Title: A Single-Arm, Multicenter, Phase 2 Study of Brigatinib in Japanese Patients With ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

NCT Number: NCT03410108

Protocol Approve Date: 22-Jul-2020

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

**PROTOCOL**

# A Single-Arm, Multicenter, Phase 2 Study of Brigatinib in Japanese Patients With ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Pharmaceutical Company Limited.<br>4-1-1 Doshomachi, Chuo-ku, Osaka 540-8645 | | |
| **Study Number:** | Brigatinib-2001 | | |
| **IND Number:** | Not applicable | **EudraCT Number:** | Not applicable |
| **Compound:** | Brigatinib (AP26113) | | |
| **Date:** | 22 July 2020 | **Amendment Number:** | 04 |

**Amendment History:**

| Date | Amendment Number | Region |
|---|---|---|
| 25 October 2017 | Initial Protocol | All sites |
| 30 November 2017 | 01 | All sites |
| 30 May 2018 | 02 | All sites |
| 10 December 2018 | 03 | All sites |
| 22 July 2020 | 04 | All sites |

Note: After a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan, this study will become a post-marketing clinical study and will be continued until the last patient get access to the commercial supply. This protocol will be continuously used for the post-marketing clinical study, and all the term "study" in this protocol shall be then deemed as appropriately replaced to "post-marketing clinical study."

# 1.0 ADMINISTRATIVE

## 1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

| Contact Type/Role | Contact |
|---|---|
| Serious adverse event and pregnancy reporting | See Section 10.0. |
| Responsible medical officer<br>(carries overall responsibility for the conduct of the study) | See protocol annex. |

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

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

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

### SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

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

PPD

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure 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 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

## 1.3 Protocol Amendment 04 Summary of Changes

This section describes the changes in reference to the Protocol Incorporating Amendment No. 04.

The primary purpose of this amendment is to revise the study completion definition. After a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan, this study will become a post-marketing clinical study and will be continued until the last patient get access to the commercial supply. This protocol will be continuously used for the post-marketing clinical study, and all the term "study" in this protocol shall be then deemed as appropriately replaced to "post-marketing clinical study."

The changes in this amendment are as follows:

1. To revise the protocol signatory.
2. To add notes regarding the transition to a post-marketing study on the title page.
3. To revise study completion definition on Section 6.3.2.
4. To update Section 2.0 Study Summary according to the revisions in Section 6.3.2.

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## 2.0 STUDY SUMMARY

| | | |
|---|---|---|
| **Name of Sponsor(s):**<br>Takeda Pharmaceutical Company, Ltd. | **Compound:**<br>Brigatinib (AP26113) | |
| **Title of Protocol:** A Single-Arm, Multicenter, Phase 2 Study of Brigatinib in Japanese Patients With ALK-Positive Non-Small Cell Lung Cancer (NSCLC) | **IND No.:**<br>Not applicable | **EudraCT No.:**<br>Not applicable |
| **Study Number:** Brigatinib-2001 | **Phase:** 2 | |

**Study Design:**

This is a nonrandomized, multicenter, phase 2, open-label study with safety evaluation lead-in, to evaluate the efficacy and safety of brigatinib in Japanese patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.

The study consists of the safety evaluation lead-in part and the expansion part. The safety evaluation lead-in part allows patients with any line of prior ALK inhibitor which includes treatment-naïve patients; however, ALK inhibitor-naïve patients may be enrolled after the confirmation of first 3 dose-limiting toxicity (DLT) evaluable patients to have no more than 1 DLT during Cycle 1 by investigator's judgement. The expansion part consists of the tyrosine kinase inhibitor (TKI) naïve expansion cohort and the refractory expansion part. The refractory expansion part includes the main cohort and a subcohort based on prior ALK inhibitor treatment. The TKI-naïve expansion cohort includes the patients who have not received any prior TKI including ALK inhibitor. In this cohort, the efficacy will be evaluated, and a total of 32 patients will be enrolled. The main cohort of the refractory expansion part includes patients who had previously received alectinib (as their only ALK inhibitor) or both crizotinib and alectinib (regardless the sequence of those 2 ALK inhibitors). The main cohort of the refractory expansion part will be used for the primary analysis of efficacy, and a total of 47 patients will be enrolled in the main cohort of the refractory expansion part. Patients with all other sequences of up to 2 prior ALK inhibitor(s) may be included in the subcohort of the refractory expansion part. Such other ALK inhibitors include 1) crizotinib only, 2) ceritinib only, 3) lorlatinib only, 4) both crizotinib and ceritinib, 5) both alectinib and ceritinib, 6) both crizotinib and lorlatinib, 7) both alectinib and lorlatinib, and 8) both ceritinib and lorlatinib. Up to 20 patients will be enrolled in the subcohort of the refractory expansion part.

In this study, brigatinib will be administered at 90 mg once daily (QD) for the first 7 days and then 180 mg QD (90 mg QD→180 mg QD). In the safety evaluation lead-in part, patients will be monitored for intensive pharmacokinetics (PK), and the tolerability of 90 mg QD→180 mg QD dosing will be confirmed. If the 90 mg QD→180 mg QD dosing regimen is considered tolerable, additional patients enrolled in the expansion part will be treated with the same dosing schedule (90 mg QD→180 mg QD).

Patients will be treated until they experience objective progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason. Treatment of patients with brigatinib may be continued at the tolerated dose level, despite investigator-assessed PD by RECIST version 1.1, if the patient otherwise has evidence of ongoing clinical benefit. In this case, discussions and agreements between the investigator and the sponsor's project clinician (or designee) are required.

<u>Safety Evaluation Lead-in Part</u>

Nine DLT–evaluable patients will be enrolled in the safety evaluation lead-in part. The patients in the safety evaluation lead-in part will be hospitalized during Cycle 1 in general (hospitalization on Days 1-10 and Days 22-23 is mandatory), and their condition will be closely monitored for safety and tolerability. Serial blood samples will be collected for the intensive PK profile. The patients in the safety evaluation lead-in part will receive brigatinib 90 mg QD→180 mg QD. A cycle of therapy comprises 28 days of treatment. If a patient is NOT considered DLT evaluable for any reason, the patient will be replaced.

Tolerability of the 90 mg QD→180 mg QD schedule will be determined on the basis of the DLTs observed in Cycle 1. If a DLT is observed in fewer than 3 of the 9 DLT-evaluable patients in the safety evaluation lead-in part, the 90 mg QD→180 mg QD regimen will be used for the patients enrolled in the expansion part. Opening of the expansion part will be determined on the basis of the total safety data available at that time, available PK results, and with

recommendation from the independent data monitoring committee (IDMC). Regarding the safety data, all AEs observed in the safety evaluation lead-in part, including those observed in DLT non-evaluable patients, will be evaluated in concert with DLTs when making the decision on opening of the expansion part.

Expansion Part (Refractory Expansion Part and TKI-Naïve Expansion Cohort)

For the TKI-naïve expansion cohort and the refractory expansion part, patients may be managed on an outpatient basis, and the number of study sites will be increased up to approximately 40. Patients in the refractory expansion part and the TKI-naïve expansion cohort will undergo less-intensive PK blood sampling than patients in the safety evaluation lead-in part.

On an outpatient basis, patients will visit the hospital on Days 1, 8, and 15 of Cycle 1, and then on Day 1 of each cycle after Cycle 2. Tumor assessment will be performed every 2 cycles from Cycle 3 Day 1 through Cycle 15 Day 1, then every 3 cycles thereafter until the last dose of study drug. For patients who discontinue study treatment in the absence of PD, additional tumor assessment should continue at the same time points as the study treatment until PD or the start of another systemic anticancer therapy.

**Primary Objective:**

To evaluate efficacy of brigatinib in Japanese patients with ALK-positive advanced NSCLC.

- The objective response rate (ORR) will be evaluated in the refractory patients.
- The progression-free survival (PFS) rate at 12 months in Kaplan-Meier plots (12 months PFS rate) will be evaluated in the TKI-naïve patients.

**Secondary Objectives:**

- To confirm the clinical dose in Japanese patients.
- To characterize the efficacy of brigatinib as shown by following parameters.
  For all enrolled patients (including TKI-naïve patients): duration of response (DOR), PFS, disease control rate (DCR), time to response, and overall survival (OS).
  For the TKI-naïve patients: ORR
- To characterize the intracranial efficacy of brigatinib, as evidenced by intracranial objective response rate (iORR) and duration of intracranial response (iDOR), and intracranial PFS (iPFS) in patients with intracranial disease at baseline, from the refractory expansion part and the TKI-naïve expansion cohort.
- To assess patient-reported outcomes (PROs) of health-related quality of life (HRQOL) and symptoms of lung cancer with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3.0), its lung cancer module QLQ-LC13, and the 5-level version of the EuroQol 5-dimensional questionnaire (EQ-5D-5L).
- To characterize the PK of brigatinib in Japanese patients.

**Safety Objective:**

The safety objective is to assess the safety and tolerability of brigatinib.

**Subject Population:**

Patients with ALK-positive advanced NSCLC.

Safety evaluation lead-in part: patients with any line of prior ALK inhibitor treatment including treatment naïve.

Expansion part:

- Patients who have progressed on prior treatment with 1 or 2 ALK inhibitors (refractory expansion part) or,
- Patients who have not received ALK inhibitors (TKI-naïve expansion cohort)

| **Number of Subjects:** | **Number of Sites:** |
|---|---|
| Approximately 110 patients:<br>Safety evaluation lead-in part: approximately 9 patients<br>Expansion part: | Estimated total: approximately 40 sites in Japan |

| | |
|---|---|
| • 47 patients in the main cohort of the refractory expansion part and<br>• Up to 20 patients in the subcohort of the refractory expansion part<br>• 32 in the TKI-naïve expansion cohort | |
| **Dose Level(s):**<br>Brigatinib will be administered as an oral single agent at 180 mg QD with a 7-day lead-in at 90 mg QD in a 28-day cycle | **Route of Administration:**<br>Oral |
| **Duration of Treatment:**<br>Patients will be treated until they experience objective PD per RECIST version 1.1, as assessed by the investigator, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason. Treatment of patients with brigatinib may be continued at the tolerated dose level, despite investigator-assessed PD by RECIST version 1.1, if the patient otherwise has evidence of ongoing clinical benefit. In this case, discussions and agreements between the investigator and the sponsor's project clinician (or designee) are required. | **Period of Evaluation:**<br>For the safety evaluation lead-in part and the refractory expansion part, the follow-up period will be for 24 months after the last patient was enrolled, or when all patients have completed the study treatment, whichever comes later. However, in case a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan before the study completion noted above, this study will become a post-marketing clinical study after the marketing approval and will be continued until all the patients who are continuing study treatment with brigatinib have access to the commercial supply.<br>For the TKI-naïve expansion cohort, after a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan, this study will become a post-marketing clinical study and will be continued until the last patient have access to the commercial supply. |

**Main Criteria for Inclusion:**

1. Male or female Japanese patients aged ≥20 years on the day of consent.
2. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Have histologically or cytologically confirmed stage IIIB, stage IIIC (locally advanced or recurrent and not a candidate for definitive multimodality therapy), or stage IV NSCLC.
4. Have documentation of ALK rearrangement that meets following criteria.

   For the safety evaluation lead-in part and the refractory expansion part, patients must meet 1 of the following 2 criteria:

   a) Have documentation of ALK rearrangement by a positive result from the Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit, the Nichirei Histofine ALK iAEP Kit, or the Ventana ALK [D5F3] CDx Assay at any time during prior disease course. The sponsor may require an adequate tissue available for central laboratory testing by the Vysis ALK Break Apart FISH test if a documented ALK rearrangement is confirmed by a positive result from the Nichirei Histofine ALK iAEP Kit "ONLY".

   b) Had a documented ALK rearrangement by a different test at any time during prior disease course, and adequate tissue available for central laboratory testing by the Vysis ALK Break Apart FISH test. Central confirmation of ALK rearrangement is not required before enrollment.

   For the TKI-naïve expansion cohort, patients must meet the following criteria:

Have documentation of ALK rearrangement by a positive result from MHLW-approved tests (e.g. Vysis ALK Break Apart FISH Probe Kit, the Nichirei Histofine ALK iAEP Kit, or the Ventana ALK [D5F3] CDx Assay) prior to enrollment, and **required to submit sufficient tumor tissue for central laboratory testing upon request of sponsor.** Central confirmation of ALK rearrangement is not required before enrollment.

5. The refractory expansion part only: had documented PD during treatment or within 30 days after discontinuation of treatment with either alectinib, crizotinib, ceritinib, or lorlatinib.
   - Note 1: The refractory expansion part consists of the main cohort and a subcohort based on prior ALK inhibitor treatment. The main cohort includes patients who had previously received alectinib (as their only ALK inhibitor) or both crizotinib and alectinib (regardless the sequence of those 2 ALK inhibitors), and a total of 47 patients will be enrolled. Patients with all other sequences of up to 2 prior ALK inhibitor(s) may be included in the subcohort, and the number of patients will be limited to 20.
   - Note 2: Patients who will be included in the main cohort of the refractory expansion should have documented PD during treatment or within 30 days after discontinuation of treatment with alectinib.
6. Have at least 1 measurable (ie, target) lesion per RECIST version 1.1.
   Note: Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may not be used as target lesions if they were 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection.
7. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 Grade ≤1.
   Note: Treatment-related alopecia is allowed.
8. Have a life expectancy of ≥3 months.
9. Have adequate organ and hematologic function, as determined by:
   a) Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of the normal range (ULN) (≤5×ULN is acceptable if liver metastases are present).
   b) Total serum bilirubin ≤1.5×ULN (<3.0×ULN for patients with Gilbert syndrome).
   c) Serum creatinine <1.5×ULN. For patients with creatinine levels above or equal to 1.5×ULN, the patient is eligible if the estimated creatinine clearance using the Cockcroft-Gault formula is ≥30 mL/minute.
   d) Serum lipase ≤1.5×ULN and serum amylase ≤1.5×ULN.
   e) Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.
   f) Platelet count $\geq 75\times10^9$/L.
   g) Hemoglobin ≥9 g/dL.
   h) Percutaneous oxygen saturation ($SpO_2$) ≥94% without oxygen support. Patients who need oxygen support are excluded.
10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
11. Must meet the following criteria:
    a) Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should

not be used together.)

b) Male patients, even if surgically sterilized (ie, status postvasectomy), who:

– Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR

– Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, during the entire study treatment period and through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

12. Have the willingness and ability to comply with scheduled visit and study procedures.

**Main Criteria for Exclusion:**

1. Previously received the following treatments.

   The refractory expansion part only: received any prior ALK inhibitor other than alectinib, crizotinib, ceritinib, or lorlatinib.

   The TKI-naïve expansion cohort only: received any prior TKI including but not limited to ALK inhibitor and vascular endothelial growth factor receptor (VEGFR) TKI.

2. The refractory expansion part only: received more than 2 prior ALK inhibitors.
   Note: The safety evaluation lead-in part allows patients with any line of prior ALK inhibitor which includes treatment-naïve patients; however, ALK inhibitor-naïve patients may be enrolled after the confirmation of first 3 DLT evaluable patients to have no more than 1 DLT during Cycle 1 by investigator's judgement.

