Clinical Study Protocol

NCT Number: NCT06132867

Title: A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution Versus an Immediate-Release Tablet in Adult Healthy Subjects

Study Number: Brigatinib-1004

Document Version and Date: Amendment 1.0, 05 January 2024

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution versus an Immediate-Release Tablet in Adult Healthy Subjects

Study Identifier: Brigatinib-1004

Compound: Brigatinib

Date: 05 Jan 2024

Version/Amendment Number: Amendment 01

Version/Amendment History:

Date	Amendment Number	Amendment Type	Region
13 Sep 2023	Initial Version	Not Applicable	United States
05 Jan 2024	01	Substantial	United States

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDCA) 95 Hayden Avenue Lexington, Massachusetts 02421 Telephone: +1 (617) 679-7000	Brigatinib
Study Identifier: Brigatinib-1004	**Phase:** 1

Protocol Title: A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Relative Bioavailability of Brigatinib Administered as an Oral Solution versus an Immediate-Release Tablet in Adult Healthy Subjects

Study Design:

This is an open-label, randomized, 2-period, 2-sequence, crossover study in healthy adult subjects to evaluate the relative bioavailability of brigatinib when administered as an oral solution versus as an immediate-release tablet ALUNBRIG®.

- Treatment A (test formulation): 90 mg oral solution dose of brigatinib administered in a fasted state
- Treatment B (reference formulation): 90 mg tablet dose of brigatinib administered in a fasted state

Approximately 12 subjects will be randomly assigned in a 1:1 ratio to one of the treatment sequences, as part of a crossover design (Table 1.a):

Table 1.a: Description of Treatment Sequences in the Study

Sequence	Approximate number of subjects	Period 1	Period 2
AB	6	A	B
BA	6	B	A

A= Oral solution dose of brigatinib, fasted state; B= Tablet dose of brigatinib, fasted state.

Subjects will be admitted to the clinical facility on Day -1, the day prior to brigatinib administration in each dosing period. On Day 1 of each period, a single 90 mg dose of brigatinib will be administered. Blood samples for the measurement of plasma concentrations of brigatinib will be collected predose and up to 168 hours postdose following each brigatinib dose. For each dosing period, subjects will be housed starting on Day-1, at the time indicated by the Clinical Research Unit (CRU), until the morning of Day 4 after the 72 hour postdose blood draw and/or study procedures (Section 9.3.4). There will be a washout period of at least 14 days between brigatinib administration in each study period. Subjects will return for dosing and/or study procedures as indicated in Section 3.0, Schedule of Study Procedures. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee. As per site preference, subjects may be confined throughout the study (ie, washout period and/or return visit[s]).

The follow-up contact will occur 14 (±2) days post the last dose of study drug by telephone. If abnormal, potentially clinically significant findings are noted during this phone follow-up, subjects may then be brought back to the clinic for re-evaluation per the Investigator's discretion. Serious adverse events (SAEs) should be followed up until resolution or permanent outcome.

Study Primary Objective:

- To determine the relative bioavailability of brigatinib after single-dose administration of an oral solution formulation versus an immediate-release tablet formulation.

Study Secondary Objective:

• To evaluate the safety and tolerability of brigatinib after single-dose administration of an oral solution formulation and an immediate-release tablet formulation.	
Study Subject Population: Healthy male or female (of non-childbearing potential) subjects aged 18 to 55 years inclusive, at screening. Body Mass Index (BMI) ≥18.0 and <32.0 kg/m^2, at screening.	
Planned Number of Subjects: Approximately 12 subjects will be enrolled	**Planned Number of Sites:** 1
Dose Levels: Treatment A: Brigatinib 90 mg oral solution Treatment B: Brigatinib 90 mg tablet	**Route of Administration:** Oral
Duration of Treatment: Single-dose on Day 1 of each period	**Planned Study Duration:** Approximately 56 ± 2 days including the following: Screening: Up to 4 weeks (28 days) Dosing Period: Two (2) dosing periods (with a minimum 14-day washout period between doses) Safety Follow-Up: 14 (± 2) days post last dose of study drug

Criteria for Inclusion:

Subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, males or females (of non-childbearing potential), 18-55 years of age, inclusive, at screening.
2. A nonvasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until at least 3 months after the last study drug dosing. (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a nonvasectomized male). A vasectomized subject may not use vasectomy as his primary/only form of contraception if he is unable to provide the surgical documentation (refer to Appendix D).
3. Male subjects must agree not to donate sperm from the first dosing until at least 3 months and female subjects must agree not to donate ova from the first dosing until at least 4 months after the last study drug dosing.
4. Female subjects of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing (hysteroscopic sterilization, bilateral tubal ligation, bilateral salpingectomy, hysterectomy, or bilateral oophorectomy); or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status (refer to Appendix D).
5. Continuous nonsmoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study.
6. BMI ≥18.0 and <32.0 kg/m^2 at screening.
7. Medically healthy with no clinically significant medical history or abnormalities in physical examination, laboratory profiles, vital signs or 12-lead electrocardiograms (ECGs) performed at the screening visit and before administration of the initial dose of trial drug, as deemed by the Investigator or designee.
8. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.
9. Pulse rate between 60 and 100 bpm and a blood pressure between 90 to 140 mmHg systolic and 40 to 90 mmHg diastolic at screening and prior to dosing of Period 1.

10. Creatine phosphokinase is ≤1.1x upper limit of normal [ULN]; lipase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glucose, and activated partial thromboplastin time (aPTT) are ≤ULN at screening and check-in of Period 1.

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, major neurological (including stroke and chronic seizures), or malignancy, active infectious diseases, ophthalmologic disorders other than presbyopia/myopia/hyperopia/astigmatism, or any other clinically significant abnormalities or disease in the opinion of the Investigator or designee.
3. Any history of major surgery, eg, cholecystectomy, intestinal resections, hepatectomy, nephrectomy, digestive organ resection that may affect absorption, metabolism or excretion of study drug. A history of appendectomy is not exclusionary.
4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
7. Positive urine drug or cotinine, or alcohol results at screening or check-in.
8. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
9. Positive COVID-19 results at first check-in.
10. Currently has an active infection, in the opinion of the Investigator.
11. QT interval corrected for heart rate using Fridericia's formula (QTcF) is >460 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
12. Estimated creatinine clearance <90 mL/minute at screening (calculated using the Cockcroft-Gault formula).
13. Unable to refrain from or anticipates the use of any drug, including prescription and nonprescription medications, herbal remedies, or vitamin supplements within 28 days prior to the first dosing and throughout the study. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study, only after the first dosing, at the discretion of the Investigator or designee, as medically indicated. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing.
14. Has been on a diet incompatible with the on-study diet, including consumption of grapefruit juice and other grapefruit containing products, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
15. Donation of blood or significant blood loss within 56 days prior to the first dosing.
16. Plasma donation within 7 days prior to the first dosing.
17. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

The primary endpoints for this study are brigatinib pharmacokinetic (PK) parameters after a single-dose of an oral solution formulation and an immediate-release tablet formulation, including:

- Maximum observed plasma concentration (C_{max});
- Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last});
- Area under the plasma concentration-time profile from time 0 to infinity (AUC_{∞}).

