-Evaluable Population

The PK-evaluable population is defined as patients who:

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

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

13.1.1.3 Response-Evaluable Population

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

The demographic and baseline characteristics will be summarized, including sex, age, race, weight, height, and other parameters as appropriate.

13.1.3 PK Analysis

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

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

For the estimation of the effect of brigatinib on midazolam PK, the ratios of geometric mean midazolam AUC_{∞} and C_{max} (with vs without brigatinib coadministration) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance calculated via a mixed-effects analysis of variance (ANOVA) fitting terms for treatment (midazolam with or without brigatinib coadministration). Patient will be treated as a random effect in the model. After log transformation, AUC_{∞} and C_{max} will be separately analyzed. Point estimates and adjusted 90% CIs for the difference in treatment will be calculated and then exponentially back transformed to provide point and CI estimates for the ratios of interest.

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

13.1.4 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from Baseline in the patient's clinical laboratory results, weight, and vital signs using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of brigatinib will be tabulated.

AEs will be tabulated according to MedDRA and will include, but are not limited to, the following subsets:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs (ie, those events occurring in ≥10% of all patients).
- Treatment-emergent AEs resulting in study drug dose reduction.
- Treatment-emergent AEs resulting in study drug dose modification (as defined as dose interruption, dose reduction, or permanently discontinued).
- SAEs.

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values (and/or change from Baseline) in clinical laboratory parameters, weight, and vital signs will be tabulated by scheduled time point. Mean or median key laboratory parameters over time will be plotted. Shift tables for laboratory parameters will be generated to show changes in NCI CTCAE grade from the Baseline value to the worst post-Baseline value.

All concomitant medications collected from Screening through the study period will be classified to generic terms according to the WHO Drug Dictionary.

Additional safety analyses may be determined to most clearly enumerate rates of toxicities and to further define the safety profile of brigatinib.

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[redacted]

13.2 Analyses For Parts A and B and Criteria for Early Termination

Analyses for Part A of the study will be performed when all patients have completed Cycle 1 (PK cycle) and will include analyses of PK and safety.

Analyses for Part B of the study will be performed when all patients have completed the study and will included analyses of safety and efficacy.

13.3 Determination of Sample Size

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

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.

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee and IRB. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of the 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.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by the US FDA. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

IRBs must be constituted according to the applicable state and local requirements. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRBs. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those sites unwilling to provide names and titles of all members due to 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 IRBs for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB'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 approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. If required by either country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation, and when applicable, the sponsor has received permission from the US FDA to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to the IRB. All IRB 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 and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, 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 informed consent form 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 informed consent form 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 approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor before use.

The informed consent form, 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 informed consent form, 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. 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 informed consent form 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 informed consent form 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 informed consent form, 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 informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms 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 informed consent form.

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedule of Events and PK Sampling Schedule

Table 1 Schedule of Events for Part A (Cycle 1, 28-Day PK Cycle)

Assessment	Screening	Visits						Day 28 (EOT Part A)
		Day 1	Day 2	Day 9	Day 15	Day 21	Day 22	
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical history	X							
Physical examination (a)	X	X					X	X (b)
ECOG Performance Status	X	X						X (b)
Height	X							
Weight		X						X (b)
Midazolam 3 mg single dose		X				X (c)		
Pulse oximetry (d)		X				X		
Brigatinib 90 mg/180 mg (or highest tolerated dose) QD			X (e)	X (f)		X (f)	X (f)	X (f)
Pregnancy test (g)	X	X						X (b)
Imaging assessments (h)	X							
12-lead ECG	X							X (b)
Vital signs	X	X	X	X		X	X	X (b)
Laboratory tests (i)	X	X (j)			X (k)			X (b)
Adverse event reporting	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug							
	Serious adverse events will be reported from the signing of the informed consent form through 30 days after the last dose of study drug.							
Monitoring of concomitant medications and procedures	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug							
Serial PK sampling for midazolam PK (l)		X	X			X	X	
Predose PK sample for brigatinib PK (m)						X	X	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen;