3. The safety evaluation lead-in part and the refractory expansion part only: received alectinib, crizotinib, ceritinib, or lorlatinib within 7 days before the first dose of brigatinib.

4. Previously received more than 1 regimen (more than 3 regimens in the safety evaluation lead-in part) of systemic anticancer therapy (other than ALK inhibitors) for locally advanced or metastatic disease.
   Note: A systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen unless it was previously used as initial anticancer therapy. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if completion of (neo) adjuvant therapy occurred <12 months before the first dose of brigatinib.

5. Treatment with any investigational products except for lorlatinib within 30 days or 5 half-lives of that investigational agent, whichever is longer, before the first dose of brigatinib.

6. Received chemotherapy or radiation within 14 days before the first dose of brigatinib, except SRS or stereotactic body radiation therapy.

7. Received antineoplastic monoclonal antibodies within 30 days before the first dose of brigatinib.

8. Received systemic treatment with strong inhibitors or strong and moderate inducers of cytochrome P450 (CYP) 3A within 7 days before the first dose of brigatinib.

9. Had major surgery within 30 days before the first dose of brigatinib. Minor surgical procedures such as venous catheter placement or minimally invasive biopsies are allowed.

10. Have been diagnosed with another primary malignancy other than NSCLC, except for the following adequately/definitively treated malignancies: nonmelanoma skin cancer, cervical cancer in situ, nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.

11. Have symptomatic central nervous system (CNS) metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days before the first dose of brigatinib.
    Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids

or use of anticonvulsants for symptomatic control) for 7 days before the first dose of brigatinib.

12. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with asymptomatic leptomeningeal disease and without cord compression are allowed.
13. Have ongoing or history of interstitial lung disease (ILD) (including interstitial pneumonitis, pneumonitis, radiation pneumonitis, drug-related pneumonitis, organized pneumonia, and pulmonary alveolitis).
14. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not limited to:
    a) Myocardial infarction within 6 months before the first dose of brigatinib.
    b) Unstable angina within 6 months before the first dose of brigatinib.
    c) Congestive heart failure within 6 months before the first dose of brigatinib.
    d) Uncontrolled atrial arrhythmias despite appropriate medical therapy.
    e) History of ventricular arrhythmia, including history of ventricular tachycardia, ventricular fibrillation, or torsade de pointes. Patients with premature ventricular contractions are allowed.
    f) Cerebrovascular accident or transient ischemic attack within 6 months before the first dose of brigatinib.
15. Have uncontrolled hypertension. Patients with hypertension should be under treatment at the start of screening and demonstrate adequate control of blood pressure.
16. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous antibiotics.
17. Have a known history of HIV infection. Testing is not required in the absence of history.
18. Hepatitis B surface antigen (HBsAg) positive, detectable hepatitis B viral load, or detectable hepatitis C virus (HCV) infection viral load.
    Note: Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B viral load. Patients who have positive HCV antibody can be enrolled but must have an undetectable hepatitis C viral load.
19. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of brigatinib.
20. Have a known or suspected hypersensitivity to brigatinib or its excipients.
21. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.
    Note: Female patients who are lactating will be excluded, even if they discontinue breastfeeding.
22. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of brigatinib.

**Main Criteria for Evaluation and Analyses:**

Primary endpoint:

- Confirmed ORR as assessed by an independent review committee (IRC), per RECIST version 1.1. in the main cohort of the refractory expansion part
- 12 months PFS rate as assessed by an IRC, per RECIST version 1.1 in the TKI-naïve expansion cohort

Secondary endpoints:

a) Efficacy endpoint in the TKI-naïve expansion cohort, the overall population of the refractory expansion part, and the safety evaluation lead-in part:
   – Confirmed ORR, as assessed by an IRC, per RECIST version 1.1.

b) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, the overall population of the refractory expansion part:
   – DOR, as assessed by an IRC, per RECIST version 1.1.
   – PFS, as assessed by an IRC, per RECIST version 1.1.
   – DCR, as assessed by an IRC, per RECIST version 1.1.

- Time to response, as assessed by an IRC, per RECIST version 1.1.
- OS.
- CNS response, as assessed by an IRC, per modified RECIST version 1.1 for assessment of intracranial efficacy (iORR and iDOR in patients who had measurable CNS metastases, and iPFS in all patients).
- Time on treatment

c) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, and the safety evaluation lead-in part:

- Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.
- PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L (except for the safety evaluation lead-in part).

d) PK endpoint in the safety evaluation lead-in part:

- Brigatinib maximum observed plasma concentration ($C_{max}$), time of first occurrence of $C_{max}$ ($t_{max}$) and area under the plasma concentration-time curve (AUC) on Cycle 1 Days 1 and 22.

Safety endpoints:

- The number and percentage of patients with treatment-emergent adverse events (TEAEs).
- The number and percentage of patients with Grade 3 or higher TEAEs.
- The number and percentage of patients with serious TEAEs.
- The number and percentage of patients discontinuing study drug because of TEAEs.
- The number of patients with DLTs during Cycle 1 in the safety evaluation lead-in part.

CCI

[redacted]

**Statistical Considerations:**

<u>The refractory expansion part and safety lead-in part</u>

For the primary endpoint, confirmed ORR as assessed by an IRC and its 2-sided 95% CI will be provided using full analysis set (FAS)-P population, defined as patients previously treated with alectinib alone or patients previously treated with both crizotinib and alectinib who have received at least 1 dose of study drug (ie, main cohort of the refractory expansion part).

In this population for the primary analysis, a 2-stage design will be used. The first 29 patients in the main cohort are included in Stage 1, and further patients will be continuously enrolled into Stage 2. An interim analysis for both futility and efficacy will be conducted in Stage 1, according to H1-minimax design (Englert and Kieser, 2012). The proportion of patients achieving an objective response, per IRC, will be used as the endpoint for the interim analysis. The interim analysis will be performed when the first 29 patients in the main cohort of the expansion part have had the opportunity to complete the Cycle 7 Day 1 disease assessment. Enrollment will not be suspended during evaluation of these 29 patients; however, patients enrolled after the 29th patient in the main cohort of the expansion part will NOT be included in the interim analysis, even if their ORR results were available on the cutoff date.

If the number of patients with confirmed ORR is 3 or fewer of the 29 patients, enrollment will be stopped entirely for futility. Additionally, if the number of patients with confirmed ORR is 10 or more of the 29 patients, it will be decided that brigatinib is efficacious in this population.

An IDMC will be formed. The IDMC will provide recommendation on the go/no go decision to move from the safety

evaluation lead-in part to the expansion part and on the futility and efficacy assessment at the interim analysis. The IDMC will also evaluate cases of ILD reported as serious adverse events and make recommendations as needed.

For all secondary endpoints, all variables will be summarized descriptively using both the FAS-P population and the FAS population for efficacy, the FAS-P population for QOL, and the FAS population for safety and PK. Continuous variables will be summarized using the number of patients, mean, standard deviation, median, minimum, and maximum, and categorical variables will be summarized using the number and percentage per category. Time-to-event variables will be summarized using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Kaplan-Meier estimates and 95% CI will be calculated for quantiles and some specified time points.

The TKI-naïve expansion cohort

For the primary endpoint, 12 months PFS rate as assessed by an IRC and its 2-sided 90% CI will be provided based on complementary log-log transformation.

For all secondary endpoints, all variables will be summarized descriptively for efficacy, QOL and safety. Continuous variables will be summarized using the number of patients, mean, standard deviation, median, minimum, and maximum, and categorical variables will be summarized using the number and percentage per category. Time-to-event variables will be summarized using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Kaplan-Meier estimates and 95% CI will be calculated for quantiles and some specified time points.

Safety and PK analysis

Safety will be analyzed in the population of patients who have received at least 1 dose of brigatinib.

The PK population will include patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist. The PK population will be used for all PK analyses.

**Sample Size Justification:**

In the safety evaluation lead-in part, 9 DLT-evaluable patients will be enrolled for intensive safety and PK monitoring. This number of patients was derived from the following considerations: The meaningful intensive PK characterization needs to be conducted with more than 6 patients. It is assumed that 9 patients may be reasonable to secure the number of patients needed for intensive PK characterization, even with the potential dropouts, and to evaluate the tolerability of the study drug. Also, 9 DLT-evaluable patients is enough to evaluate tolerability before expanding the dose cohort to larger a population using a conventional 3+3 design.

The sample size in the main cohort of the refractory expansion part was determined to allow confirmation that the true ORR (expected response rate) is greater than the threshold response rate of 15% for patients previously treated with alectinib alone and those treated with both alectinib and crizotinib. The rationale for the 15% response rate for the alectinib (with or without crizotinib) pretreated population is based on the consideration that compared with crizotinib, patients who have failed alectinib are less likely to respond to subsequent therapy because of alectinib's greater potency and better coverage of ALK mutations compared with crizotinib.

A sample size of 47 patients in the post-alectinib population of the refractory expansion part with the stopping rule mentioned in in the Statistical Considerations section will allow the study to have more than 90% power to rule out a threshold response rate when the true ORR is expected or higher than 35% with a 1-sided alpha of 0.025, according to the H1-minimax design (Englert and Kieser, 2012).

The number of patients in the subcohort of the refractory expansion part (ie, patients previously treated with crizotinib only, ceritinib only, lorlatinib only, both crizotinib and ceritinib, both alectinib and ceritinib, both crizotinib and lorlatinib, both alectinib and lorlatinib, and both ceritinib and lorlatinib) will be limited to 20.

The sample size in the TKI-naïve expansion cohort was determined to allow confirmation that the true 12 months PFS rate (expected response rate) is greater than the threshold of 42.6% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L crizotinib arm) for TKI-naïve patients.

A sample size of 32 patients in the TKI-naïve expansion cohort will allow the study to have approximately 80% power to rule out the threshold rate (42.6%) when the true 12 months PFS rate is expected or higher than 66.5% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L brigatinib arm) with a 1-sided alpha of 0.05, considering 10% patients will discontinue the study follow-up before the 12 months milestone due to reasons other than disease progression assessed by IRC or death, and 8 months enrollment period. The primary analysis will be

performed at around 10 months after the enrollment of the last subject in the TKI-naïve expansion cohort. The sample size and evaluation timing may be adjusted based on results of second interim analysis of ALTA-1L study, and actual enrollment period of the TKI-naïve expansion cohort.

Overall, the total number of patients will be approximately 110 patients.

# 3.0 STUDY REFERENCE INFORMATION

## 3.1 Study-Related Responsibilities

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

## 3.2 Coordinating Investigator

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

## 3.3 List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| ALK | anaplastic lymphoma kinase |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve |
| BID | twice daily |
| BUN | blood urea nitrogen |
| CL/F | oral clearance |
| $C_{max}$ | maximum observed plasma concentration |
| CNS | central nervous system |
| CPK | creatine phosphokinase |
| CR | complete response |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CSR | clinical study report |
| CT | computed tomography |
| ctDNA | circulating tumor DNA |
| CxDx | Cycle x Day x |
| CYP | cytochrome P450 |
| DCR | disease control rate |
| DDI | drug-drug interaction |
| DLSS | Dohmen Life Science Services |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EGFR | epidermal growth factor receptor |
| EOPE | early onset pulmonary event |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EOT | end of treatment |
| EQ-5D-5L | the 5-level version of the EuroQol 5-dimensional questionnaire |
| EU | European Union |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FFPE | formalin-fixed, paraffin-embedded |
| FISH | fluorescence in situ hybridization |

| | |
|---|---|
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GM-CSF | granulocyte macrophage-colony stimulating factor |
| HbA1c | hemoglobin A1c |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HCVAb | hepatitis C virus antibody |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| HRQOL | health-related quality of life |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IDMC | independent data monitoring committee |
| iDOR | duration of intracranial response |
| IGF1R | insulin-like growth factor receptor 1 |
| ILD | interstitial lung disease |
| iORR | intracranial objective response rate |
| iPFS | intracranial progression-free survival |
| IRB | institutional review board |
| IRC | independent review committee |
| IUD | intrauterine device |
| KD | kinase domain |
| KL-6 | Krebs von den Lungen-6 |
| KRAS | v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue |
| LDH | lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHLW | Ministry of Health, Labour and Welfare |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRI | magnetic resonance imaging |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NGS | next-generation sequencing |
| NSCLC | non-small cell lung cancer |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PMDA | Pharmaceuticals and Medical Devices Agency of Japan |

| | |
|---|---|
| PP | per-protocol |
| PR | partial response |
| PRO | patient-reported outcome |
| QD | once daily |
| QLQ | Quality of Life Questionnaire |
| QOL | quality of life |
| QTc | heart rate-corrected QT interval (calculated) |
| QTcF | corrected QT interval by the Fridericia formula |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| ROS1 | c-ros oncogene 1 |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SLD | sum of the longest diameters |
| SP-D | surfactant protein-D |
| $SpO_2$ | percutaneous oxygen saturation |
| SRS | stereotactic radiosurgery |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TKI | tyrosine kinase inhibitor |
| $t_{max}$ | time of first occurrence of $C_{max}$ |
| ULN | upper limit of the normal range |
| US | United States |
| VEGFR | vascular endothelial growth factor receptor |
| WBRT | whole brain radiation therapy |
| WHO | World Health Organization |

# 4.0 INTRODUCTION

## 4.1 Background

### 4.1.1 Epidemiology and Pathology

Lung cancer is one of the most common cancers in the world (1.8 million new cases in 2012) 12.9% of all new cancers worldwide [1]. Globally, lung cancer accounted for 1.6 million cases and 1.4 million deaths in 2008 [2]. It is the leading cause of cancer death in the United States (US), in the European Union (EU), and in Japan. In Japan, lung cancer is ranked as the third most frequent cancer; approximately 113,000 new cases were diagnosed in 2012 and approximately 71,500 deaths in that year [3].

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults [4]. The first genetic rearrangement of ALK seen in non-small cell lung cancer (NSCLC) involved a fusion between the EML4 gene and the ALK tyrosine kinase domain (KD). EML4-ALK has the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts to induce tumor formation [5]. Since then, a number of additional ALK fusion partners have been described in NSCLC that are believed to result in aberrant signaling and oncogenic transformation [6,7]. ALK rearrangements are more common among patients with adenocarcinoma histology, patients who have never smoked, and patients who have wild-type epidermal growth factor receptor (EGFR) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS) [4].

Estimates of the frequency of ALK rearrangement in the overall population of NSCLC patients range from 2% to 7% [8,9], which represent, based on proportionality of total populations in the US, EU, and Japan, approximately 7000 to 25,000 ALK+ NSCLC patients in the US, 11,000 to 39,000 patients in the EU, and 1900 to 6700 patients in Japan in 2016.

In Japan, crizotinib, alectinib, ceritinib, and lorlatinib are approved for treatment of ALK-positive NSCLC as of September 2018.