Secondary Endpoints:

The secondary endpoints will be assessed through evaluation of the following parameters:

- Number of subjects with at least one treatment-emergent adverse event (TEAE) and/or serious adverse event (SAE).

Exploratory Endpoints:

The following PK parameters for brigatinib after administration of each formulation:

- Time of first occurrence of C_{max} (t_{max});
- Apparent clearance after extravascular administration (CL/F);
- Apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F);
- Terminal disposition phase half-life ($t_{½z}$);
- Terminal disposition phase rate constant (λ_z);
- The area under the curve from the last quantifiable concentration to infinity, expressed as a percentage of AUC_{∞} ($AUC_{\%extrap}$).

Data related to the acceptability and palatability of the oral solution formulation will also be collected.

Statistical Considerations:

Plasma PK parameters of brigatinib will be derived using standard noncompartmental analysis methods. A linear mixed-effects analysis of variance model will be used for the analysis on the natural log (ln)-transformed brigatinib PK parameters (C_{max}, AUC_{last}, and AUC_{∞}). The model will include sequence, treatment, and period as fixed effects. Subject nested within sequence will be included as a random effect. Each model will include calculation of least squares means (LSM) as well as the difference between treatment LSM. Geometric mean ratios (GMR) and 90% confidence intervals (CIs) will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞}. These ratios will be expressed as a ratio of the test treatment (ie, oral solution) relative to the reference treatment (ie, tablet).

Sample Size Justification:

The sample size calculation was based on the expected 2-sided 90% CIs for the difference in the paired, ln-transformed AUC_{∞} means of brigatinib after administration as an oral solution versus an immediate-release tablet. The within-subject percent coefficient of variation (%CV) for brigatinib AUC_{∞} was estimated to be 12% on the basis of data from previous clinical studies conducted in healthy subjects (Studies AP26113-15-106 and AP26113-16-110). If the observed GMR for brigatinib AUC_{∞} after administration as an oral solution versus a tablet is 1, with a sample size of 8, the 90% CIs for the GMR is expected to be 0.89 to 1.12 on the basis of the variance assumptions.

It is anticipated that a total of approximately 12 subjects will be enrolled to obtain at least 8 PK-evaluable subjects. Subjects will be randomized into 2 treatment sequences, as indicated in Table 1.a.

2.0 STUDY SCHEMATIC

Pretreatment		**Treatment Periods 1 & 2 (a)**			
Screening	**Check-in (b) (Periods 1 & 2)**	**Dosing and Study Assessments**	**PK Assessments**		**Follow-up (c)**
Within 28 days of first dosing	Day -1	Day 1	Days 1-4 (d)	Days 6 & 8 (d)	14 (±2) Days following last dose
	◄---------- Confinement (d) ----------►				

(a) There will be a washout period of at least 14 days between brigatinib administration in each study period.

(b) Subjects will be admitted on Day -1.

(c) The follow-up contact will occur 14 (±2) days after the last dose.

(d) For each dosing period, subjects will be housed starting on Day-1, at the time indicated by the CRU, until the morning of Day 4, after the 72 hours postdose blood draw and/or study procedures (Section 9.3.4). Subjects will return for study procedures on Days 6 and 8. As per site preference, subjects may be confined throughout the study (ie, washout period[s] and/or return visit[s]).

3.0 SCHEDULE OF STUDY PROCEDURES

Study Procedure↓		**Scr**		**Study Days of Periods 1 and 2[a]**																**ET**	**Safety F/U Call[p]**
	Study Day→	**Day-28 to Day 1 dosing**	**Day -1**	**Day 1**											**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 8**		
	Hours→		**Check-in[b]**	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**		
Administrative Procedures																					
Informed Consent		X																			
Inclusion/Exclusion Criteria		X	X[c]																		
Medical History/Demographics		X																			
Prior and Concomitant Medication		X	---------- Continuous Monitoring ----------																		X
Clinical Procedures/Assessments																					
Full Physical Examination[d]		X	X										X						X[o]	X	
Height, BMI		X																			
Weight		X	X																		
Supine Safety 12-lead ECG[f]		X		X[e]									X						X[o]	X	
Semi-Recumbent Vital Signs (Pulse Rate, Systolic Blood Pressure and Diastolic Blood Pressure)[g]		X		X[e]				X			X				X	X	X	X	X[o]	X	
Vital signs (Respiratory Rate, Oral [at the floor of the mouth] or Tympanic Temperature)[g]		X		X[e]											X	X			X[o]	X	
Dosing of Brigatinib[h]					X																
AE Monitoring		X	---------- Continuous Monitoring ----------																		
Laboratory Procedures/Assessments																					
Hematology		X	X										X			X			X[o]	X	
Urinalysis		X																	X[o]	X	
Chemistry[i]		X	X										X			X			X[o]	X	

Study Procedure↓		Scr		Study Days of Periods 1 and 2[a]																ET	Safety F/U Call[p]
	Study Day→	Day-28 to Day 1 dosing	Day -1	Day 1											Day 2	Day 3	Day 4	Day 6	Day 8		
	Hours→		Check-in[b]	Predose	0	0.25	0.5	1	1.5	2	4	6	8	12	24	48	72	120	168		
Coagulation		X	X										X			X			X[o]	X	
Serum Pregnancy Test[j]		X	X																X[o]	X	
Serum FSH[j]		X																			
Urine Drug Screen		X	X																		
Urine Cotinine Screen		X	X																		
Urine Alcohol Test[k]		X	X																		
Serology (HBsAg, HCV, HIV)		X																			
COVID-19 Screen			X																		
Pharmacokinetics Evaluations																					
Blood Sample for PK[l]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																					
Palatability Questionnaire (Treatment A only)							X														
Confinement			X[m]																		
Discharge from CRU																	X[n]				
Outpatient Visit		X																X	X		