CK=creatine kinase; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; β-HCG=β-human chorionic gonadotropin; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); QD=once daily.
(a) A complete physical examination will be performed during Screening, with symptom-directed physical examinations performed on Day 1 and Day 22, and at EOT (for patients who discontinue the study during Part A).
(b) For patients who discontinue from the study during Part A.
(c) To be administered only to patients who have escalated to brigatinib 180 mg QD.
(d) Performed after administration of midazolam on Days 1 and 21.
(e) Brigatinib 90 mg QD (or highest tolerated dose) from Day 2 through Day 8.
(f) Brigatinib 180 mg QD (or highest tolerated dose) from Day 9 through Day 28.
(g) β-HCG test (urine or serum) within 7 days before first dose of study drug for all women of childbearing potential.
(h) Baseline disease assessments during Screening should be performed as close to Cycle 1 Day 1 as possible and will consist of CT scans of the chest, abdomen, and pelvis for all patients. A CT scan of the head and neck or extremities is to be included if the primary tumor or metastases are present in the head, neck, and/or extremities. An MRI scan of the brain should be performed at Baseline for lung cancer patients and patients with known brain metastases.
(i) Laboratory tests to include hematology (complete blood count with 5-part differential and platelet count); serum chemistry (sodium, potassium, chloride, bicarbonate [or total carbon dioxide], BUN [or urea], albumin and total protein, creatinine, bilirubin [at least total and direct or total and indirect], ALT, AST, ALP, magnesium, phosphate, calcium, LDH, CK, uric acid, amylase, lipase, and glucose); and urinalysis.
(j) Before dosing on Day 1.
(k) Laboratory tests to include ALT, AST, and total bilirubin.
(l) Refer to Appendix A Table 2 (Sampling Schedule for Midazolam PK in Part A) for PK sample collection times.
(m) A predose PK sample to measure trough concentrations of brigatinib will be collected within 1 hour before brigatinib administration on Days 21 and 22 of Part A.

Table 2 Sampling Schedule for Midazolam PK in Part A

PK Sampling Time	Part A (Cycle 1)			
	Day 1	Day 2	Day 21	Day 22
Predose (within 1 hour before dosing)	X			
0.25 hours postdose (±3 minutes)	X			
0.5 hours postdose (±5 minutes)	X			
1 hour postdose (±15 minutes)	X			
1.5 hours postdose (±15 minutes)	X			
2 hours postdose (±15 minutes)	X			
4 hours postdose (±30 minutes)	X			
6 hours postdose (±1 hour)	X			
8 hours postdose (±1 hour)	X			
10 hours postdose (±1 hour)	X			
24 hours postdose (±2 hours)		X		
Predose (within 1 hour before dosing)			X	
0.25 hours postdose (±3 minutes)			X	
0.5 hours postdose (±5 minutes)			X	
1 hour postdose (±15 minutes)			X	
1.5 hours postdose (±15 minutes)			X	
2 hours postdose (±15 minutes)			X	
4 hours postdose (±30 minutes)			X	
6 hours postdose (±1 hour)			X	
8 hours postdose (±1 hour)			X	
10 hours postdose (±1 hour)			X	
24 hours postdose (±2 hours)				X

PK=pharmacokinetic(s).

Table 3 Schedule of Events for Part B (Repeat 28-day Treatment Cycles)

Assessment	**Treatment Cycles (a)**									
Cycle	**Cycle 2**			**Cycle 3**			**Cycle 4 and Every Cycle Thereafter Through EOT**		**EOT**	**Follow-up (b)**
Cycle Days	**Day 1**	**Day 15**	**Days 2-28**	**Day 1**	**Day 15**	**Days 2-28**	**Day 1**	**Days 2-28**		
ECOG Performance Status	X			X			X		X	
Symptom-directed physical exam	X			X			X		X (c)	X
Weight	X			X			X		X	
Pregnancy test (d)							X (d)		X	
Vital signs (e)	X			X			X		X	
Laboratory tests (f)	X	X (g)		X	X (g)		X		X	
12-lead ECG	X								X	
Adverse event reporting	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug									
	Serious adverse events will be reported from the signing of the informed consent form through 30 days after the last dose of study drug.									
Monitoring of concomitant medications and procedures	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug									
Imaging assessments (h)			X (i)					X (i)	X	
Brigatinib once daily	X		X	X		X	X	X		
Predose PK sample for brigatinib PK (j)	X									

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; β-HCG=β-human chorionic gonadotropin; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PK=pharmacokinetics.