### 4.1.2 Brigatinib

Brigatinib (AP26113) is a novel, orally administered tyrosine kinase inhibitor (TKI) discovered and developed by ARIAD Pharmaceuticals, Inc. (ARIAD; Cambridge, Massachusetts), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Primary targets are activated, mutant forms of ALK and c-ros oncogene 1 (ROS1), which play important roles in NSCLC and other cancers.

A series of in vitro and in vivo studies has been performed to characterize the pharmacodynamic profile of brigatinib. These studies have demonstrated that brigatinib potently inhibits the in vitro activity of all tested secondary mutations in the ALK KD that confer resistance to crizotinib, ceritinib, and alectinib. No ALK mutations have been identified in in vitro mutagenesis assays that confer resistance to brigatinib at clinically achievable concentrations. Brigatinib also potently inhibits ROS1 and demonstrates activity against insulin-like growth factor receptor 1 (IGF-1R) and certain mutant variants of EGFR.

### 4.1.3 Nonclinical Summary: Nonclinical Activity Against ALK

In nonclinical studies, brigatinib has been shown to:

- Inhibit growth of ALK+ human tumor-derived cell lines with potency at least 9-fold greater than that of crizotinib.
- Potently inhibit ALK variants with secondary mutations that confer resistance to crizotinib, ceritinib, or alectinib.
- Suppress the emergence of any resistant ALK mutant in an in vitro mutagenesis assay, at concentrations that can be achieved clinically.
- Induce regressions or inhibit growth of tumor xenografts driven by native ALK or mutant variants that confer clinical resistance.
- Prolong survival of mice in an ALK-dependent orthotopic brain tumor model.

Refer to the Investigator's Brochure for a more comprehensive presentation of the nonclinical data.

### 4.1.4 Brigatinib Clinical Summary

#### *4.1.4.1 Study AP26113-11-101 (Phase 1/2)*

This is a first-in-human, open-label, multicenter, dose escalation (3+3 design) study to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of brigatinib.

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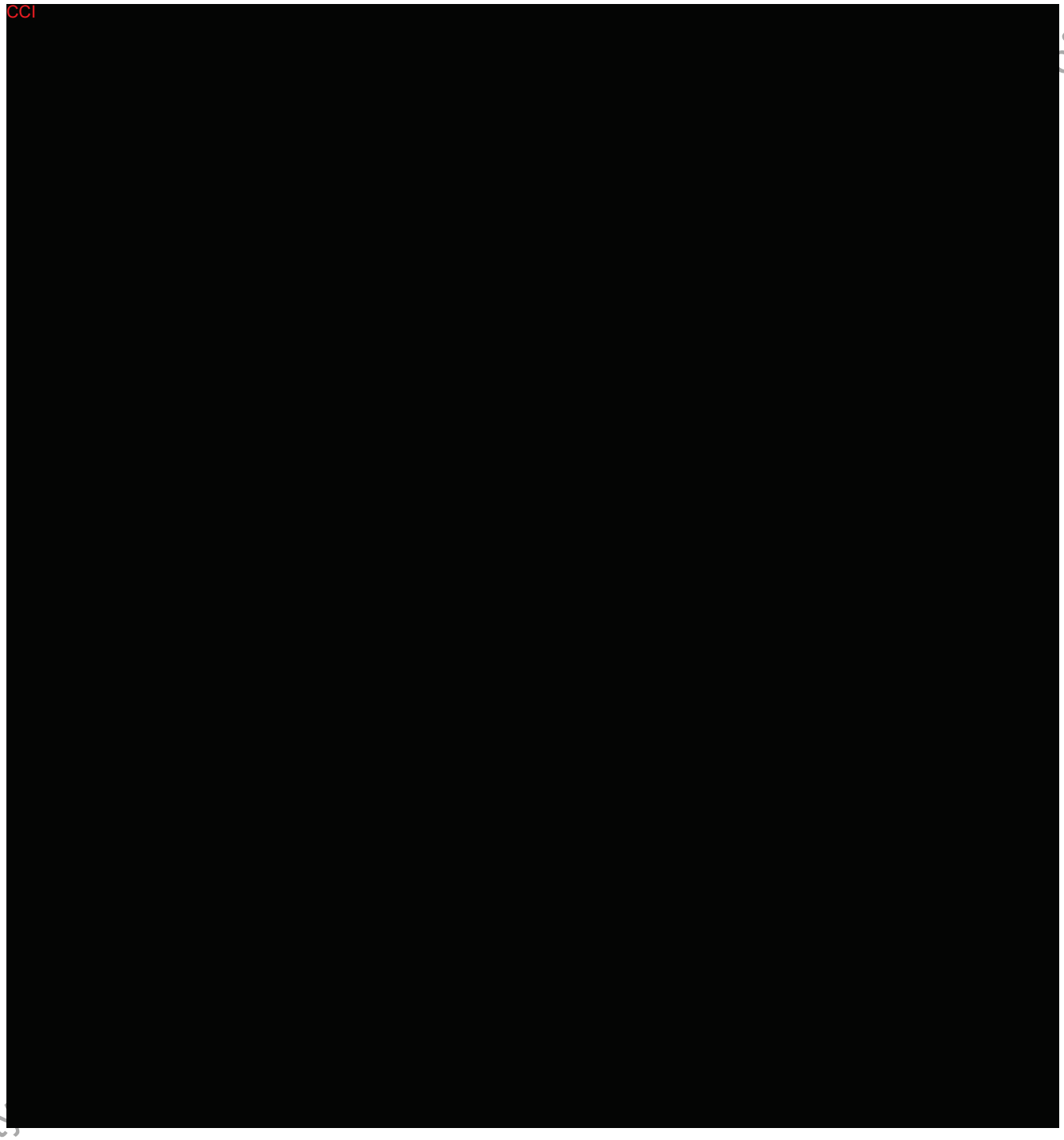
[redacted]






*4.1.4.2 Study AP26113-13-201 (ALTA)*

This is a pivotal phase 2, randomized, multicenter, international study of brigatinib in patients with ALK+ NSCLC who previously progressed on crizotinib.

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[redacted]

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[redacted]

*4.1.4.3 Study AP26113-13-301 (ALTA-1L)*

This is a phase 3, randomized, open label, comparative, multicenter, international study in patients with advanced ALK+ NSCLC who had not previously received an ALK targeted TKI.

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[redacted]

CCI

## 4.2 Rationale for the Proposed Study

Rearrangements of the ALK gene encode an oncogenic fusion protein in several human cancers, including NSCLC. Crizotinib, alectinib, and ceritinib are the oral ALK inhibitors approved in Japan for treatment of patients with metastatic ALK-positive NSCLC. Despite the high initial activity of ALK inhibitors, resistance inevitably develops in most patients. Analysis of tumor specimens collected at the time of acquired resistance to the ALK inhibitors has implicated multiple resistance mechanisms, including mutations in the ALK KD, increases in copy number of the rearranged ALK gene, and activation of ALK-independent bypass signaling pathways.

Brigatinib is a novel, synthetic, orally active ALK TKI that is being developed to address the limitations of currently approved ALK inhibitors by maximizing selective inhibition of ALK-positive NSCLC cells through optimal binding to the ALK KD. Brigatinib received accelerated approval by the US Food and Drug Administration (FDA) on 28 April 2017 with an indication for the treatment of patients with ALK positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

In Japan, crizotinib, alectinib, ceritinib, and lorlatinib are approved for treatment of ALK-positive NSCLC as of September 2018. In the Japanese Guideline [10], alectinib and crizotinib are recommended as first-line treatment, and both alectinib and ceritinib are recommended as second-line ALK inhibitor treatments after crizotinib failure, as of September 2017. However, after becoming refractory to alectinib in both first- and second-line treatment, and refractory to ceritinib in second-line treatment, no molecular targeting agent is recommended, and the treatment is limited to "1st line treatment for non-squamous cell carcinoma".

The current study is planned to evaluate the efficacy and safety of brigatinib in Japanese patients with ALK-positive advanced NSCLC that has progressed after prior ALK inhibitor therapy. In Japan, after the release of the J-ALEX study results [11] and an amendment to the guideline, the first-line treatment of ALK+ positive patients shifted from crizotinib to alectinib rapidly. Crizotinib is still recommended in the guideline, and there are several patients who receive

sequential treatment with crizotinib and alectinib. On the basis of Japanese clinical practice, and to achieve a homogeneous population to assess the efficacy of brigatinib in patients who have progressed on alectinib, the main cohort in this study for efficacy evaluation is defined as patients who have progressed after treatment with alectinib (with or without previous treatment with crizotinib). Taking the current medical practice in Japan into consideration, there are treatment sequences available other than the above (such as the inclusion of ceritinib); therefore, patients will also be enrolled in a subcohort to accumulate clinical data for a preliminary assessment of efficacy in these populations. The patients in the subcohort will not be included in the main efficacy analysis but will be included in a secondary analysis of efficacy and primary safety assessments.

Although treatment for ALK+ NSCLC can be highly effective by implementing the ALK-TKI, most patients with ALK+ NSCLC treated with first-line treatment will eventually relapse. Brain metastasis to the central nervous system occurs in almost half of patients, which can have a negative impact on quality of life of the patients. Patients with ALK+ NSCLC after first-line failure are available for other ALK-TKI. However disease progression has been appeared in re-treating patients as a second-line treatment within 1 year. Several secondary mutations of ALK kinase domain that are associated with clinical tolerance to crizotinib, ceritinib and alectinib have been identified, and those mutations lead to treatment failure of ALK-TKI.

For treatment of 1L, there is a need for a more potent ALK inhibitor that extends the PFS and that has adequate CNS penetration with robust intracranial responses compared with existing treatment. Although crizotinib is an effective treatment for ALK+ NSCLC, almost half of ALK+ NSCLC patients in the pivotal trials that supported its accelerated approval failed to achieve a response. PFS was relatively short in the 2 randomized phase 3 trials, with a median duration of 7.7 to 10.9 months. Chemotherapy is also used although it is not specifically approved for use in ALK+ NSCLC patients, with median PFS duration of 7.0 months with first line platinum doublet chemotherapy. Building on the strong efficacy results observed in the post-crizotinib setting, newer ALK inhibitors have recently been examined in previously untreated ALK+ NSCLC, resulting in FDA approval of alectinib [12,13] as first-line treatments in this population, and shifting the standard of care. For alectinib, clinically meaningful improvements in PFS were noted in the first-line setting when compared with crizotinib in the global, head-to-head ALEX study, with a median PFS (by IRC) of 25.7 months versus 10.4 months, respectively (HR = 0.53) [13,14] consistent results were also observed in a similar study (J-ALEX) in previously untreated Japanese patients [11]. In addition, alectinib was better tolerated than crizotinib, with an improved safety profile. Nonetheless, there are risks with alectinib, including severe hepatic and renal toxicity, as well as other class effects (ie, interstitial lung disease [ILD] and bradycardia).

Alectinib is also approved as first line treatment in Japan for ALK+ NSCLC.

New therapies are needed to improve response rates, provide greater durability of response, and to overcome potential mechanisms of resistance to ALK-targeted therapy, including the emergence of secondary resistance mutations in ALK and progression in the CNS. Such a new therapeutic option could result in significant prognostic improvement in ALK+ NSCLC patients.

For the first interim analysis of ALTA-1L, which is a pivotal randomized phase 3 study in patients naïve to ALK-TKI treatment, The primary endpoint of BIRC-assessed PFS was met with statistical and clinical superiority in favor of brigatinib (Section 4.1.4.3). In order to evaluate efficacy and safety of brigatinib in Japanese patients with ALK+ NSCLC who are naïve to ALK-TKI therapy, an expansion cohort in patients naïve to ALK-TKI treatment was added to the ongoing Brigatinib-2001.

### 4.2.1 Rationale for Dose

In this study, brigatinib will be administered as an oral single agent at 180 mg QD with a 7-day lead-in at 90 mg QD (90 mg QD→180 mg QD). This dose/schedule is the same used in the ALTA study, and is the approved dosage in the US. The ALTA study showed that the benefit-risk profile of the 90 mg QD→180 mg QD regimen was improved over that of 90 mg QD. In a Western clinical pharmacology study (AP26113-13-102), Caucasian and Japanese healthy subjects had comparable systemic exposure of brigatinib with a single dose of 90 mg, 120 mg, or 180 mg, supporting extrapolation of the Western safety and efficacy experience to define the recommended phase 2 dose of brigatinib in Japanese patients for evaluation in this study.

The safety and tolerability of the 90 mg QD→180 mg QD regimen will be confirmed in patients enrolled at a limited number of study sites before expanding to all sites in this study. The safety evaluation lead-in part is incorporated to confirm the safety and tolerability of this dose regimen. Patients will be enrolled in this safety evaluation lead-in part until 9 dose-limiting toxicity (DLT)-evaluable patients are accrued. Patients will be hospitalized during Cycle 1 (Days 1-10 and Days 22-23), and their condition will be closely monitored for safety and assessment of DLTs. Serial blood samples will be also collected for intensive PK evaluation in these patients.

For patients in the TKI-naïve expansion cohort, the overseas study ALTA-1L in patients untreated with TKIs including ALK inhibitors demonstrated a statistically significant increase in the primary endpoint PFS assessed by the BIRC in the brigatinib group (90 mg QD→180 mg QD) compared to the crizotinib group (250 mg BID) as well as obvious improvements in the following secondary endpoints: DOR, iORR and iPFS. ORR assessed by the BIRC was numerically better in the brigatinib group than in the crizotinib group. The subgroup analysis in Asians also demonstrated consistently clear benefits in the brigatinib group relative to the crizotinib group.

The efficacy of brigatinib 90 mg QD→180 mg QD in TKI-naïve Japanese patients is expected to be comparable to that seen in Study ALTA-1L.

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

The primary objective is to evaluate efficacy of brigatinib in Japanese patients with ALK-positive advanced NSCLC.

- ORR will be evaluated in the refractory patients.
- PFS rate at 12 months in Kaplan-Meier plots (12 months PFS rate) will be evaluated in the TKI-naïve patients.

### 5.1.2 Secondary Objectives

The secondary objectives are:

- To confirm the clinical dose in Japanese patients.
- To characterize the efficacy of brigatinib as shown by following parameters
  For all enrolled patients (including TKI-naïve patients): DOR, PFS, disease control rate (DCR), time to response, and overall survival (OS).
  For the TKI-naïve patients: ORR
- To characterize the intracranial efficacy of brigatinib, as evidenced by iORR, duration of intracranial response (iDOR), and iPFS in patients with intracranial disease at baseline, from refractory and TKI-naïve cohorts.
- To assess patient-reported outcomes (PROs) of health-related quality of life (HRQOL) and symptoms of lung cancer with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3.0), its lung cancer module QLQ-LC13, and the 5-level version of the EuroQol 5-dimensional questionnaire (EQ-5D-5L).
- To characterize the PK of brigatinib in Japanese patients.

### 5.1.3 Safety Objectives

The safety objective is to assess the safety and tolerability of brigatinib.