Abbreviations: AE = Adverse events, BMI = Body mass index, COVID-19 = Coronavirus Disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, ET = Early termination, FSH = Follicle stimulating hormone, F/U = Follow-up, HCV = Hepatitis C virus, HBsAg = Hepatitis B surface antigen, HIV = Human immunodeficiency virus, PK = Pharmacokinetics, Scr = Screening

a There will be a washout period of at least 14 days between brigatinib doses in each study period.

b Subjects will be admitted on Day -1.

c To be performed in Period 1 only.

d Symptom-driven physical examinations may be performed at other times, at the Investigator's or designee's discretion.

e Predose assessments on Day 1 of Period 1 and Period 2 may be done within approximately 24 hours prior to study drug administration.

f Single ECG will be conducted. Subject should have rested in a supine position for at least 5 minutes before ECG measurement. When ECG coincides with other assessments post brigatinib administration, the sequence of procedures will be PK sampling, safety ECG, vital signs assessment, and then the safety laboratory blood draw.

g Postdose vital sign (ie, pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and oral or tympanic temperature) will be measured at times relative to the brigatinib dosing. Subjects should have rested in a semi-recumbent position for at least 5 minutes before the measurements are acquired at all timepoints including screening.

h Dosing will occur at the CRU based on the treatment that the subjects are randomized to receive within a study period (Treatment A or B). Treatment A: 90 mg oral solution dose of brigatinib
(ie, 9 mL of the 10 mg/mL solution) immediately followed by approximately 240 mL (8 fluid ounces) of water. Treatment B: 90 mg tablet dose of brigatinib (ie, one 90 mg tablet) with approximately 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours postdose in each period, water is allowed as desired except for one hour before and one hour after study drug administration and as dosing water.

i Serum chemistry tests will be performed after at least an 8-hour fast with the exception of the Hour 8 postdose laboratory assessment on Day 1; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is being taken.

j Serum pregnancy tests are to be performed for all females and serum FSH tests are to be performed for all postmenopausal females only.

k A urine alcohol test will be performed at the indicated scheduled timepoints and at the discretion of the Investigator, as applicable.

l PK blood samples for the measurement of plasma concentrations of brigatinib will be collected starting Day 1 in Period 1 and Period 2 at times relative to the brigatinib dose (Hour 0).

m Subjects will be confined from Day -1 until after the Day 4 study assessments are completed in each period. As per site preference, subjects may be confined throughout the study (ie, washout period and/or return visit[s]).

n Discharge will occur on the morning of Day 4 after collection of the 72 hour PK sample and/or study procedures, unless the subject will be confined for a longer duration at the discretion of the Investigator.

o To be performed at the end of Period 2 only.

p The F/U contact will occur 14 (±2) days after the last dose of the study drug.

4.0 INTRODUCTION

4.1 Background

Brigatinib is an anaplastic lymphoma kinase (ALK) inhibitor approved for the treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC). The recommended clinical dose of brigatinib in adults is 90 mg once daily (QD) for 7 days, followed by 180 mg QD thereafter. ALK is also known to play a role in inflammatory myofibroblastic tumor and anaplastic large cell lymphoma, two cancers that occur in pediatric patients. Pediatric development of brigatinib is planned; however, brigatinib is currently available only as an immediate release tablet formulation in strengths of 30 mg, 90 mg, and 180 mg. Therefore, an age appropriate formulation of brigatinib has been developed and consists of an oral solution at a strength of 10 mg/mL.

In addition to PK characterization in patients with cancer, a total of 10 clinical pharmacology studies have been completed for brigatinib. Seven (7) clinical pharmacology studies in healthy subjects have been completed to assess single-dose PK, drug-drug interaction potential, food effects, mass balance, metabolism and excretion, potential ethnic differences in PK, and bioequivalence of tablets of different strengths. Two studies have been completed to evaluate the PK of brigatinib in subjects with organ impairment (renal and hepatic impairment) in comparison with healthy subjects. Additionally, one clinical pharmacology study evaluated the effect of repeat dose administration of brigatinib on the PK of the sensitive cytochrome P450 (CYP) 3A substrate, midazolam, in patients with cancer.

Brigatinib exhibits linear PK after single- and multiple-dose administration and dose proportional increases in exposure have been observed over the dose range of 60 mg to 240 mg. The median t_{max} of brigatinib ranges from 1-4 hours postdose and a high-fat meal was found to have no clinically meaningful effect on systemic exposure. The mean apparent oral clearance at steady-state is 8.9 L/h and the mean plasma elimination half-life is 25 hours. In the human absorption, distribution, metabolism and excretion study, 65% of the administered dose was recovered in the feces and 25% of the administered dose was recovered in the urine. CYP3A-mediated metabolism is considered to be the primary contributor to brigatinib systemic clearance in humans, with additional contributions from CYP2C8 and renal clearance. Results from in vitro transporter studies indicated that brigatinib is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP) [1].

The most common adverse reactions (≥25%) reported for brigatinib are nausea, diarrhea, fatigue, cough, and headache. Also reported with brigatinib administration is interstitial lung disease/pneumonitis, hypertension, bradycardia, elevated creatine phosphokinase, visual disturbance, elevated pancreatic enzymes, hyperglycemia, and embryofetal toxicity [1, 2].

Testicular toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2 month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period [2].

Refer to the Investigator's Brochure [1] and the United States Prescribing Information [2] for additional information regarding brigatinib.

4.2 Rationale for the Proposed Study

The purpose of this relative bioavailability study is to compare the PK of brigatinib following a single dose of 90 mg of the oral solution relative to a 90 mg dose of the immediate-release tablet formulation in adult healthy subjects. Brigatinib is currently available as an immediate-release tablet and is approved for the treatment of adult patients with ALK-positive advanced NSCLC. However, clinical studies in pediatric patients are planned. Therefore, an oral solution formulation has been developed to support administration of brigatinib to pediatric patients who are unable to swallow solid oral dosage forms. The results of this relative bioavailability study will subsequently be used to inform dose selection for the oral solution in the pediatric development program.

4.3 Benefit/Risk Profile

The dose of brigatinib will be administered according to the product label and the adult dosing recommendations found therein [1, 2].