(a) Treatment cycles are 28 days, and are to continue until disease progression, intolerable toxicity, or another discontinuation criterion is met.
(b) The 30-day follow-up period after EOT will capture adverse events and subsequent therapy.
(c) Complete physical examination at EOT.
(d) For women of childbearing potential, β-HCG pregnancy test using urine or serum, performed within 7 days before first dose of study drug (Cycle 1 Day 1, Part A), every 12 weeks (~3 cycles) thereafter, and at EOT. Additional pregnancy testing may be required or recommended based on local guidelines or regulations.
(e) Vital signs measurements are to be performed just before dosing on Day 1 of each cycle, as needed, and at EOT.
(f) Laboratory tests for drug safety are to be performed on Day 1 of each cycle before dosing and at EOT. They are to include hematology (complete blood count with 5-part differential and platelet count); and serum chemistry (sodium, potassium, chloride, bicarbonate [or total carbon dioxide], BUN [or urea], albumin and total protein, creatinine, bilirubin [at least total and direct or total and indirect], ALT, AST, ALP, phosphate, calcium, LDH, CK, amylase, lipase, and glucose).
(g) Laboratory tests to include ALT, AST, and total bilirubin.
(h) CT/MRI to be conducted every 8 weeks, at the end of every even-numbered cycle (ie, 2, 4, 6, etc) up to Cycle 14, and every 3 cycles thereafter and at EOT. Imaging assessments will consist of CT scans of the chest, abdomen, and pelvis for all patients. For patients whose primary tumor or metastases are present in the head, neck, or extremities, a CT scan of the head and neck or extremities is to be included. Brain MRI should be performed at Baseline (ie, during Screening) for patients with lung cancer and patients with known brain metastases. Brain MRI, CT of the head/neck or extremities should be repeated every 8 weeks for the first 14 cycles and every 3 cycles thereafter, if disease is present in these sites at Screening/Baseline.
(i) To be performed on Day 28 (±3 days).
(j) A predose PK sample to measure the trough concentration of brigatinib will be collected within 1 hour before brigatinib administration on Day 1 of Cycle 2 of Part B.

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 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. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/independent ethics committee (IEC) that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB 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, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. 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. Each informed consent form 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 informed consent form 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. 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, United States, 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 et al, 1982 [19].

Appendix E Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Update Table 8.a (Recommended Brigatinib Dose Reduction Levels)

The primary change occurs in Section 8.2.2 Dose Modifications for Treatment-Related AEs.

Description of change: An additional column was added to Table 8.a to describe a fourth dose reduction.

- In the row *90 mg QD (first week of treatment)*, the following text was added: **Not applicable.**
- In the row *180 mg QD*, the following text was added: **Permanently discontinue.**

Rationale for Change: To provide guidance to sites on the fourth dose reduction.

Change 2: Update Table 8.b (Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events).

The primary change occurs in Section 8.2.2 Dose Modifications for Treatment-Related AEs.

Initial wording	Recommendations for dose modification of brigatinib for the management of treatment-related AEs are provided in Table 8.b and are based on the US Prescribing Information for brigatinib (ALUNBRIG). Unless otherwise noted, reduce the dose as indicated in Table 8.b if 1 or more dose reductions are necessary because of Grade 3/4 treatment-related AEs (as defined by NCI CTCAE version 4.03).
Amended text:	Recommendations for dose modification of brigatinib for the management of treatment-related AEs are provided in Table 8.b and are based on the ~~US Prescribing Information~~ **CCDS** for brigatinib (ALUNBRIG). Unless otherwise noted, reduce the dose as indicated in Table 8.b if 1 or more dose reductions are necessary because of Grade 3/4 treatment-related AEs (as defined by NCI CTCAE version 4.03).

Description of change:

Text has been modifed to Table 8.b as follows:

In the row *Hypertension* the following text was amended:

- Withhold brigatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume brigatinib at ~~next lower~~**same** dose.