### 5.1.4 CCI [redacted]

CCI [redacted]

## 5.2 Endpoints

### 5.2.1 Primary Endpoint

The primary endpoints are:

- Confirmed ORR as assessed by an IRC, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the main cohort of the refractory expansion part
- 12 months PFS rate as assessed by an IRC, per RECIST version 1.1 in the TKI-naïve expansion cohort

### 5.2.2 Secondary Endpoints

The secondary endpoints are:

a) Efficacy endpoint in the TKI-naïve expansion cohort, the overall population of the refractory expansion part, and the safety evaluation lead-in part:

– Confirmed ORR, as assessed by an IRC, per RECIST version 1.1.

b) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, the overall population of the refractory expansion part:

– DOR, as assessed by an IRC, per RECIST version 1.1.

– PFS, as assessed by an IRC, per RECIST version 1.1.

– DCR, as assessed by an IRC, per RECIST version 1.1.

– Time to response, as assessed by an IRC, per RECIST version 1.1.

– OS.

– CNS response, as assessed by IRC, per modified RECIST version 1.1 for assessment of intracranial efficacy (Appendix H) (iORR and iDOR in patients who had measurable CNS metastases, and iPFS in all patients).

– Time on treatment.

c) Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, and the safety evaluation lead-in part:

– Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.

– PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L (except for the safety evaluation lead-in part).

d) PK endpoint in the safety evaluation lead-in part:

– Brigatinib maximum observed plasma concentration ($C_{max}$), time of first occurrence of $C_{max}$ ($t_{max}$), and area under the plasma concentration-time curve (AUC) on Cycle 1 Days 1 and 22.

### 5.2.3 Safety Endpoints

The safety endpoints are:

- The number and percentage of patients with TEAEs.
- The number and percentage of patients with Grade 3 or higher TEAEs.
- The number and percentage of patients with serious TEAEs.
- The number and percentage of patients discontinuing study drug because of TEAEs.
- The number of patients with DLTs during Cycle 1 in the safety evaluation lead-in part.

### 5.2.4 CCI

CCI

# 6.0 STUDY DESIGN

## 6.1 Overview of Study Design

This is a nonrandomized, multicenter, phase 2, open-label study with a safety evaluation lead-in, to evaluate the efficacy and safety of brigatinib in Japanese patients with ALK-positive advanced NSCLC.

The study consists of the safety evaluation lead-in part and the expansion part. The safety evaluation lead-in part allows patients with any line of prior ALK inhibitor which includes treatment-naïve patients; however, ALK inhibitor-naïve patients may be enrolled after the confirmation of first 3 DLT evaluable patients to have no more than 1 DLT during Cycle 1 by investigator's judgement. The expansion part consists of the TKI-naïve expansion cohort and the refractory expansion part, and the refractory expansion part includes the main cohort and a subcohort based on prior ALK inhibitor treatment. The TKI-naïve expansion cohort includes the patients who have not received any prior TKI including ALK inhibitor. In this cohort, the efficacy will be evaluated, and total of 32 patients will be enrolled. The main cohort of the refractory expansion part includes patients who had previously received alectinib (as their only ALK inhibitor) or both alectinib and crizotinib (regardless the sequence of those 2 ALK inhibitors). The main cohort of the refractory expansion part will be used for the primary analysis of efficacy, and a total of 47 patients will be enrolled in the main cohort of the refractory expansion part. Patients with all other sequences of up to 2 prior ALK inhibitor(s) may be included in the subcohort of the refractory expansion part. Such other ALK inhibitors include 1) crizotinib only, 2) ceritinib only, 3) lorlatinib only, 4) both crizotinib and ceritinib, 5) both alectinib and ceritinib, 6) both crizotinib and lorlatinib, 7) both alectinib and lorlatinib, and 8) both ceritinib and lorlatinib. Up to 20 patients will be enrolled in the subcohort of the refractory expansion part.

In this study, brigatinib will be administered at 90 mg QD for the first 7 days and then 180 mg QD (90 mg QD→180 mg QD). In the safety evaluation lead-in part, patients will be monitored for intensive PK, and the tolerability of 90 mg QD→180 mg QD dosing will be confirmed. If the 90 mg QD→180 mg QD dosing regimen is considered tolerable, additional patients enrolled in the expansion part will be treated with the same dosing schedule (90 mg QD→180 mg QD).

For the TKI-naïve expansion cohort, 32 patients will be enrolled and12 month PFS rate will be evaluated as the primary endpoint. The primary analysis will be performed at around 10 months after the enrollment of the last subject in TKI-naïve expansion cohort. The sample size and evaluation timing may be adjusted based on results of second interim analysis of ALTA-1L study, and actual enrollment period of the TKI-naïve expansion cohort.

For the main cohort of the refractory expansion part, there are 2 stages: the first 29 patients in the main cohort are included in Stage 1, and further patients will be continuously enrolled into Stage 2. An interim analysis for futility and efficacy will be performed in the Stage 1 population when the first 29 post-alectinib patients have had the opportunity to complete at least 3 postbaseline scans (ie, after the Cycle 7 Day 1 disease assessment). Enrollment will not be suspended during evaluation of those 29 patients.

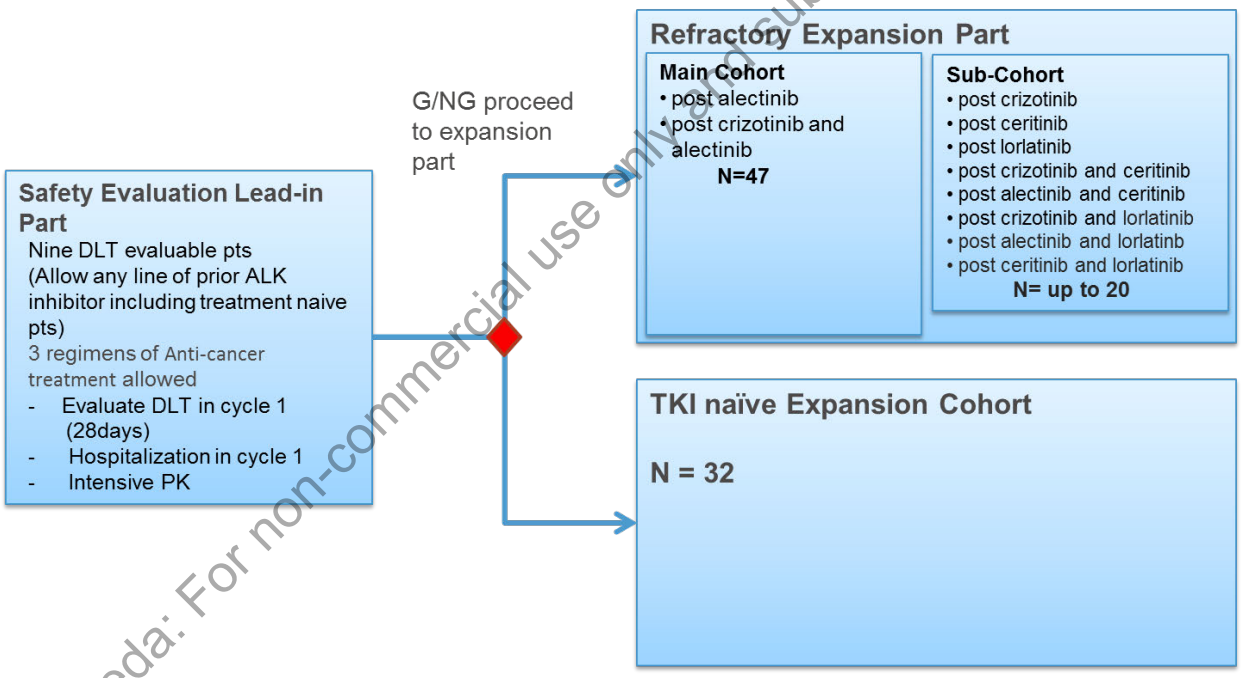
Following the screening period, eligible patients will be enrolled and treated with brigatinib. A patient is considered to be enrolled in the study when the first dose of brigatinib is administered.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [15].

Response evaluation per RECIST version 1.1 will be done by both the investigator and an IRC. The primary analysis will performed on the results from the IRC.

Patients will be treated until they experience objective progressive disease (PD) per RECIST version 1.1, as assessed by the investigator, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason. Treatment of patients with brigatinib may be continued at the tolerated dose level, despite investigator-assessed PD by RECIST version 1.1, if the patient otherwise has evidence of ongoing clinical benefit. In this case, discussions and agreements between the investigator and the sponsor's project clinician (or designee) are required.

**Figure 6.a Overview of Study Design**




Safety Evaluation Lead-in Part

Nine DLT-evaluable patients will be enrolled in the safety evaluation lead-in part. The patients in the safety evaluation lead-in part will be hospitalized during Cycle 1 in general, and their condition will be closely monitored for safety and tolerability. Serial blood samples will be collected for the intensive PK profile. If a patient wishes to return home temporarily and the investigator confirms that the patient's symptoms are stable per the available data, then the patient may return home temporarily except on Days 1 through 10 and Days 22 and 23, provided this does not interfere with the study assessments. The investigator must document the confirmation record for stabilization of

the patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary leave.

The patients in the safety evaluation lead-in part will receive brigatinib 90 mg QD→180 mg QD. A cycle of therapy comprises 28 days of treatment. If a patient is NOT considered DLT evaluable for any reason, the patient will be replaced.

DLTs are defined in Section 8.2. Tolerability of the 90 mg QD→180 mg QD schedule will be determined on the basis of the DLTs observed in Cycle 1. If a DLT is observed in fewer than 3 of the 9 DLT-evaluable patients in the safety evaluation lead-in part, the 90 mg QD→180 mg QD regimen will be used for the patients enrolled in the expansion part. Further details on the dose expansion rules are described in Section 8.3.

Expansion Part (Refractory Expansion Part and TKI-Naïve Expansion Cohort)

Patients in the refractory expansion part and the TKI-naïve expansion cohort may be managed on an outpatient basis, and the number of study sites will be increased up to approximately 40. Patients in the refractory expansion part and the TKI-naïve expansion cohort will undergo less-intensive PK blood sampling than patients in the safety evaluation lead-in part.

On an outpatient basis, patients will visit the hospital on Days 1, 8, and 15 of Cycle 1, and then on Day 1 of each cycle after Cycle 2. Tumor assessment will be performed every 2 cycles from Cycle 3 Day 1 through Cycle 15 Day 1, then every 3 cycles thereafter until the last dose of study drug. For patients who discontinue study treatment in the absence of PD, additional tumor assessment should continue at the same time points as the study treatment until PD or the start of another systemic anticancer therapy.

## 6.2 Number of Patients

Approximately 110 patients (approximately 9 patients in the safety evaluation lead-in part, 32 patients in the TKI-naïve expansion cohort, 47 patients in the main cohort of the refractory expansion part and up to 20 in the subcohort of the refractory expansion part) will be enrolled in this study at approximately 40 study sites in Japan. A patient is considered to be enrolled in the study when the first dose of brigatinib is administered.

## 6.3 Duration of Study

### 6.3.1 Duration of an Individual Patient's Study Participation

Patients will be treated until they experience objective PD per RECIST version 1.1, as assessed by the investigator, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason. Treatment of patients with brigatinib may be continued at the tolerated dose level, despite investigator-assessed PD by RECIST version 1.1, if the patient otherwise has evidence of ongoing clinical benefit. In this case, discussions and agreements between the investigator and the sponsor's project clinician (or designee) are required.

The follow-up period for a patient begins after the last completed site visit and continues until patient contact ceases. The follow-up assessments (ie, contacting the patient for survival and

subsequent anticancer therapy) must be performed every 12 weeks after the end of treatment (EOT). For patients who discontinue study treatment in the absence of PD, survival should be tracked and additional tumor assessment should be performed at the same time points as the study treatment (every 8 weeks until Week 57 [equivalent to Cycle 15 Day 1] and every 12 weeks thereafter) until PD or the start of another systemic anticancer therapy. After that, survival must be tracked every 12 weeks, and subsequent anticancer therapy should be recorded.

### 6.3.2 End of Study/Study Completion Definition and Planned Reporting

#### *6.3.2.1 The Safety Evaluation Lead-In Part and The Refractory Expansion Part*

Primary Completion

The primary analysis for the primary endpoint, and authoring of a CSR may be conducted after all patients that enrolled in the main cohort of the refractory expansion part have had the opportunity to complete 6 cycles of treatment with study drug.

Other Planned Analyses

A CSR efficacy and safety addendum is planned at study completion.

Study Completion

The study will be considered completed when all patients have discontinued study treatment, or 24 months after enrollment of the last patient, whichever occurs later. The estimated time frame for study completion is approximately 53 months.

However, in case a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan before the study completion noted above, this study will become a post-marketing clinical study after the marketing approval and will be continued until all the patients who are continuing study treatment with brigatinib have access to the commercial supply. In this case, each patient who enters the post-marketing clinical study will complete the study participation when the patient get access to the commercial supply. The post-marketing clinical study will be conducted in compliance with the GCP and the Good Post-Marketing Study Practice, and all the terms "study" in this protocol shall be then deemed as appropriately replaced to "post-marketing clinical study."

#### *6.3.2.2 The TKI-Naïve Expansion Cohort*

Primary Completion

The primary analysis for the primary endpoint, and authoring of a CSR may be conducted at around 10 months after the enrollment of the last subject in the TKI-naïve expansion cohort.

Other Planned Analyses

A CSR efficacy and safety addendum is planned at study completion.

Study Completion

After a marketing approval of brigatinib for both first-line and second-line settings is obtained in Japan, this study will become a post-marketing clinical study and will be continued until the last patient have access to the commercial supply. Each patient who enters the post-marketing clinical study will complete the study participation when the patient get access to the commercial supply. The post-marketing clinical study will be conducted in compliance with the GCP and the Good Post-Marketing Study Practice, and all the term "study" in this protocol shall be then deemed as appropriately replaced to "post-marketing clinical study."