There will be no direct health benefit for study subjects from receipt of study drugs. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examination) are adequate to protect the subject's safety and should detect all TEAEs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable

5.2 Study Objectives

5.2.1 Study Primary Objective

To determine the relative bioavailability of brigatinib after single-dose administration of an oral solution formulation versus an immediate-release tablet formulation.

5.2.2 Study Secondary Objective

To evaluate the safety and tolerability of brigatinib after single-dose administration of an oral solution formulation and an immediate-release tablet formulation.

5.3 Endpoints

5.3.1 Primary Endpoints

The primary endpoints for this study are brigatinib PK parameters after a single-dose of an oral solution formulation and an immediate-release tablet formulation, including:

- C_{max}
- AUC_{last}
- AUC_{∞}

5.3.2 Secondary Endpoints

The secondary endpoints will be assessed through evaluation of the following parameters:

- Number of subjects with at least one TEAE and/or SAE.

5.3.3 Exploratory Endpoints

The following PK parameters for brigatinib after administration of each formulation:

- tmax
- CL/F
- Vz/F
- t½z
- λz
- AUC%extrap

Data related to the acceptability and palatability of the oral solution formulation will also be collected.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an open-label, randomized, 2-period, 2-sequence, crossover study in healthy adult subjects to evaluate the relative bioavailability of brigatinib when administered as an oral solution versus as an immediate-release tablet (ALUNBRIG®).

- Treatment A (test formulation): 90 mg oral solution dose of brigatinib administered in a fasted state
- Treatment B (reference formulation): 90 mg tablet dose of brigatinib administered in a fasted state

Approximately 12 subjects will be randomly assigned in a 1:1 ratio to one of the treatment sequences, as part of a crossover design (Table 6.a):

Table 6.a: Description of Treatment Sequences in the Study

Sequence	Approximate number of subjects	Period 1	Period 2
AB	6	A	B
BA	6	B	A

A= Oral solution dose of brigatinib, fasted state; B= Tablet dose of brigatinib, fasted state.

Subjects will be admitted to the clinical facility on Day -1, the day prior to brigatinib administration in each dosing period. On Day 1 of each period, a single 90 mg dose of brigatinib will be administered. Blood samples for the measurement of plasma concentrations of brigatinib will be collected predose and up to 168 hours postdose following each brigatinib dose. For each dosing period, subjects will be housed starting on Day -1, at the time indicated by the CRU, until the morning of Day 4 after the 72 hour postdose blood draw and/or study procedures (Section 9.3.4). There will be a washout period of at least 14 days between brigatinib administration in each study period. Subjects will return for dosing and/or study procedures as indicated in Section 3.0, Schedule of Study Procedures. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee. As per site preference, subjects may be confined throughout the study (ie, washout period and/or return visit[s]).

The follow-up contact will occur 14 (±2) days post the last dose of study drug by telephone. If abnormal, potentially clinically significant findings are noted during this phone follow-up, subjects may then be brought back to the clinic for re-evaluation per the Investigator's discretion. SAEs should be followed up until resolution or permanent outcome.

The planned dose levels/treatments of brigatinib to be evaluated are outlined in Table 6.b.

Table 6.b: Planned Brigatinib Dose Levels/Treatments

Treatment	Brigatinib Dose	Formulation	State
A	90 mg	Oral Solution	Fasted
B	90 mg	Tablet	Fasted

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

Enrollment and dosing will be suspended if Grade ≥3 adverse events (AE) considered at least possibly related to the study drug are observed in two participants in a dosing cohort (refer to Section 10.2.1 and 10.2.2) after review by the Investigator and the Sponsor. If appropriate, the protocol will be amended after safety review.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

An oral solution formulation has been developed to support administration of brigatinib to pediatric patients who are unable to swallow solid oral dosage forms. The purpose of this relative bioavailability study is to compare the PK of brigatinib following a single dose of 90 mg of the oral solution relative to a 90 mg dose of the immediate-release tablet formulation in adult healthy subjects. The results of this study will subsequently be used to inform dose selection for the oral solution in the pediatric development program.

6.4.2 Rationale for Dose

A 90 mg oral dose of brigatinib was selected for this study based on the following considerations:

- Brigatinib exhibits linear PK over the dose range of 60 mg to 240 mg;
- The 90 mg QD dose of brigatinib is the recommended starting dose in adult patients with NSCLC, which if tolerated for 7 days, is escalated to 180 mg QD thereafter;
- Single doses as high as 180 mg of brigatinib have been previously administered to adult healthy subjects during development and have been found to be safe and generally well-tolerated.

However, because brigatinib systemic exposures with the oral solution may be higher than those observed with the tablet, this relative bioavailability study will utilize a 90 mg brigatinib dose in order to allow for the achievement of the scientific objectives of the study while minimizing the potential risks to study subjects.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of relative bioavailability study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies.

6.4.4 Future Biomedical Research

Not applicable.

6.4.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood sample collection for the measurement of plasma concentrations of brigatinib, and the samples are to be collected as close to the scheduled times defined in this protocol as possible. When an ECG event coincides with other assessments,

the sequence of procedures will be PK sampling, safety ECG, vital signs assessment, and then the safety laboratory blood draw.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of the study drugs to any subject may not be modified. If necessary, a subject may be discontinued for the reasons described in Section 7.5 and Section 7.6 Unscheduled procedures might be performed for safety reasons.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (i.e., signing of the ICF) of the first subject.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0).

6.6.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up contact for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.6.4 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.5 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.6.6 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Criteria for Inclusion:

Subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, males or females (of non-childbearing potential), 18-55 years of age, inclusive, at screening.
2. A nonvasectomized male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until at least 3 months after the last study drug dosing. (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a nonvasectomized male). A vasectomized subject may not use vasectomy as his primary/only form of contraception if he is unable to provide the surgical documentation (refer to Appendix D).
3. Male subjects must agree not to donate sperm from the first dosing until at least 3 months and female subjects must agree not to donate ova from the first dosing until at least 4 months after the last study drug dosing.
4. Female subjects of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing (hysteroscopic sterilization, bilateral tubal ligation, bilateral salpingectomy, hysterectomy, or bilateral oophorectomy); or be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status (refer to Appendix D).
5. Continuous nonsmoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study.
6. BMI $\geq$18.0 and <32.0 kg/m^2 at screening.
7. Medically healthy with no clinically significant medical history or abnormalities in physical examination, laboratory profiles, vital signs or 12-lead ECGs performed at the screening visit and before administration of the initial dose of trial drug, as deemed by the Investigator or designee.
8. Understands the study procedures in the ICF and be willing and able to comply with the protocol.
9. Pulse rate between 60 and 100 bpm and a blood pressure between 90 to 140 mmHg systolic and 40 to 90 mmHg diastolic at screening and prior to dosing of Period 1.