In the row *CPK elevation*, *Grade 3 CPK elevation (>5.0×ULN)* the following text was added:

- **If Grade 3 elevation of CPK recurs, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 2.5 x ULN) or to baseline, then resume at the next lower dose level per Table 8.a.**

In the row *CPK elevation*, *Grade 4 CPK elevation (>10.0×ULN)* the following text was amended:

~~or recurrence of Grade 3 elevation~~

- **If Grade 4 elevation of CPK recurs, permanently discontinue brigatinib.**

In the row *Lipase/amylase elevation*, *Grade 3 lipase or amylase elevation (>2.0×ULN)* the following text was added:

- **If Grade 3 elevation of lipase and amylase recurs, brigatinib should be witheld until recovery to Grade 1 or less (less than or equal to 1.5×ULN) or to baseline, then resume at the next lower dose level per Table 8.a.**

In the row *Lipase/amylase elevation*, *Grade 4 lipase or amylase elevation (>5.0×ULN)* the following text was amended:

~~or recurrence of Grade 3 elevation~~

- **If Grade 4 elevation of lipase/amylase recurs, permanently discontinue brigatinib.**

Rationale for Change: To align brigatinib dose modification for treatment-related adverse events with the CCDS.

Change 3: Update Excluded Concomitant Medications and Procedures (Section 8.3) to include moderate cytochrome P450 (CYP) 3A inhibitors in Part B of the study and to provide further guidance to investigators.

The primary change occurs in Section 8.3 Excluded Concomitant Medications and Procedures

Added text:

- **Moderate CYP3A inhibitors: amprenavir, aprepitant, atazanavir, ceritinib, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, diltiazem, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, 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 the moderate CYP3A inhibitor was initiated.**

...

Because 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.

Rationale for Change: To include moderate CYP3A inhibitors to list of excluded medications and to provide further guidance to investigators regarding classification of excluded medications.

Change 4: Add information regarding administration of brigatinib with certain concomitant medications to Precautions and Restrictions (Section 8.5).

The primary change occurs in Section 8.5 Precautions and Restrictions

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

Brigatinib is an in vitro inhibitor of P-gp, breast cancer resistance protein, organic cation transporter 1, multidrug and toxin extrusion protein 1 and 2K. 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.

Rationale for Change: To clarify that brigatinib may induce other enzymes and transporters via the same mechanism responsible for induction of CYP3A and to provide guidance to investigators regarding monitoring of patients who may be receiving certain concomitant medications.

Change 5: Update adverse event (AE) definition (Section 10.1.2) to provide guidance on reporting of disease progression.

The primary change occurs in Section 10.1.2 AE Definition

Added text: AE means any untoward medical occurrence in a patient or subject 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.

Rationale for Change: To provide guidance on reporting of disease progression.

Change 6: Update Schedule of Events (Appendix E) to include laboratory tests on Day 15 of Cycle 1.

The primary change occurs in Appendix A Schedule of Events and PK Sampling Schedule

Description of change:
- Day 15 column added for Table 1: Schedule of Events for Part A (Cycle 1, 28-Day PK Cycle).
- Laboratory tests added for Day 15.

Added text in footnotes for Schedule of Events Table: **(k) Laboratory tests to include ALT, AST, and total bilirubin.**

Rationale for Change: To be consistent with Summary of Product Characteristics.

Section 9.3 also contains this change.

Change 7: Update Schedule of Events (Appendix E) to include laboratory tests on Day 15 of Cycles 2 to 3.

The primary change occurs in Appendix A Schedule of Events and PK Sampling Schedule

Description of change:
- Day 15 column added for Cycles 1 and 2 in Table 3 Schedule of Events for Part B (Repeat 28-day Treatment Cycles).
- Laboratory tests added for Day 15.

Added text in footnotes for Schedule of Events Table: **(g) Laboratory tests to include ALT, AST, and total bilirubin.**

Rationale for Change: To be consistent with Summary of Product Characteristics.

Section 9.3 also contains this change.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	14-May-2019 20:34 UTC
	Clinical Pharmacology Approval	14-May-2019 23:11 UTC
	Clinical Science Approval	15-May-2019 02:26 UTC
	Biostatistics Approval	21-May-2019 12:56 UTC