### 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

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

## Table 6.a Primary and Secondary Endpoints for Disclosures

| Endpoint | Definition | Maximum Time Frame |
|---|---|---|
| **Primary** | | |
| **Efficacy endpoint in the main cohort of the refrectory expansion part:** | | |
| Confirmed ORR as assessed by an IRC, per RECIST version 1.1 | The proportion of the patients who are confirmed to have achieved CR or partial response (PR) per IRC using RECIST version 1.1 after the initiation of study treatment. | Up to 23 months |
| **Efficacy endpoint in the TKI naïve expansion cohort:** | | |
| 12 months PFS rate as assessed by an IRC, per RECIST version 1.1 | The PFS rate in Kaplan-Meier plot at 12 months after the initiation of study treatment, assessed by IRC, per RECIST version 1.1. | Up to 36 months |
| **Secondary** | | |
| a) **Efficacy endpoint in the TKI-naïve expansion cohort, the overall population of the refractory expansion part, and the safety evaluation lead-in part:** | | |
| Confirmed ORR, as assessed by an IRC, per RECIST version 1.1 | The proportion of the patients who are confirmed to have achieved CR or PR per IRC using RECIST version 1.1 after the initiation of study treatment. | Up to 53 months |
| b) **Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, and the overall population of the refractory expansion part:** | | |
| DOR, as assessed by an IRC, per RECIST version 1.1 | The time between the first documentation of objective tumor response (CR or PR) and the first subsequent documentation of objective PD or death due to any cause, whichever occurs first. | Up to 53 months |
| PFS, as assessed by an IRC, per RECIST version 1.1 | The time from the start of study treatment to the first documentation of objective PD or to death due to any cause, whichever occurs first. | Up to 53 months |
| DCR, as assessed by an IRC, per RECIST version 1.1 | The proportion of patients who are confirmed to have achieved CR or PR or have a best overall response of stable disease (SD), per RECIST version 1.1, for 6 weeks or more after initiation of study drug. | Up to 53 months |
| Time to response, as assessed by an IRC, per RECIST version 1.1 | The time interval from the date of the first dose of study treatment until the initial observation of CR or PR for patients with confirmed CR/PR. | Up to 53 months |
| OS | The time from the start of study treatment to the date of death. | Up to 53 months |
| CNS response, as assessed by an IRC, per modified RECIST version 1.1 for assessment of intracranial efficacy (iORR and iDOR in patients who had measurable CNS metastases, and iPFS in all patients) | The proportion of the patients who have achieved CR or PR in the intracranial CNS per modified RECIST version 1.1 as evaluated by an IRC after the initiation of study treatment. | Up to 53 months |
| Time on treatment | The time interval from the first dose to the last dose of brigatinib. | Up to 53 months |
| c) **Efficacy endpoints in the TKI-naïve expansion cohort, the main cohort of the refractory expansion part, and the safety evaluation lead-in part:** | | |
| Confirmed ORR, as assessed by the investigator, per RECIST version 1.1 | The proportion of the patients who are confirmed to have achieved CR or PR per investigator using RECIST version 1.1 after the initiation of study treatment. | Up to 53 months |
| PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L (except for the safety evaluation lead-in part) | PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L. | Up to 53 months |
| d) **PK endpoint in the safety evaluation lead-in part:** | | |
| Brigatinib $C_{max}$, $t_{max}$, and AUC on Cycle 1 Days 1 and 22 | $C_{max}$, $t_{max}$, and AUC are defined as maximum observed plasma concentration, time of first occurrence of $C_{max}$, and area under the plasma concentration-time curve, respectively. | Up to Cycle 1 Day 22 |

### 6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 53 months.

## 6.4 Study Discontinuation and Closure

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or the sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient, incomplete, and/or unevaluable data.
- Determination of futility based on the interim analysis.
- Plans to modify, suspend, or discontinue the development of the study drug.

# 7.0 STUDY POPULATION

## 7.1 Inclusion Criteria

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

1. Male or female Japanese patients aged ≥20 years on the day of consent.
2. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Have histologically or cytologically confirmed stage IIIB, stage IIIC (locally advanced or recurrent and not a candidate for definitive multimodality therapy), or stage IV NSCLC.
4. Have documentation of ALK rearrangement that meets following criteria.

   For the safety evaluation lead-in part and the refractory expansion part, patients must meet 1 of the following 2 criteria:

   a) Have documentation of ALK rearrangement by a positive result from the Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit, the Nichirei Histofine ALK iAEP Kit, or the Ventana ALK (D5F3) CDx Assay at any time during prior disease course. The sponsor may require an adequate tissue available for central laboratory testing by the Vysis ALK Break Apart FISH test if a documented ALK rearrangement is confirmed by a positive result from the Nichirei Histofine ALK iAEP Kit "ONLY".

   b) Had a documented ALK rearrangement by a different test at any time during prior disease course, and adequate tissue available for central laboratory testing by the Vysis ALK Break Apart FISH test. Central confirmation of ALK rearrangement is not required before enrollment.

   For TKI-naïve expansion cohort, patients must meet the following criteria

   Have documentation of ALK rearrangement by a positive result from MHLW Approved tests (e.g. Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit, the Nichirei Histofine ALK iAEP Kit, or the Ventana ALK [D5F3] CDx Assay) prior to enrollment, and **required to submit sufficient tumor tissue for central laboratory testing** upon request of sponsor. Central confirmation of ALK rearrangement is not required before enrollment

5. The refractory expansion part only: had documented PD during treatment or within 30 days after discontinuation of treatment with either alectinib, crizotinib, ceritinib, or lorlatinib.

   – Note 1: The refractory expansion part consists of the main cohort and a subcohort based on prior ALK inhibitor treatment. The main cohort includes patients who had previously received alectinib (as their only ALK inhibitor) or both crizotinib and alectinib (regardless the sequence of those 2 ALK inhibitors), and a total of 47 patients will be enrolled. Patients with all other sequences of up to 2 prior ALK inhibitor(s) may be included in the subcohort, and the number of patients will be limited to 20.

- Note 2: Patients who will be included in the main cohort of the refractory should have documented PD during treatment or within 30 days after discontinuation of treatment with alectinib.

6. Have at least 1 measurable (ie, target) lesion per RECIST version 1.1 (Appendix G).
   Note: Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may not be used as target lesions if they were 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by stereotactic radiosurgery (SRS) or surgical resection.
7. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE version 4.03 Grade ≤1.
   Note: Treatment-related alopecia is allowed.
8. Have a life expectancy of ≥3 months.
9. Have adequate organ and hematologic function, as determined by:
   a) Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of the normal range (ULN) (≤5×ULN is acceptable if liver metastases are present).
   b) Total serum bilirubin ≤1.5×ULN (<3.0×ULN for patients with Gilbert syndrome).
   c) Serum creatinine <1.5×ULN. For patients with creatinine levels above or equal to 1.5×ULN, the patient is eligible if the estimated creatinine clearance using the Cockcroft-Gault formula is ≥30 mL/minute.
   d) Serum lipase ≤1.5×ULN and serum amylase ≤1.5×ULN.
   e) Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L.
   f) Platelet count $\geq 75\times10^9$/L.
   g) Hemoglobin ≥9 g/dL.
   h) Percutaneous oxygen saturation ($SpO_2$) ≥94% without oxygen support. Patients who need oxygen support are excluded.
10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
11. Must meet the following criteria:
    a) Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method at the same time, from

the time of signing the informed consent through 4 months after the last dose of study drug, OR

– Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

b) Male patients, even if surgically sterilized (ie, status postvasectomy), who:

– Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR

– Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, during the entire study treatment period and through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

12. Have the willingness and ability to comply with scheduled visit and study procedures.

### 7.2 Exclusion Criteria

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

1. Previously received the following treatments.

   The refractory expansion part only: received any prior ALK inhibitor other than alectinib, crizotinib, ceritinib, or lorlatinib.

   TKI-naïve expansion cohort only: received any prior TKI including but not limited to ALK inhibitor and VEGFR TKI.

2. The refractory expansion part only: received more than 2 prior ALK inhibitors.
   Note: The safety evaluation lead-in part allows patients with any line of prior ALK inhibitor which includes treatment-naïve patients; however, ALK inhibitor-naïve patients may be enrolled after the confirmation of first 3 DLT evaluable patients to have no more than 1 DLT during Cycle 1 by investigator's judgement.

3. The safety evaluation lead-in part and the refractory expansion part only: received alectinib, crizotinib, ceritinib, or lorlatinib within 7 days before the first dose of brigatinib.

4. Previously received more than 1 regimen (more than 3 regimens in the safety evaluation lead-in part) of systemic anticancer therapy (other than ALK inhibitors) for locally advanced or metastatic disease.
   Note: A systemic anticancer therapy regimen will be counted if it is administered over at least 1 cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen

unless it was previously used as initial anticancer therapy. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if completion of (neo) adjuvant therapy occurred <12 months before the first dose of brigatinib.

5. Treatment with any investigational products within 30 days or 5 half-lives of that investigational agent, whichever is longer, before the first dose of brigatinib.
6. Received chemotherapy or radiation within 14 days before the first dose of brigatinib, except SRS or stereotactic body radiation therapy.
7. Received antineoplastic monoclonal antibodies within 30 days before the first dose of brigatinib.
8. Received systemic treatment with strong inhibitors or strong and moderate inducers of cytochrome P450 (CYP) 3A within 7 days before the first dose of brigatinib.
9. Had major surgery within 30 days before the first dose of brigatinib. Minor surgical procedures such as venous catheter placement or minimally invasive biopsies are allowed.
10. Have been diagnosed with another primary malignancy other than NSCLC, except for the following adequately/definitively treated malignancies: nonmelanoma skin cancer, cervical cancer in situ, nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
11. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days before the first dose of brigatinib.
    Note: If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient needs to complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants for symptomatic control) for 7 days before the first dose of brigatinib.
12. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with asymptomatic leptomeningeal disease and without cord compression are allowed.
13. Have ongoing or history of interstitial lung disease (ILD) (including interstitial pneumonitis, pneumonitis, radiation pneumonitis, drug-related pneumonitis, organized pneumonia, and pulmonary alveolitis).
14. Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not limited to:
    a) Myocardial infarction within 6 months before the first dose of brigatinib.
    b) Unstable angina within 6 months before the first dose of brigatinib.
    c) Congestive heart failure within 6 months before the first dose of brigatinib.
    d) Uncontrolled atrial arrhythmias despite appropriate medical therapy.

e) History of ventricular arrhythmia, including history of ventricular tachycardia, ventricular fibrillation, or torsade de pointes. Patients with premature ventricular contractions are allowed.

f) Cerebrovascular accident or transient ischemic attack within 6 months before the first dose of brigatinib.

15. Have uncontrolled hypertension. Patients with hypertension should be under treatment at the start of screening and demonstrate adequate control of blood pressure.
16. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous antibiotics.
17. Have a known history of human immunodeficiency virus (HIV) infection. Testing is not required in the absence of history.
18. Hepatitis B surface antigen (HBsAg) positive, detectable hepatitis B viral load, or detectable hepatitis C virus (HCV) infection viral load.
    Note: Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B viral load. Patients who have positive HCV antibody can be enrolled but must have an undetectable hepatitis C viral load.
19. Have malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of brigatinib.
20. Have a known or suspected hypersensitivity to brigatinib or its excipients.
21. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.
    Note: Female patients who are lactating will be excluded, even if they discontinue breastfeeding.
22. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of brigatinib.

# 8.0 STUDY DRUG

## 8.1 Study Drug Administration

Brigatinib will be administered orally at a dose of 90 mg QD for first 7 days followed by 180 mg QD continuously at the same time each day (preferably in the morning). A cycle of therapy will comprise 28 days of treatment. Patients will take the prescribed dose with water (recommended approximately 240 mL). Brigatinib can be administered with or without food.

Patients who forget to take their scheduled dose of brigatinib should be instructed not to make up the missed dose. A missed dose is defined as a dose not taken within 12 hours of the intended scheduled administration. Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary card, and study drug administration electronic case report form (eCRF).

## 8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010 [15]. DLT evaluation applies only to the first 9 DLT-evaluable patients in the safety evaluation lead-in part. DLTs will be defined as any of the following events occurring within the first 28 days of treatment (end of Cycle 1) that are considered by the investigator to be at least possibly related to therapy with brigatinib (note that adverse events [AEs] for which the relationship to study drug cannot be ruled out should be considered possibly related to study drug):

- Nonhematologic toxicities include any nonhematologic toxicity Grade ≥3 with the following **exceptions**:
  - Self-limiting or medically controllable toxicities (ie, nausea, vomiting, diarrhea, fatigue, and electrolyte disturbances) lasting ≤3 days.
  - Isolated asymptomatic Grade ≥3 laboratory abnormalities that resolve to Grade ≤1 or baseline in ≤7 days.
- Hematologic toxicities:
  - Febrile neutropenia not related to underlying disease (ANC <1000/mm$^3$ with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
  - Prolonged (>7 days) Grade 4 neutropenia (if granulocyte-colony stimulating factor [G-CSF] is used, the event will be considered as DLT irrespective of the duration).
  - Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection.
  - Thrombocytopenia Grade ≥3 with bleeding, Grade ≥3 requiring platelet transfusion, or Grade 4 lasting >7 days.
  - Anemia Grade ≥3 requiring blood transfusion.
    Note: Prophylactic transfusions of blood products or any prophylactic use of hematopoietic growth factors (such as erythropoietin, thrombopoietin, G-CSF, and granulocyte

macrophage-colony stimulating factor [GM-CSF]) is not permitted during the DLT evaluation period.

- Missed >25% of planned cumulative doses (ie, 1102.5 mg) of brigatinib over 28 days because of treatment-related AEs (except Grade 1 or 2 ILD/pneumonitis in the first 7 days) in the first cycle.
  Note: In case of Grade 1 or 2 ILD/pneumonitis in the first 7 days, before escalation to 180 mg QD:
  1) If the event does not resolve within 14 days (ie, the patient misses 14 or more doses of brigatinib), then the events will be considered as a DLT.
  2) If the event resolves within 14 days and the administration of brigatinib can be resumed before 14 missed doses, then the patient will be considered DLT nonevaluable in condition that the patient does not have any other events qualifying as DLTs later. In case that the event resolves within 14 days but the patient does not resume brigatinib based on investigator's judgment or patient's request, those patients will also be considered DLT nonevaluable. (See Table 8.b for detail of dose modification based on ILD/pneumonitis.)

Although the above toxicities may occur at any point during treatment, these toxicities are considered DLTs only if they occur during Cycle 1 of treatment, in which case, they will influence decisions regarding opening the expansion part. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

DLT-evaluable patients must complete at least 75% (ie, 3,307.5 mg of 4,410 mg in 28 days of Cycle 1) of their planned cumulative doses, unless missed doses are due to related AEs. DLT-nonevaluable patients in the safety evaluation part of the study will be replaced. The timing of adding patients for DLT evaluation may be decided with advice from the chairperson of the independent data monitoring committee (IDMC), if needed.

### 8.3 Patient Expansion After the Safety Evaluation Lead-in Part

If a DLT is observed in fewer than 3 patients in the 9 DLT-evaluable patients of the safety evaluation lead-in part, the 90 mg QD→180 mg QD regimen will be used in the patients enrolled in the expansion part. Opening of the expansion part will be determined on the basis of the total safety data available at that time, available PK results, and with recommendation from the IDMC. Regarding the safety data, all AEs observed in the safety evaluation lead-in part, including those observed in DLT non-evaluable patients, will be evaluated in concert with DLTs when making the decision on opening of the expansion part.

If a DLT is observed in 3 or more patients of the 9 DLT-evaluable patients, the 90 mg QD→180 mg QD dose regimen will NOT be considered tolerable. If 3 DLT cases are confirmed before completion of enrolling 9 DLT-evaluable cases, the enrollment of subsequent patients may be halted. If the dose of 90 mg QD→180 mg QD is NOT considered tolerable, the dose for subsequent patients will be selected on the basis of the toxicity observed and available PK data in the 9 DLT-evaluable patients. This will require a protocol amendment and possibly changes to the inclusion/exclusion criteria and/or modification of the dose regimen. If another

dose regimen will be used, the safety evaluation part described above with close safety monitoring and intensive PK sampling will be repeated for the new dose regimen.

## 8.4 Dose Modification Guidelines

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

Brigatinib dose modification levels are summarized in Table 8.a.