10. Creatine phosphokinase is ≤1.1x ULN; lipase, amylase, ALT, AST, total bilirubin, glucose, and aPTT are ≤ULN at screening and check-in of Period 1.

7.2 Exclusion Criteria

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiration, genitourinary, major neurological (including stroke and chronic seizures), or malignancy, active infectious diseases, ophthalmologic disorders other than presbyopia/myopia/hyperopia/astigmatism, or any other clinically significant abnormalities or disease in the opinion of the Investigator or designee.
3. Any history of major surgery, eg, cholecystectomy, intestinal resections, hepatectomy, nephrectomy, digestive organ resection that may affect absorption, metabolism or excretion of study drug. A history of appendectomy is not exclusionary.
4. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
5. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing.
6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
7. Positive urine drug or cotinine, or alcohol results at screening or check-in.
8. Positive results at screening for HIV, HBsAg, or HCV.
9. Positive COVID-19 results at first check-in.
10. Currently has an active infection, in the opinion of the Investigator.
11. QTcF interval is >460 msec or ECG findings are deemed abnormal with clinical significance by the Investigator or designee at screening.
12. Estimated creatinine clearance <90 mL/minute at screening (calculated using the Cockcroft-Gault formula).
13. Unable to refrain from or anticipates the use of any drug, including prescription and nonprescription medications, herbal remedies, or vitamin supplements within 28 days prior to the first dosing and throughout the study. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study, only after the first dosing, at the discretion of the Investigator or designee, as medically indicated. Thyroid hormone replacement

medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing.

14. Has been on a diet incompatible with the on-study diet, including consumption of grapefruit juice and other grapefruit containing products, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
15. Donation of blood or significant blood loss within 56 days prior to the first dosing.
16. Plasma donation within 7 days prior to the first dosing.
17. Participation in another clinical study within 30 days prior to the first dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. Acetaminophen (up to 2 g per 24-hour period) may be permitted during the study, only after the first dosing, at the discretion of the Investigator or designee, as medically indicated. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing.

If deviations occur, the Investigator or designee, in consultation with the Sponsor if needed, will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -28 to predose [Day 1])	After First Dosing (Day 1 of Period 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to dosing in each period	Prohibited from dosing in each period until the last PK sample collection of that period.
Xanthine and/or caffeine	Prohibited from 24 hours prior to dosing in each period [a]	Prohibited from dosing in each period until the last PK sample collection of that period.
Grapefruit juice and other grapefruit containing products	Prohibited from within 30 days prior to dosing in Period 1	Prohibited from dosing in Period 1 and throughout the study.
Medications	See Sections 7.1 and 7.2	See Sections 7.1 and 7.2
Nicotine- and tobacco-containing and/or cannabis products	Prohibited from 3 months prior to dosing in Period 1	Prohibited from first dosing in Period 1 and throughout the study.

(a) small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be

considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Subjects will fast overnight for at least 10 hours prior to each study drug administration. Subjects will continue the fast for at least 4 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when subjects are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snack served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time in each period.

7.4.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when subjects are supine or semi-recumbent for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Subjects will also be advised to avoid prolonged exposure to natural or artificial sunlight (e.g., tanning beds, ultraviolet A/B treatment) at any time starting from check-in for Period 1 until completion of the study. Subjects will be advised to wear protective clothing and sunglasses when they are in the sun, and use sunscreen with a high protection factor (Sun Protection Factor 30 and above).

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

- AEs (note that dosing and enrollment will be suspended as per the stopping criterion outlined in Section 6.3).
- A positive pregnancy test for females.*

- Positive urine drug or alcohol results.
- Difficulties in blood collection.

*This study includes females of non-childbearing potential. In the unlikely event of a female becoming pregnant during this study, the female will be withdrawn and will be followed up as detailed in Appendix D.

A subject may be withdrawn by the Investigator (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

If a subject is withdrawn prior to study completion, efforts should be made to perform all procedures scheduled for early termination as outlined in the Section 3.0, Schedule of Study Procedures.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Subject Replacement

Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and Investigator to ensure a minimum of 8 PK-evaluable subjects complete the study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Brigatinib will be supplied by the Sponsor and administered as a 90 mg oral solution dose (Treatment A, test formulation) and as a 90 mg immediate-release tablet dose (Treatment B, reference formulation [ALUNBRIG®]).

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

8.1.2 Clinical Study Drug Inventory and Storage

The same lot number for each formulation will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs will be stored according to the product label provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician.

A Celerion biostatistician will create a randomization schedule with a SAS program that includes a block size of 2 which randomly assigns each subject to a treatment group of A or B.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused brigatinib will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed and dated ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a randomization number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

All subjects will receive the treatments as detailed in Section 9.2.7.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, collection of blood for brigatinib PK is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time. When ECG coincides with other assessments, the sequence of procedures will be safety ECG, vital signs assessment, and then the safety laboratory blood draw.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Examination

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of temperature, respiratory rate, blood pressure and pulse rate, will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Vital sign measurements will be performed with subjects rested in a semi-recumbent position for at least 5 minutes before the measurements are acquired, except when they are supine because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Vital signs will be measured within 24 hours prior to Day 1 dosing of each period for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with subjects in a supine position (following a 5-minute rest, minimum). All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing of each period for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Palatability Assessment

Subjects will be asked to complete a questionnaire for assessment of palatability of the oral solution formulation. Palatability assessments, following Treatment A (oral solution) only, will be performed as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.7 Study Drug Administration

Brigatinib formulations will be provided as described in Section 8.1.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject, according to the randomization schedule.

Treatments will be administered as follows:

Oral Solution Administration (Treatment A, test): following an overnight fast of at least 10 hours, subjects receiving Treatment A will receive a 90 mg oral solution dose of brigatinib (ie, 9 mL of the 10 mg/mL solution) immediately followed by approximately 240 mL (8 fluid

ounces) of water. No food will be allowed for at least 4 hours postdose. Water is allowed as desired except for one hour before and one hour after drug administration, except for water at dosing.

Tablet Administration (Treatment B, reference): following an overnight fast of at least 10 hours, subjects receiving Treatment B will receive a 90 mg tablet dose of brigatinib (ie, one 90 mg tablet) with approximately 240 mL (8 fluid ounces) of water. No food will be allowed for at least 4 hours postdose. Water is allowed as desired except for one hour before and one hour after drug administration, except for water at dosing.

Subjects will be instructed not to crush, split, or chew the brigatinib tablets.

The date and exact clock time of dosing will be recorded.

Hour 0 will be set as the dosing time of tablet and relative to the start of dosing for the oral solution.

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 3.0.

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Coagulation

Coagulation will consist of the following tests:

Prothrombin time/ International normalized ratio (INR)	aPTT

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast with the exception of the Hour 8 postdose laboratory assessment on Day 1; however, in case of dropouts or rechecks,

subjects may not have fasted for 8 hours prior to when the serum chemistry sample is being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Albumin
Lipase	Sodium
Blood Urea Nitrogen	Potassium
Bilirubin (total and direct)	Chloride
Alkaline phosphatase	Glucose
AST	Creatinine *
Total Protein	Lactate dehydrogenase
Phosphorous	Testosterone (males only)
ALT	Magnesium
Calcium	Creatine phosphokinase
Insulin	

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

9.2.9.1.1 Other

HIV test	Urine drug screen
HBsAg	Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and hydromorphone)
HCV *(if antibody positive, confirm RNA negative)*	Opioids (includes methadone, oxycodone, and fentanyl)
Urine alcohol screen	Amphetamines
Serum pregnancy test (females only)	Barbiturates
FSH (postmenopausal females only)	Benzodiazepines
Urine cotinine	Cocaine
COVID-19 screen	Cannabinoids

9.3 PK Samples

Instructions for sample collection, processing, and shipping will be provided in separate documents. The date and exact clock time of each PK sample collection will be recorded.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a: Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for PK	Plasma	Plasma sample for brigatinib PK analysis	Mandatory

9.3.1 PK Measurements

Samples from all subjects will be assayed even if the subjects do not complete the study. Samples for determination of plasma concentrations of brigatinib will be analyzed using a validated bioanalytical method.

PK parameters of brigatinib will be calculated from the individual concentration-time profiles from all evaluable subjects using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma PK Measurements

The following PK parameters will be calculated from plasma concentrations of brigatinib, as appropriate:

AUC_{last}:	Area under the plasma concentration-time profile, from time 0 to the time of the last quantifiable concentration.
AUC_{∞}:	Area under the plasma concentration-time profile, from time 0 to infinity calculated using the observed value of the last quantifiable concentration.
$AUC_{\%extrap}$:	Area under the curve from the last quantifiable concentration to infinity, expressed as a percentage of AUC_{∞}.
CL/F:	Apparent clearance after extravascular administration.
C_{max}:	Maximum observed plasma concentration.
t_{max}:	Time of first occurrence of C_{max}.
$t_{½z}$:	Terminal disposition phase half-life.
λ_z:	Terminal disposition phase rate constant.
V_z/F:	Apparent volume of distribution during the terminal disposition phase after extravascular administration.

No value for λ_z, AUC_∞, $AUC_{\%extrap}$, CL/F, V_z/F, or $t_{½z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

PK parameters will not be calculated for subjects with less than 3 consecutive postdose time points with quantifiable concentrations.

Individual and mean plasma concentration-time profiles (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

9.3.2 Biomarker Measurements

Not applicable.

9.3.3 PGx Measurements

Not applicable.

9.3.4 Confinement

Subjects will be housed on Day -1 of each period, at the time indicated by the CRU, until after the 72-hour blood draw and/or study procedures. Subjects will return for dosing and/or study procedures as outlined in the Schedule of Study Procedures (Section 3.0).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

As per site preference, subjects may be confined throughout the study (i.e., washout period and/or return visits).

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed ICF to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.

- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of…”).
- If a subject has a pre-existing episodic condition, any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, Investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg “worsening of…”).
- If a subject has a concurrent condition, worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of…”).

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the Investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (electronic [e]) case report form (CRF), in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a: Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

AEs of special interest identified from previous studies include the following: early onset pulmonary events, later-onset pneumonitis, bradycardia, hypertension, gastrointestinal events, elevated creatine phosphokinase, pancreatic enzyme elevation, increased insulin/hyperglycemia events, vision impairment events, photosensitivity, and liver enzyme increases.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The Investigator must categorize the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher [3].

For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of one through five using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

*Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or Investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE (see Section 6.3 for study stopping criterion)
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.

Recommendations for the management of adverse reactions are provided in the ALUNBRIG® Prescribing Information (2022). Discontinuation of brigatinib administration should be additionally considered for the following: pulmonary symptoms for interstitial lung disease/pneumonitis, severe hypertension, severe visual disturbance, symptomatic bradycardia, creatine phosphokinase elevation, pancreatic enzyme elevation, uncontrolled hyperglycaemia, and photosensitivity.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).

- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal Liver Function Tests (LFT)

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the ICF. Routine collection of AEs will continue until the follow-up contact ie, Day 14 (± 2 days) after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the Investigator or designee will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

- Concomitant medication administered and/or procedures performed related to the AE.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event, with event onset date and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed beneath:

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Email: PVSafetyAmericas@tpna.com Fax: 224-554-1052

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

10.2.8.3.1 SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it 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.

10.2.8.4 Reporting Special Interest AEs

AEs of special interest are presented in Section 10.1.2.

10.2.8.5 Close Monitoring and Treatment Discontinuation for Potential Drug-Induced Liver Injury (DILI)

Subjects who develop ALT/AST >3xULN after first dosing should be monitored closely and the clinical significance of the elevation should be assessed by the investigator. Close observation includes the following:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

If a subject develops any of the following after the first dose, treatment should be discontinued, the medical monitor should be contacted immediately, and the subject should be withdrawn from the study:

- ALT or AST >5xULN
- ALT or AST >3xULN at the end of the minimum 14 days washout period
- ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The above criteria if met will be reported as SAEs. All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. Pertinent elements of the case should be captured in the DILI CRF.

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

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and Institutional Review Board (IRB) or Independent Ethics Committee (IEC), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee,

SUSARs will be submitted 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 products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

All subjects who received at least one dose of the study drug(s) will be included in the safety evaluations.

11.1.1.2 PK Set

All subjects who comply sufficiently with the protocol and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

Statistical analysis of PK data will be based on the PK analysis data set. Additional details related to the PK analyses will be described in a separate analysis plan.