**Table 8.a Recommended Brigatinib Dose Reduction Levels**

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

Permanently discontinue brigatinib if patients are unable to continue the 60 mg QD dose because of treatment related-AEs.

Recommendations for dose modifications of brigatinib for the management of treatment-related AEs are provided in Table 8.b.

**Table 8.b Recommended Brigatinib Dose Modifications for Treatment-Related AEs**

| Treatment-Related AE | Severity (a) | Dose Modification |
|---|---|---|
| ILD/pneumonitis | Grade 1 | • If ILD/pneumonitis occurs (or is suspected) during the first 7 days of treatment, interrupt brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected.<br>• If ILD/pneumonitis occurs (or is suspected) after the first 7 days of treatment, interrupt brigatinib until recovery to baseline, then resume at same dose.<br>• If ILD/pneumonitis recurs, permanently discontinue brigatinib. |
| | Grade 2 | • If ILD/pneumonitis occurs (or is suspected) during the first 7 days of treatment, interrupt brigatinib until recovery to baseline. Resume at next lower dose (Table 8.a) and do not dose escalate if ILD/pneumonitis is suspected.<br>• If ILD/pneumonitis occurs (or is suspected) after the first 7 days of treatment, interrupt brigatinib until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 8.a); otherwise, resume at same dose.<br>• If ILD/pneumonitis recurs, permanently discontinue brigatinib. |
| | Grade 3 or 4 | Permanently discontinue brigatinib for ILD/pneumonitis. |

| Treatment-Related AE | Severity (a) | Dose Modification |
|---|---|---|
| Hypertension | Grade 3 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg, medical intervention indicated, more than 1 antihypertensive drug, or more-intensive therapy than previously used indicated) | • Interrupt brigatinib until hypertension has recovered to Grade 1 or less (SBP <140 mmHg and DBP <90 mmHg), then resume brigatinib at next lower dose (Table 8.a).<br>• Recurrence: interrupt brigatinib until recovery to Grade 1 or less then resume at next lower dose (Table 8.a), or permanently discontinue treatment. |
| | Grade 4 hypertension (life-threatening consequences, urgent intervention indicated) | • Interrupt brigatinib until recovery to Grade 1 or less then resume at next lower dose (Table 8.a), or permanently discontinue treatment.<br>• Recurrence: permanently discontinue brigatinib for recurrence of Grade 4 hypertension. |
| Bradycardia (HR <60 bpm) | Symptomatic bradycardia | • Interrupt brigatinib until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.<br>• If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume brigatinib at the same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.<br>• If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose adjusted, resume brigatinib at the next lower dose (Table 8.a) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. |
| | Bradycardia with life-threatening consequences, urgent intervention indicated | • Permanently discontinue brigatinib if no contributing concomitant medication is identified.<br>• If contributing concomitant medication is identified and discontinued or dose adjusted, resume brigatinib at the next lower dose (Table 8.a) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated.<br>• Recurrence: permanently discontinue brigatinib. |
| Visual disturbance | Grade 2 or 3 visual disturbance | Interrupt brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 8.a). |
| | Grade 4 visual disturbance | Permanently discontinue brigatinib. |
| Creatine phosphokinase (CPK) elevation | Grade 3 CPK elevation (>5.0×ULN) | Interrupt brigatinib until recovery to Grade 1 or less (≤2.5×ULN) or to baseline, then resume brigatinib at the same dose. |
| | Grade 4 CPK elevation (>10.0×ULN) or recurrence of Grade 3 elevation | Interrupt brigatinib until recovery to Grade 1 or less (≤2.5×ULN) or to baseline, then resume brigatinib at the next lower dose (Table 8.a). |
| Lipase/amylase elevation | Grade 3 lipase or amylase elevation (>2.0×ULN) | Interrupt brigatinib until recovery to Grade 1 or less (≤1.5×ULN) or to baseline, then resume brigatinib at the same dose. |

| Treatment-Related AE | Severity (a) | Dose Modification |
|---|---|---|
| | Grade 4 lipase or amylase elevation (>5.0×ULN) or recurrence of Grade 3 elevation | Interrupt brigatinib until recovery to Grade 1 or less (≤1.5×ULN) or to baseline, then resume brigatinib at the next lower dose (Table 8.a). |
| Hyperglycemia | Grade 3 (>250 mg/dL or 13.9 mmol/L) or greater | If adequate hyperglycemic control cannot be achieved with optimal medical management, interrupt brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next dose (Table 8.a), or permanently discontinue brigatinib. |
| Other | Grade 3 | • First occurrence: interrupt brigatinib until recovery to baseline, then resume at same dose.<br>• Recurrence: interrupt brigatinib until recovery to baseline then resume at next lower dose, or discontinue brigatinib (Table 8.a). |
| | Grade 4 | • First occurrence: either interrupt brigatinib until recovery to baseline and resume at next lower dose (Table 8.a) or permanently discontinue brigatinib.<br>• Permanently discontinue brigatinib for recurrence. |

bpm=beats per minute; DBP=diastolic blood pressure; HR=heart rate; SBP=systolic blood pressure.
(a) Graded per the NCI CTCAE, version 4.03.

### 8.4.1 Criteria for Dose Interruption During a Cycle

See Table 8.b.

### 8.4.2 Criteria for Dose Reduction

See Table 8.b.

### 8.4.3 Reintroducing Brigatinib After Dose Interruption

If brigatinib treatment interruption lasts ≥14 days, and the prior dose was >90 mg QD, patients should resume treatment at 90 mg QD for 7 days, before escalating the dose back to 120 mg QD or 180 mg QD. The dose should not be escalated higher than the prior dose level before treatment interruption.

### 8.4.4 Reescalation After Dose Modification

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

### 8.4.5 Criteria for Discontinuation of Brigatinib

See Table 8.b.

In addition, the investigator should discontinue brigatinib at any time and for any reason if it is determined to be in the best interest of the patient.

## 8.5 Excluded Concomitant Medications and Procedures

The following concomitant medications and procedures are prohibited during the treatment period:

- Any other systemic anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS and WBRT, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Hormonal contraception is not allowed.
- Use of any other investigational drug or device.
- Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 14 days should emergency surgery be required).

If a patient's clinical condition requires treatment with one of the prohibited classes of medications specified above, the clinical details of the situation should be discussed with the sponsor's project clinician (or designee) as soon as possible to determine whether it is safe for the patient to continue treatment with brigatinib.

On the basis of the metabolism of brigatinib being primarily via CYP3A and the results of clinical drug-drug interaction (DDI) studies in healthy subjects, the following should be followed:

- Avoid the concomitant use of strong CYP3A inhibitors (see Appendix F). Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided.
- Avoid the concomitant use of strong and moderate CYP3A inducers with brigatinib (see Appendix F).

## 8.6 Permitted Concomitant Medications and Procedures

Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant medication or therapy. Patients with CNS lesions requiring local radiotherapy such as SRS or WBRT are allowed to continue study drug after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have PD.

## 8.7 Precautions and Restrictions

It is not known what effects brigatinib has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of the

reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method (eg, intrauterine device [IUD]) with a condom, which is an effective barrier method of contraception, at the same time, from the time of signing of the informed consent form (ICF) through 4 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, from the time of signing the informed consent through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 month after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient, during the entire study treatment period and through 4 months after that last dose of study drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

## 8.8 Management of Clinical Events

### 8.8.1 ILD/Pneumonitis

During early clinical development of brigatinib, moderate and severe pulmonary AEs (eg, dyspnea, hypoxia, cough, pneumonia, and pneumonitis) were observed early after initiation of the drug in a subset of patients. To better characterize early pulmonary AEs observed with brigatinib treatment, a strategy for systematic analysis of these events according to a case definition for EOPE was developed. In Study AP26113-11-101, pulmonary events occurring within the first 7 days of treatment with brigatinib, consistent in some cases with pneumonitis, were observed shortly after treatment initiation in 2% of patients who had received brigatinib at a starting dose of 90 mg QD (including patients who escalated to 180 mg QD after 7 days). No such events were observed in the 7 days after escalation to 180 mg QD. In Study AP26113-13-201, of 219 treated patients, 4 cases were determined to meet the criteria for definite EOPE, and 10 cases met the criteria for possible EOPE. In total, 6.4% of patients had an event that was at least possibly an EOPE. All EOPEs occurred at a dose of 90 mg QD, regardless of dose group (ie, within the first 7 days of treatment in

the 90 mg QD→180 mg QD dose group). No EOPEs were identified after escalation to 180 mg QD in the 90 mg QD→180 mg QD dose group.

Pulmonary symptoms have been observed after a single dose of brigatinib in some patients. The pulmonary symptoms are associated in more severe cases with hypoxia and chest CT findings of ground glass opacities consistent with pneumonitis. These events have been managed with treatment interruption and medical management as clinically indicated (eg, steroids, antibiotics). Most events resolved with interruption or discontinuation of brigatinib. Two fatal pulmonary events (hypoxia and pneumonia) and 1 fatal pulmonary event (pneumonia) starting within the first 7 days of treatment were observed in Studies AP26113-11-101 and AP26113-13-201, respectively. Upon resumption of dosing, some patients had events recur, and others did not have recurrence with continued dosing. As such, investigators and patients must be aware that pneumonitis-like events may present as early as 24 to 48 hours after initial dosing.

Later-onset pneumonitis has also occurred in the brigatinib development program.

Pulmonary events occurring after initiation of brigatinib treatment including, but not limited to, dyspnea, hypoxia, dry cough, chest tightness, and presumptive lung infection (pneumonia) should be monitored and reported.

To reiterate, some events occur after a single dose of brigatinib, and physicians should be aware of this possibility and discuss it with patients. Newly developed or worsening of pulmonary symptoms in the first week of study drug administration, specifically with hypoxia and ground glass opacity on radiographic imaging indicative of ILD or pneumonitis, could suggest a relationship to brigatinib. Other etiologies, including pulmonary embolism and infectious pneumonia, should be ruled out if possible. If no evidence of other etiology is identified, a causal relationship to brigatinib should be considered.

The management of new or worsening pulmonary symptoms after initiation of brigatinib treatment should include drug interruption; monitoring of oxygen saturation and biomarkers (Serum Krebs von den Lungen-6 [KL-6] and surfactant protein-D [SP-D]); thoracentesis, bronchoscopy, open lung biopsy, chest x-ray, or CT; and appropriate work up for infectious or other etiology, with high-dose corticosteroids, supplemental oxygen therapy, and empiric antibiotics as indicated. After drug interruption and workup of symptoms, dose modification should be accomplished according to the recommendations in Table 8.b.

### 8.8.2 Hypertension

Blood pressure should be monitored and recorded at each visit. Hypertension detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE, version 4.03, which defines hypertension as a disorder characterized by a pathological increase in blood pressure: a repeated elevation in the blood pressure exceeding 140 mmHg for systolic and exceeding 90 mmHg for diastolic. For patients who either develop hypertension or experience worsening hypertension during treatment with study drug, at the discretion of the investigator, aggressive antihypertensive medication should be initiated or optimized to achieve target blood pressure

before interruption or dose reduction of the study drug. If Grade 3 or Grade 4 hypertension develops, dose interruption and reduction is recommended according to Table 8.b.

### 8.8.3 Bradycardia

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

### 8.8.4 Nausea and Emesis

Nausea should be treated with standard-of-care antiemetics. Prophylactic antiemetics may be used.

### 8.8.5 Visual Disturbance

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

### 8.8.6 Diarrhea

For Grade 1 diarrhea, symptomatic care such as loperamide may be given, or no intervention may be undertaken, according to the investigator's clinical judgment. For Grade 2 diarrhea, administer loperamide until the patient is symptom-free for 12 hours. No dose modification is necessary unless the patient does not tolerate brigatinib or the symptom recurs. For Grade ≥3 despite loperamide, treatment should be interrupted or permanently discontinued according to Table 8.b. Secondary prophylaxis in patients who have experienced diarrhea with brigatinib treatment is allowed. Other medications and supportive care may be added according to the institution's standard of care.

## 8.9 Blinding and Unblinding

This is an open-label study.

## 8.10 Description of Investigational Agents

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

For additional details, refer to the Investigator's Brochure and Pharmacy Manual.

## 8.11 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing brigatinib tablets are provided in the Pharmacy Manual.

Brigatinib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brigatinib.

## 8.12 Packaging and Labeling

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

## 8.13 Storage, Handling, and Accountability

The recommended storage condition for brigatinib is to store at 15°C to 30°C. Do not refrigerate or freeze. A daily temperature log of the drug storage area must be maintained each working day. Temperature excursions must be reported to the sponsor or designee.

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

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

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

No other utilization of brigatinib intended for use in this study is authorized by the sponsor. The on-site pharmacist will immediately return unused study drugs to the sponsor after the study is closed at the study site.

Please refer to the Pharmacy Manual for additional instructions.

## 8.14 Other Protocol-Specified Materials

Not applicable

# 9.0 STUDY CONDUCT

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

## 9.1 Study Personnel and Organizations

The contact information for the sponsor's project clinician (or designee), the central laboratory, any additional clinical laboratories or vendors participating in the study, and the list of investigators can be found in the protocol annex or the Study Manual.

## 9.2 Arrangements for Recruitment of Patients

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

## 9.3 Treatment Group Assignments

After written informed consent has been obtained, the patient will be assigned a patient identification code.

Patient eligibility will be confirmed by the sponsor's project clinician (or designee) before enrollment by the investigator into the study. Reenrollment of the same patient will not be permitted. If a patient is discontinued from the study, that patient identification code will not be reused.

The first 9 patients will be enrolled in the safety evaluation lead-in part. Enrollment will be interrupted after the ninth potentially DLT-evaluable patient is enrolled until the DLTs are assessed. After the decision to open the expansion part, patient enrollment will be resumed.

Patients in the expansion part will be assigned to the refractory expansion cohort (including the main cohort or the subcohort) or TKI-naïve expansion cohort at enrollment on the basis of prior ALK inhibitor treatment.

## 9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, EOT, and follow-up. This protocol generally presents scheduled timelines for study procedures by abbreviated references to cycle (C) and day (D) relative to the date of the first dose of study treatment (defined as C1D1).

The ICF may be signed more than 21 days before C1D1. Screening assessments must be performed within 14 days before C1D1, with the exception of tumor imaging assessment, for which the allowable window is 21 days before C1D1. However, whenever feasible, baseline imaging should be performed as close as possible to C1D1.

Vital signs should be repeated on C1D1 before the first dose, regardless of the time from screening. Physical examination, ECOG performance status assessments, hematology, chemistry, insulin, testosterone (male patients only), and pregnancy test assessments do not need to be repeated on C1D1 if they were performed for screening within 7 days before C1D1 and, in the opinion of the investigator, there is no reason to believe they have substantially changed. If screening laboratory assessments need to be repeated on C1D1, they should be obtained before starting treatment.

In the safety evaluation lead-in part, patients will be hospitalized during Cycle 1 in general. If a patient wishes to return home temporarily and the investigator confirms that the patient's symptoms are stable on the basis of the available data, then the patient may return home temporarily except on Days 1 through 10 and Days 22 and 23, provided this does not interfere with the study assessments. The investigator must document the confirmation record for stabilization of the patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary leave.

Refer to the Schedule of Events (Appendix A) for the timing of assessments. Refer to Table B for Cycle 1 of the safety evaluation lead-in part; for all other cycles of the safety evaluation lead-in part, refer to Table A. The timing of PK assessments is specified in Table C (safety evaluation lead-in part) and Table D (expansion part). Additional details are provided as necessary in the sections that follow.

### 9.4.1 Informed Consent

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

### 9.4.2 Patient Demographics

Demographic information will be obtained at screening and will consist of the date of birth, sex, race, and smoking history.

### 9.4.3 Medical History

Medical/Surgical History

A complete medical history will be taken at screening. Information to be documented includes relevant past illnesses, including other cancers, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).

Diagnosis and Cancer History

The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology, and all sites of primary and metastatic disease, should be recorded.

Prior Cancer Therapy

Prior cancer therapy history will be taken at screening and will include cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative, palliative, and diagnostic procedures (eg, biopsy). Radiation will include both definitive and palliative treatment.

Systemic therapy should include all regimens given, each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation. Experimental or investigational therapy history must also be recorded.

ALK Mutation Status

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

Patients entering the study either must have a history of a positive result from the Vysis ALK Break Apart FISH Probe Kit, the Nichirei Histofine RALK iAEP Kit, the Ventana ALK (D5F3) CDx Assay or DNA/RNA sequencing (except for the patients in TKI-naïve expansion cohort), or must submit tissue samples for analysis using a local regulatory authority-approved test. Specifications for handling and processing of tissue for this test are described in Section 9.4.17.1 and in the Study Manual.

### 9.4.4 Physical Examination

A complete physical examination must be performed at screening, the extent of which should be consistent with medical history and the patient's underlying disease. Subsequent physical examinations as described in the Schedule of Events may be directed to relevant findings. Of note, because of adverse reactions reported during treatment with brigatinib, investigators are cautioned to monitor patients for signs of vision dysfunction. For new or worsening severe vision disorders, an ophthalmological evaluation should be performed. If new or worsening of vision disorder is suspected, investigators should consult and ophthalmologist, and ophthalmological evaluation should be performed as needed.

The EOT physical examination should be a complete physical examination.

### 9.4.5 Height and Weight

Height and weight will be measured during screening only (within 14 days before C1D1).

### 9.4.6 Vital Signs

Vital signs include temperature, pulse, respiratory rate, $SpO_2$, and blood pressure (when patient is seated).

Vital signs should be repeated on C1D1, before the first dose, regardless of the time from screening. Vital signs will also be assessed per the Schedule of Events throughout the study.

### 9.4.7 ECOG Performance Status

The patient's performance status must be assessed using the ECOG performance scale during screening. ECOG performance status will also be assessed per the Schedule of Events throughout the study. The ECOG performance scale is provided in Appendix D.

### 9.4.8 Chest X-ray

The chest x-ray as referenced for ILD assessment must be performed during screening. See Section 8.8.1 for the management of new or worsening pulmonary symptoms.

### 9.4.9 Pregnancy Test

The pregnancy test must be a human chorionic gonadotropin test, and either urine or serum can be used. A serum pregnancy test must be performed within 7 days before the first dose of study drug in women of childbearing potential at screening.

Women of childbearing potential will be defined as sexually mature females who meet the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy, and
- Those who have not had natural menopause for 12 consecutive months or longer. Note that a loss of menopausal periods following chemotherapy may not rule out childbearing potential.

The results from these tests must be available and negative before the first dose of study drug is administered. If C1D1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed. Women of childbearing potential at study start must also complete the pregnancy test at the EOT visit.

Pregnancy test is to be done by the local laboratory. Results or status from this test will be recorded on eCRFs.

### 9.4.10 Concomitant Medications and Procedures

Concomitant medications for all ongoing medical history conditions or AEs, and prophylactic treatments and supplements must be recorded in the eCRF from the date the informed consent is signed until at least 30 days after the last dose of brigatinib or initiation of the subsequent anticancer therapies (whichever comes first).

### 9.4.11 AEs

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

### 9.4.12 Study Enrollment

A patient is considered to be enrolled in the study when the first dose of brigatinib has been administered. Procedures for completing the enrollment information are described in the Study Manual.

### 9.4.13 Electrocardiogram

All electrocardiograms (ECGs) must be 12-lead ECGs and will be assessed per the Schedule of Events throughout the study. The C1D1 ECG should be performed before the first dose of brigatinib.

Additional ECGs may be performed at the investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval (other than medications explicitly prohibited).

The uncorrected QT interval and the QT interval corrected by the Fridericia formula (QTcF) will be recorded on eCRFs.

For consistency, the Fridericia correction (QTcF=QT interval/$(RR)^{1/3}$ interval) method must be used for all calculations of heart rate–corrected QT (calculated) (QTc) intervals.

When the timing of a PK, biomarker, or safety laboratory blood sample collection coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection, if possible. In some cases, it may be appropriate to repeat an ECG to rule out improper lead placement contributing to the ECG abnormality. ECGs should be reviewed by the investigator or delegate before the patient leaves the clinic on visit days.

### 9.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the Study Manual.

Serum insulin, testosterone (male patients only), KL-6, and SP-D are to be performed by a central laboratory, including labs obtained at unscheduled visits, whenever possible. All central laboratory results will be provided to the investigator.

Laboratory tests to establish eligibility must be done within 14 days before C1D1 (Appendix A).

#### *9.4.14.1 Hematology and Chemistry*

Blood samples for analysis of parameters shown in Table 9.a will be obtained as specified in the Schedule of Events (Appendix A).

C1D1 hematology and chemistry blood draws should be performed before the first dose of brigatinib. All scheduled chemistry blood draws should be performed in a fasting state.

To estimate creatinine clearance, the Cockcroft-Gault formula will be employed (Appendix E).

**Table 9.a Hematology and Chemistry Tests**

| Hematology | Serum Chemistry |
|---|---|
| White blood cell count with differential (ANC, basophils, eosinophils, lymphocytes, monocytes).<br>Hematocrit.<br>Platelet count.<br>Hemoglobin. | Albumin.<br>Alkaline phosphatase (ALP).<br>Amylase.<br>ALT.<br>AST.<br>Blood urea nitrogen (BUN).<br>Calcium.<br>Creatine phosphokinase (CPK).<br>Bicarbonate (or total carbon dioxide) (a).<br>Chloride.<br>Creatinine.<br>C-reactive protein (CRP).<br>Glucose (fasted).<br>Lactate dehydrogenase (LDH).<br>Lipase.<br>Magnesium.<br>Phosphorus.<br>Potassium.<br>Sodium.<br>Bilirubin (total bilirubin, conjugated and unconjugated bilirubin).<br>Protein (total protein).<br>Uric acid.<br>HbA1c. |

(a) To be included if the testing is available as part of blood chemistry panel at the local laboratory.

*9.4.14.2 Insulin*

Serum insulin measurement will be performed according to the Schedule of Events throughout the study. Serum insulin and glucose should be measured concurrently. C1D1 insulin blood draws should be performed before the first dose of brigatinib. All scheduled insulin blood draws should be performed in a fasting state (at least 6 hours passed since last meal).

*9.4.14.3 Testosterone (Male Patients Only)*

In male patients, serum testosterone will be performed according to the Schedule of Events throughout the study. The C1D1 testosterone blood draw should be performed before the first dose of brigatinib.

*9.4.14.4 KL-6 and SP-D*

KL-6 and SP-D are used for evaluation of ILD. KL-6 and SP-D measurement must be performed during screening as referenced for the ILD assessment. All evaluations of KL-6 and SP-D, including for new or worsening pulmonary symptoms, must be performed centrally. See Section 8.8.1 for the management of new or worsening pulmonary symptoms.

### 9.4.15 Hepatitis Testing

Hepatitis testing will be performed and interpreted locally during the screening period. HBsAg should be checked for hepatitis B virus (HBV), and if negative, patients can be enrolled. For patients who are HBsAb and/or HBcAb positive, HBV DNA will also be assessed at screening. Hepatitis C virus antibody (HCVAb) should be checked for HCV. Patients who test positive for HCVAb will also be tested for HCV RNA at screening.

Note that patients who have negative HBsAg but are known to be HBcAb and/or HBsAb positive may be enrolled but must have an undetectable HBV viral load. Patients who have a positive HCVAb can be enrolled but must have an undetectable HCV viral load.

Patients who are HBsAg negative but HBsAb and/or HBcAb positive, and/or HCVAb positive with a negative viral load at screening, will be monitored by assessment of viral load (DNA titers for HBV, RNA titers for HCV) every 3 months.

### 9.4.16 Disease Assessment

At screening, disease assessment must include imaging of the chest, abdomen (covering adrenal glands) and pelvis, using appropriate radiological procedures (CT scans or magnetic resonance imaging [MRI] with contrast, unless contrast media is contraindicated). Contrast-enhanced MRI of the brain (such as gadolinium) is required at screening for all patients. If contrast for MRI is contraindicated, use CT with contrast. All radiographic images (eg, CT scan, MRI) performed during the study will be submitted to the IRC. Details regarding the collection and transmission of images can be found in the Study Manual. Patients must have at least 1 measurable lesion per RECIST version 1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. Brain lesions may be used as target lesions provided they are ≥10 mm and have not been 1) previously treated with WBRT within 3 months, or 2) previously treated by SRS or surgical resection.

Disease assessment by CT or MRI scans will be performed for all patients at screening, every 2 cycles (8 weeks) from C3D1 (±7 days) through C15D1, and every 3 cycles (12 weeks) thereafter until EOT. Imaging of the chest, abdomen, pelvis and brain will occur at each assessment for all patients (with or without brain metastasis at screening in the expansion cohort). More-frequent imaging is recommended at any time, if clinically indicated; confirmation of CR or PR can be performed at least 4 weeks after initial response. Imaging assessment will also be performed at the EOT visit if more than 4 weeks have passed since the last imaging assessment. The same imaging modality at the same institution should be used at each assessment, if possible. SD can be evaluated at least 8 weeks after initiation of study drug administration (considering the allowance of the evaluation, Day 50 since C1D1 as the earliest).

For patients who discontinue study treatment in the absence of PD, additional tumor assessment should continue at the same time points as study treatment until PD or the start of another systemic anticancer therapy.

### 9.4.17 CCI [redacted]

CCI [redacted]

#### *9.4.17.1* CCI [redacted]

CCI [redacted]

CCI [redacted]

*9.4.17.3* CCI [redacted]

CCI [redacted]

*9.4.17.4 Biomarker Sample Retention*

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

### 9.4.18 PK Measurements

PK blood samples will be obtained from all patients as described in Appendix A Table C for patients in the safety evaluation lead-in part and in Appendix A Table D for patients in the expansion part. The dates and exact times of administration of brigatinib before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF. Plasma will be obtained from each blood sample, and concentrations of brigatinib and AP26123 in the plasma will be simultaneously determined by the designee using a validated bioanalytical method. Detailed instructions for sample preparation will be provided in the Study Manual.

### 9.4.19 Patient-Reported Outcomes Questionnaire (Expansion Part Only)

In the expansion part, the PRO questionnaires (EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L; (Appendix I) will be administered at specified scheduled visits and at the visit 30 days after the last dose of brigatinib. The PRO questionnaires should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed.

## 9.5 Documentation of Subject Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible before the first dose, the investigator should complete the eCRF.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death.
- AE.
- Screen failure (failed inclusion criteria or did meet exclusion criteria).
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Study terminated by sponsor.

Patient identification codes assigned to subjects who fail screening should not be reused.

### 9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they receive the study treatment until PD or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. Patients will attend an EOT visit approximately 30 days after receiving their last dose of the study drug and will continue to be followed for other follow-up assessments specified in the Schedule of Events (Appendix A). Refer to the Schedule of Events (Appendix A) for EOT visit assessments.

### 9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

### 9.8 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- AE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. Before starting subsequent anticancer therapy,

all study procedures outlined for the EOT visit should be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients in the safety evaluation lead-in part who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedule of Events until PD occurs.

### 9.9 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Death.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

### 9.10 Study Compliance

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

Patients will be provided a diary card or equivalent where the date of study drug administration will be recorded. Patients who forget to take their dose should not make up the missed dose. A missed dose is defined as a dose not taken within 12 hours of the intended scheduled administration. Any missed doses must be recorded in an appropriate source record (eg, clinic chart), patient diary card, and study drug administration eCRF. Training of patients should be documented in the appropriate source record (eg, clinic chart). When possible, patients should take the study drug under observation during scheduled study visits to the clinic where a predose blood sample is collected. The investigator is responsible for ensuring that the patient diary cards are retained and noted in source documentation.

### 9.11 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be performed every 8 weeks until Week 57 (equivalent to Cycle 15 Day 1), and every 12 weeks (±14 days) thereafter, from the EOT visit until the occurrence of PD or the start of subsequent anticancer therapy.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits. The OS follow-up visits should be performed every 12 weeks (±14 days) after documented PD until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.9 occur. For the safety evaluation lead-in part and the refractory expansion part, the duration of OS follow-up will be 2 years after enrollment of the last patient or until all patients have discontinued study treatment, whichever occurs later. For the TKI naïve expansion cohort, the duation of OS follow-up will be until all patients have discontinud study treatment, or at the time of commercial brigatinib placing on the market for TKI-naïve patients in Japan, whichever occurs first.

Survivor information and death details may be collected by methods that include, but are not limited to, telephone, email, and mail. NOTE: Related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

# 10.0 ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Pretreatment Event Definition

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

### 10.1.2 AE Definition

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

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

### 10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

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

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [15]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or Grade 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or Grade 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm$^3$ to less than 2000/mm$^3$ is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

## 10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

**SAE Reporting Contact Information**

**BI Medical, Inc.**

Toll-free fax: PPD

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

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

pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [15].

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

If ILD (regardless of causality and grade) occurs from the first of study drug through 30 days after administration of the last dose of study drug, or initiation of the subsequent anticancer therapy (whichever comes first), it should be recorded as an SAE. The SAE Form should be completed and reported as described above. Images used for evaluating the clinical course of ILD (eg, chest CT, chest x-ray) should be submitted to the sponsor promptly. The sponsor may request additional images as needed. Refer the Study Manual for instructions for submitting images.

### 10.3 Monitoring of AEs and Period of Observation

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

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

### 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

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

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

| Call center | Phone number | Email | Fax |
|---|---|---|---|
| Dohmen Life Science Services (DLSS) | PPD<br>Non-toll-free number: PPD | PPD | PPD |

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to BI Medical, Inc (refer to Section 10.2).

## 10.6 Safety Reporting to Investigators, IRBs, 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, IRBs and/or the head of each study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial.

# 11.0 STUDY-SPECIFIC COMMITTEES

## 11.1 Steering Committee

A steering committee will be formed when the study is initiated. Its purpose is to function in an advisory capacity to 1) provide input on study conduct and progress; 2) ensure scientific and ethical integrity of the study; and 3) provide ongoing oversight of safety and efficacy in this open-label study. The steering committee will include clinician experts in the clinical care and investigation of the targeted patient population, and will include sponsor representatives. In addition to general study oversight, it will provide input on operational aspects of the study. The committee may make recommendations for the sponsor's consideration based on periodic review.