Plasma PK parameters of brigatinib will be derived using standard noncompartmental analysis methods. A linear mixed-effects analysis of variance model will be used for the analysis on the ln-transformed brigatinib PK parameters (C_{max}, AUC_{last}, and AUC_{∞}). The model will include sequence, treatment, and period as fixed effects. Subject nested within sequence will be included

as a random effect. Each model will include calculation of LSM as well as the difference between treatment LSM. Geometric mean ratios and 90% CIs will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed C_{max}, AUC_{last}, and AUC_{∞}. These ratios will be expressed as a ratio of test treatment (ie, oral solution) relative to the reference treatment (ie, tablet).

11.1.4 PD Analysis

Not applicable.

11.1.5 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

TEAEs will be tabulated. The remaining quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.5.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.5.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.5.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by subject.

11.2 Palatability

Palatability results for Treatment A only will be presented in the data listings and summarized as appropriate.

11.3 Interim Analysis and Criteria for Early Termination

Not applicable.

11.4 Determination of Sample Size

The sample size calculation was based on the expected 2-sided 90% CIs for the difference in the paired, ln-transformed AUC_{∞} means of brigatinib after administration as an oral solution versus an immediate-release tablet. The within-subject %CV for brigatinib AUC_{∞} was estimated to be 12% on the basis of data from previous clinical studies conducted in healthy subjects (Studies AP26113-15-106 and AP26113-16-110). If the observed GMR for brigatinib AUC_{∞} after administration as an oral solution versus a tablet is 1, with a sample size of 8, the 90% CIs for the GMR is expected to be 0.89 to 1.12 on the basis of the variance assumptions.
It is anticipated that a total of approximately 12 subjects will be enrolled to obtain at least 8 PK-evaluable subjects. Subjects will be randomized into 2 treatment sequences, as indicated in Table 6.a.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 CRFs. Source documents are defined as original documents, data, and records. The Investigator and study site guarantee access to source documents by the Sponsor or its designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of CRFs 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.

12.2 Protocol Deviations

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

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 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 regulatory agency, the Food and Drug Administration (FDA). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 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 International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas 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 respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and subject

authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

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

All revised ICFs must be reviewed, signed, and dated 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 signed and dated ICF.

13.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

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 CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

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.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites 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.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the Investigator name, address, and phone number to the 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 the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 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 study subjects. Refer to the 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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Email: PVSafetyAmericas@tpna.com Fax: 224-554-1052

14.1.2 INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

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/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

ADL	Activities of Daily Living
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time profile
AUC_{∞}	Area under the plasma concentration-time profile from time 0 to infinity
$AUC_{\%extrap}$	Percent of AUC_{∞} extrapolated
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration
BMI	Body mass index
bpm	Beats per minute
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent clearance after extravascular administration
Cm	Centimeter
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus Disease-2019
CRF	Case report form
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
%CV	Percent coefficient of variation
CYP	Cytochrome P450
DILI	Drug-induced liver injury
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GMR	Geometric mean ratio
h	Hour
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International units
kg	Kilogram
L	Liter
LFT	Liver function tests
ln	Natural log
LSM	Least squares mean
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
QD	Once daily
QTcF	An electrocardiographic finding in which the QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
$t_{½z}$	Terminal disposition phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of first occurrence of maximum observed plasma concentration
ULN	Upper limit of normal
USPI	United States Prescribing Information
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration
WHO	World Health Organization
λ_z	Terminal disposition phase rate constant

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the WHO Drug Dictionary.

15.1 CRFs (Electronic and Paper)

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English. Data are transcribed directly onto CRFs.

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.

Corrections 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. Reasons for significant corrections should additionally be included.

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

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator with use of change and modification records of the CRFs. The Principal Investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs 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 CRFs. The completed CRFs 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.

15.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, 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 and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. Brigatinib (AP26113), Investigators Brochures, Edition 9.0, 12 Jun 2019.
2. ALUNBRIG® (Brigatinib). Prescribing Information. Revised 02/2022. Available at: https://www.alunbrig.com/assets/pi.pdf
3. National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, Nov 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that 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, prior to 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/IEC that conform to 21 Code of federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
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/IEC. 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 CRFs, 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 B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or

the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

24. Female subjects of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing (hysteroscopic sterilization, bilateral tubal ligation, bilateral salpingectomy, hysterectomy, or bilateral oophorectomy);

or be postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.

25. Male subjects must agree to use a condom with spermicide (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for at least 3 months after the last dose of study drug (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a nonvasectomized male). A vasectomized subject may not use vasectomy as his primary/only form of contraception if he is unable to provide the surgical documentation (refer to Appendix D).
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the 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 Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

Based on findings in male reproductive organs in animals, brigatinib may cause reduced fertility in males. From signing of informed consent, throughout the duration of the study, and for at least 3 months after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicide). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

Female Subjects and Their Male Partners

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). Females of reproductive potential should be advised to use effective non-hormonal contraception during treatment with brigatinib and for at least 4 months following the final dose of brigatinib.

In this study, the only acceptable methods of contraception for female participating subjects are:

- Non-Hormonal Methods:
  - hysteroscopic sterilization,
  - bilateral tubal ligation or bilateral salpingectomy,
  - hysterectomy,
  - bilateral oophorectomy.

– postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status.

2. Unacceptable methods of contraception are:

- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
- Spermicides only.
- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and condom without spermicide.
- Sexual abstinence is NOT an acceptable method of contraception.

3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study and poststudy.
4. All subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm and ova donations as part of the study procedures. Such guidance should include a reminder of the following:

a) contraceptive requirements of the study

b) reasons for use of barrier methods (ie, condom with spermicide) in males with pregnant partners

c) assessment of subject compliance through questions such as

i. Have you used the contraception consistently and correctly since the last visit?

ii. Have you forgotten to use contraception since the last visit?

iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)

iv. Is there a chance you or your partner could be pregnant?

5. In addition to a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening, female subjects must also have a negative serum hCG pregnancy test prior to receiving first dose of investigational drug as close as possible and prior to first dose of investigational drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.

- reasons for use of barrier methods (ie, condom with spermicide) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

Women of childbearing potential will not be included in this study.

Any pregnancies in the partner of a male subject during the study or for at least 3 months after the last dose, should also be recorded following authorization from the subject's partner.

If the female partner of a male subject agrees to the primary care physician being informed, the Investigator or designee should notify the primary care physician that the female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

After obtaining consent, all pregnancies of female partners of male subjects, in subjects on active study drug (including comparator, if applicable) will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

This study includes females of non-childbearing potential. In the unlikely event of a female subject becoming pregnant during this study, the pregnancy will also be followed up as detailed above.

Appendix E Detailed Description of Amendments to Text

Amendment 01

Change 1. The verbiage in the criteria for inclusion (#3) (Section 1.0 - STUDY SUMMARY and Section 7.1 – Inclusion Criteria) was updated.
Rationale for the change: Verbiage was updated as per FDA communication under IND 110935 dated October 27, 2023 to include information regarding duration of ova donation for females: Update in ~~strikethrough~~ for text removed and in **bold** for text added. Male ~~or female~~ subjects must agree not to donate sperm ~~or ova~~ from the first dosing until at least 3 months **and female subjects must agree not to donate ova from the first dosing until at least 4 months** after the last study drug dosing.
Change 2. The verbiage in the introduction (Section 4.1 - Background) was updated.
Rationale for the change: Verbiage was added to include information regarding male fertility from previous studies. Added the paragraph in **bold**: **Testicular toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2 month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period [2].**
Change 3. Verbiage was added to initiate study suspension in the event of AEs (Section 6.3 - Stopping Rules)
Rationale for the change: Verbiage was updated to include a study stopping criterion as per FDA communication under IND 110935 dated October 27, 2023. Update in ~~strikethrough~~ for text removed and in **bold** for text added. ~~Not applicable~~ Enrollment and dosing will be suspended if Grade ≥3 adverse events (AE) considered at least possibly related to the study drug are observed in two participants in a dosing cohort (refer to Section 10.2.1 and 10.2.2) after review by the Investigator and the Sponsor. If appropriate, the protocol will be amended after safety review.
Change 4. Verbiage was added for consistency (Section 7.5 – Criteria for Discontinuation or Withdrawal of a Subject)
Rationale for the change: Verbiage was added to include reference to the stopping criterion. Update in **bold** for text added (first bullet). In addition, subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

• AEs **(note that dosing and enrollment will be suspended as per the stopping criterion outlined in Section 6.3)**
Change 5. Verbiage was added for consistency (Section 10.2.6– Action Taken With Study Treatment
Rationale for the change: Verbiage was added to include reference to the stopping criterion. Update in **bold** for text added (first bullet). • Drug withdrawn – a study medication is stopped due to the particular AE (**see Section 6.3 for study stopping criterion)**
Change 6. The verbiage for #25 (Appendix B – Elements of the Subject Informed Consent) was updated
Rationale for the change: Verbiage was updated for consistency with Inclusion #2: Update in ~~strikethrough~~ for text removed and in **bold** for text added (#25). Male subjects ~~must use~~ must agree to use a condom with spermicide (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for at least 3 months after the last dose of study drug**. (No restrictions are required for a vasectomized male provided his bilateral vasectomy procedure has been performed at least 1 year prior to the first dosing of study drug. A male who has been vasectomized less than 1 year prior to study first dosing must follow the same restrictions as a nonvasectomized male). A vasectomized subject may not use vasectomy as his primary/only form of contraception if he is unable to provide the surgical documentation (refer to Appendix D)**.
Change 7. The verbiage for describing fertility and contraceptive measures (Appendix D - Pregnancy and Contraception) was updated as per FDA communication under IND 110935 dated October 27, 2023.
Rationale for the change: Verbiage was included to provide information on fertility for male subjects and for contraceptive measures for females of reproductive potential. Update in **bold** for text added. *Male Subjects and Their Female Partners* **Based on findings in male reproductive organs in animals, brigatinib may cause reduced fertility in males.** From signing of informed consent, throughout the duration of the study, and for at least 3 months after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicide). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

The following procedures apply for contraception and pregnancy avoidance: Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). **Females of reproductive potential should be advised to use effective non-hormonal contraception during treatment with brigatinib and for at least 4 months following the final dose of brigatinib USPI.**
Change 8. Text was updated to correct a missing infinity symbol from a PK parameter (Section 1.0 - STUDY SUMMARY, Sample Size Justification)
Rationale for the change: Correction to PK parameter symbol. Update in ~~strikethrough~~ for text removed and in **bold** for text added The sample size calculation was based on the expected 2-sided 90% CIs for the difference in the paired, ln-transformed AUC□-∞ means of brigatinib after administration as an oral solution versus an immediate-release tablet. The within-subject percent coefficient of variation (%CV) for brigatinib AUC□-∞ was estimated to be 12% on the basis of data from previous clinical studies conducted in healthy subjects (Studies AP26113-15-106 and AP26113-16-110). If the observed GMR for brigatinib AUC□ ∞ after administration as an oral solution versus a tablet is 1, with a sample size of 8, the 90% CIs for the GMR is expected to be 0.89 to 1.12 on the basis of the variance assumptions. It is anticipated that a total of approximately 12 subjects will be enrolled to obtain at least 8 PK-evaluable subjects. Subjects will be randomized into 2 treatment sequences, as indicated in Table 1.a.
Change 9. Verbiage was updated to correct a protocol discrepancy (Section 3.0 - Schedule of Study Procedures [Footnote "i"] and Section 9.2.9.1 - Clinical Laboratory Tests)
Rationale for the change: A protocol clarification letter (dated 28 November 2023) was written and submitted detailing an exemption from the fasting requirement for the laboratory assessment (chemistry) scheduled at Hour 8 on Day 1, as there will be a meal served less than 8 hours prior to the laboratory assessment. Updated text in **bold**. Serum chemistry tests will be performed after at least an 8-hour fast **with the exception of the Hour 8 postdose laboratory assessment on Day 1**; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample is being taken.
Change 10. Section 14.1.4 – List of Abbreviations
Section was updated to include abbreviation, USPI (United States Prescribing Information).

Signature Page for Brigatinib-1004 Protocol Amend 1 2024-01-05
Title: Amend 1 to A Phase 1, Open-Label, Randomized, Single-Dose, 2-Period, Cros

Approval	[redacted] Clinical 05-Jan-2024 14:03:21 GMT+0000

Approval	[redacted] Clinical 05-Jan-2024 15:14:33 GMT+0000

Approval	[redacted] Statistics 05-Jan-2024 16:52:11 GMT+0000

Document Number: TDN-000230049 v1.0