The steering committee charter will define the responsibilities of the committee.

## 11.2 IDMC

An IDMC, consisting of 3 to 5 members not associated with the conduct of the study, will be established for this study.

The IDMC will provide recommendation on the go/no go decision to move from the safety evaluation lead-in part to the expansion part and on futility and efficacy assessment at the interim analysis. The IDMC will also evaluate cases of ILD reported as SAEs and make recommendations as needed.

The IDMC will communicate the recommendations to the sponsor. The final decision to act on the IDMC recommendations will be made by the sponsor.

Details of the IDMC will be captured in a charter.

## 11.3 IRC

An IRC will evaluate all images collected during the study for the primary and certain secondary endpoints. An IRC charter will define the procedures used by the committee.

## 12.0 DATA HANDLING AND RECORDKEEPING

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

### 12.1 eCRFs

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

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

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

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

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

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

### 12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs, including the audit trails, 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 and J-GCP requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8), or local laws, regulations and guidelines. 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/or the head of the institution and sponsor.

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

# 13.0 STATISTICAL METHODS

## 13.1 Statistical and Analytical Plans

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

In general, summary tabulations will be presented and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

### 13.1.1 Analysis Sets

The populations used for analysis will include the following:

The refractory expansion part and safety evaluation lead-in part:

- Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses. All patients in the safety population will be analyzed according to the actual treatment received.
- Full analysis set (FAS) population: all patients who receive at least 1 dose of study drug. All patients in the FAS population will be analyzed according to the actual treatment received (ie, overall population).
- FAS-P population: a subset of the FAS population consisting of first 47 patients in the main cohort of the refractory expansion part.
- Per-protocol set (PPS) population: a subset of the FAS-P population including patients who do not have a major protocol violation as determined by the sponsor's project clinician (or designee). Each decision to exclude patients from the PPS population at interim analysis and at the end of the study will be made before respectively the interim analysis and each snapshot.
- PK population: patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist for safety evaluation lead-in part. Patients who receive at least 1 dose of briganitib and have at least 1 plasma concentration data after administration of brigatinib will be used for other PK analyses (PK-evaluable patients).

The TKI-naïve expansion cohort:

- Safety population: patients who receive at least 1 dose of study drug will be used for all safety analyses. All patients in the safety population will be analyzed according to the actual treatment received.
- Full analysis set (FAS) population: all patients who receive at least 1 dose of study drug. All patients in the FAS population will be analyzed according to the actual treatment received (ie, overall population).

- Per-protocol set (PPS) population: a subset of the FAS population including patients who do not have a major protocol violation as determined by the sponsor's project clinician (or designee). Each decision to exclude patients from the PPS population at the end of the study will be made before snapshot.
- PK population: patients who receive at least 1 dose of briganitib and have at least 1 plasma concentration data after administration of brigatinib will be used (PK-evaluable patients).

Further criteria for each analysis set will be detailed in a SAP.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

The refractory expansion part and safety evaluation lead-in part:

Demographics and other baseline characteristics will be summarized using the FAS population and FAS-P population.

The TKI-naïve expansion cohort:

Demographics and other baseline characteristics will be summarized using the FAS population.

### 13.1.3 Efficacy Analysis

*13.1.3.1 Primary Endpoint and Analytical Methods*

The refractory expansion part and safety evaluation lead-in part:

The primary endpoint is confirmed ORR in the main cohort of the refractory expansion part, as assessed by an IRC, per RECIST version 1.1, defined as the proportion of the patients who are confirmed to have achieved CR or PR per IRC using RECIST version 1.1 after the initiation of study treatment.

Primary Analysis

For the primary endpoint, confirmed ORR as assessed by an IRC and its 2-sided 95% CI will be provided using the FAS-P population.

Sensitivity Analysis

Confirmed ORR will be determined using the PPS population.

The TKI-naïve expansion cohort:

The primary endpoint is 12 months PFS rate in the TKI-naïve expansion cohort, as assessed by an IRC, per RECIST version 1.1, defined as the PFS rate in Kaplan-Meier plot at 12 months after the initiation of study treatment, assessed by IRC, per RECIST version 1.1.

Primary Analysis

For the primary endpoint, 12 months PFS rate as assessed by an IRC and its 2-sided 90% CI will be provided using the FAS population based on the complementary log-log transformation. If the

lower bound of confidence interval is above 42.6%, we will show the efficacy of brigatinib in the TKI-naïve population.

Sensitivity Analysis

12 months PFS rate will be determined using the PPS population.

*13.1.3.2 Secondary Endpoints and Analytical Methods*

The safety evaluation lead-in part, the main cohort of the refractory expansion part, and the TKI naïve expansion cohort:

- Confirmed ORR as assessed by the investigator, per RECIST version 1.1.

The safety evaluation lead-in part, the overall population of the refractory expansion part, and the TKI naïve expansion cohort:

- Confirmed ORR as assessed by an IRC, per RECIST version 1.1.

The main cohort of the refractory expansion part, the overall population of the refractory expansion part, and the TKI naïve expansion cohort:

- DOR as assessed by an IRC, per RECIST version 1.1, defined as the time between the first documentation of objective tumor response (CR or PR) and the first subsequent documentation of objective PD or death due to any cause, whichever occurs first.
- PFS as assessed by an IRC, per RECIST version 1.1, defined as the time from the start of study treatment to the first documentation of objective PD or to death due to any cause, whichever occurs first.
- DCR as assessed by an IRC, per RECIST version 1.1, defined as the proportion of patients who are confirmed to have achieved CR or PR or have a best overall response of stable disease (SD), per RECIST version 1.1, for 6 weeks or more after initiation of study drug.
- Time to response as assessed by an IRC, per RECIST version 1.1, defined as the time interval from the date of the first dose of study treatment until the initial observation of CR or PR for patients with confirmed CR/PR.
- OS defined as the time from the start of study treatment to the date of death.
- CNS response as assessed by an IRC, per modified RECIST version 1.1 for assessment of intracranial efficacy (iORR and iDOR in patients who had measurable CNS metastases, and iPFS in all patients), defined as the proportion of the patients who have achieved CR or PR in the intracranial CNS per modified RECIST version 1.1 as evaluated by an IRC after the initiation of study treatment.
- Time on treatment defined as the time interval from the first dose to the last dose of brigatinib.

The main cohort of the refractory expansion part, and the TKI naïve expansion cohort:

- PROs of HRQOL scores and symptoms of lung cancer, assessed with the EORTC QLQ-C30 (version 3.0), its lung cancer module QLQ-LC13, and the EQ-5D-5L.

The refractory expansion part and safety evaluation lead-in part:

Secondary endpoints will be summarized descriptively using the FAS-P population or the FAS population.

The TKI-naïve expansion cohort:

Secondary endpoints will be summarized descriptively using the FAS population.

*13.1.3.3 Methods of Data Transformation and Handling of Missing Data*

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in a SAP.

*13.1.3.4 Significance Level and Confidence Coefficient*

Statistical inference will be performed at a 1-sided 0.025 level of significance or a 2-sided 0.05 level of significance as appropriate to preserve an overall type I error rate at or below a 1-sided 0.025 or 2-sided 0.05.

### 13.1.4 PK Analysis

The refractory expansion part and safety evaluation lead-in part:

Plasma concentrations of brigatinib will be summarized using descriptive statistics according to nominal (scheduled) time postdose and day. Mean and individual plasma concentration data of brigatinib from Cycle 1 will be plotted over time for each day (Days 1 and 22) in PK population of the safety evaluation lead-in part. Mean and individual plasma concentration data of brigatinib predose also will be plotted in Cycles 1, 2, 3, 4, and 5 in all PK-evaluable patients. The same analyses will be applied for plasma concentration of AP26123. All plasma concentration data of brigatinib and AP26123 will be listed.

PK parameters will be calculated on Cycle 1 Days 1 and 22 for brigatinib by noncompartmental analysis as permitted by the data from PK population of the safety evaluation lead-in part. These parameters will include, but will not be limited to, $C_{max}$, $t_{max}$, and AUC. PK parameters will be summarized using descriptive statistics for each day. The PK parameters of AP26123 also will be calculated and summarized using the same procedures. Individual PK parameters of brigatinib and AP26123 will be listed.

The TKI-naïve expansion cohort:

Mean and individual plasma concentration data of brigatinib predose also will be plotted in Cycles 1, 2, 3, 4, and 5 in PK-evaluable patients. The same plotting will be applied for plasma concentration of AP26123. All plasma concentration data of brigatinib and AP26123 will be listed.

Where appropriate, the plasma concentration data of brigatinib may be analyzed using population PK models and/or combined with data from other studies as part of a pooled analysis. The influence of exposure on biomarkers, clinical safety parameters (eg, selected AEs), and clinical response may also be explored.

### 13.1.5 Safety Analysis

AEs will be summarized using the safety analysis set in each cohort separately. Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population.

*13.1.5.1 AEs (TEAEs)*

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose or initiation of the subsequent anticancer therapies, whichever comes first will be tabulated.

TEAEs will be coded using the MedDRA dictionary. The frequency distribution will be provided by system organ class and preferred term as follows:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs.

*13.1.5.2 Laboratory Test Results, 12-Lead ECGs, and Vital Signs*

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated showing changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of brigatinib.

## 13.2 Interim Analysis and Criteria for Early Termination

<u>The main cohort of the refractory expansion part</u>

In this study, a 2-stage design will be used. An interim analysis for both futility and efficacy will be conducted in Stage 1, according to H1-minimax design in Englert [16]. The proportion of patients achieving a confirmed objective response, per IRC, will be used as the endpoint for the interim analysis. The interim analysis will be performed when the first 29 patients in the main cohort of the refractory expansion part have had the opportunity to complete the Cycle 7 Day 1 disease assessment. Enrollment will not be suspended during evaluation of these 29 patients; however,

patients enrolled after the 29th patient in the main cohort of the expansion part will not be included in the interim analysis even if their ORR results were available on the cutoff date.

If the number of patients with confirmed ORR is 3 or fewer of the 29 patients, enrollment will be stopped entirely for futility. Additionally, if the number of patients with confirmed ORR is 10 or more of the 29 patients, it will be decided that brigatinib has demonstrated sufficient efficacy to reject the null hypothesis and declare superiority to the uninteresting ORR of 15%, and enrollment may be stopped upon recommendation of IDMC, and analysis on all enrolled population will be conducted as descriptive analysis. Otherwise, the study will continue until the 47 patients have had the opportunity to complete the Cycle 7 Day 1 disease assessment. If the number of patients with confirmed ORR at the primary analysis is more than the number determined by the number at the interim analysis mentioned in Table 13.a, it will be decided that brigatinib has demonstrated sufficient efficacy to reject the null hypothesis.

**Table 13.a Minimum Number of Confirmed ORR at the Primary Analysis**

| No. ORR at Interim Analysis | No. ORR at Primary Analysis |
|---|---|
| 4/29 | 13/47 |
| 5/29 | 13/47 |
| 6/29 | 13/47 |
| 7/29 | 13/47 |
| 8/29 | 13/47 |
| 9/29 | 12/47 |

An IDMC will be formed. The IDMC will provide recommendation on the go/no go decision to move from the safety evaluation lead-in part to the expansion part, and on the futility and efficacy assessments performed at the interim analysis.

TKI-naïve expansion cohort

Iinterim analysis is not planned for this cohort.

### 13.3 Determination of Sample Size

The purpose of this phase 2 study is to determine efficacy of brigatinib in patients with ALK-positive NSCLC.

In the safety evaluation lead-in part, 9 DLT-evaluable patients will be enrolled for intensive safety and PK monitoring. This number of patients was derived from the following considerations: The meaningful intensive PK characterization needs to be conducted with more than 6 patients. It is assumed that 9 patients may be reasonable to secure the number of patients needed for intensive PK characterization, even with potential dropouts, and to evaluate the tolerability of the study drug. Also, 9 DLT-evaluable patients is enough to evaluate tolerability before expanding the dose cohort to a larger population using a conventional 3+3 design.

The sample size in the main cohort of the refractory expansion part was determined to allow confirmation that the true ORR (expected response rate) is greater than the threshold response rate of 15% for patients previously treated with alectinib alone and those treated with both alectinib and crizotinib. The rationale for the 15% response rate for the alectinib (with or without crizotinib) pretreated population is based on the consideration that compared with crizotinib, patients who have failed alectinib are less likely to respond to subsequent therapy because of alectinib's greater potency and better coverage of ALK mutations compared with crizotinib.

A sample size of 47 patients in the post-alectinib population of the refractory expansion part with the stopping rule mentioned in Section 13.2 will allow the study to have more than 90% power to rule out a threshold response rate when the true ORR is expected or higher than 35% with a 1-sided alpha of 0.025, according to the H1-minimax design in Englert [16].

The number of patients in the subcohort of the refractory expansion part (ie, patients previously treated with crizotinib only, ceritinib only, lorlatinib only, both crizotinib and ceritinib, both alectinib and ceritinib, both crizotinib and lorlatinib, both alectinib and lorlatinib, or both ceritinib and lorlatinib) will be limited to 20. These patients will be included in evaluations of the overall population.

The sample size in the TKI-naïve expansion cohort was determined to allow confirmation that the true 12 months PFS rate (expected response rate) is greater than the threshold of 42.6% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L Crizotinib arm) for TKI-naïve patients.

A sample size of 32 patients in the TKI-naïve expansion cohort will allow the study to have approximately 80% power to rule out the threshold rate (42.6%) when the true 12 months PFS rate is expected or higher than 66.5% (estimated PFS rate at 12 months in Kaplan-Meier plots observed in ALTA-1L Brigatinib arm) with a 1-sided alpha of 0.05, considering 10% patients will discontinue the study follow-up before the 12 months milestone due to reasons other than disease progression assessed by IRC or death, and 8 months enrollment period. The primary analysis will be performed at around 10 months after the enrollment of the last subject in the TKI-naïve expansion cohort. The sample size and evaluation timing may be adjusted based on results of second interim analysis of ALTA-1L study, and actual enrollment period of the TKI-naïve expansion cohort.

Overall, the total number of patients will be approximately 110 patients.

# 14.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including the Investigator's Binder, study medication, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

## 14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

Significant deviations should be recorded on the eCRFs and then confirmed by the sponsor or its designee. 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.

## 14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

## 15.0 ETHICAL ASPECTS OF THE STUDY

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

### 15.1 IRB Approval

IRBs must be constituted according to the applicable 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. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification, no protocol activities including assignment of patients may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

### 15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF describes 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 further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date that 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 principal investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by both the IRB and the sponsor before use.

The ICF 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 to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

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

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF shall be given to the subject.

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

### 15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth 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, the US FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication

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

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

### 15.4.2 Clinical Trial Registration

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

### 15.4.3 Clinical Trial Results Disclosure

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

## 15.5 Insurance and Compensation for Injury

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

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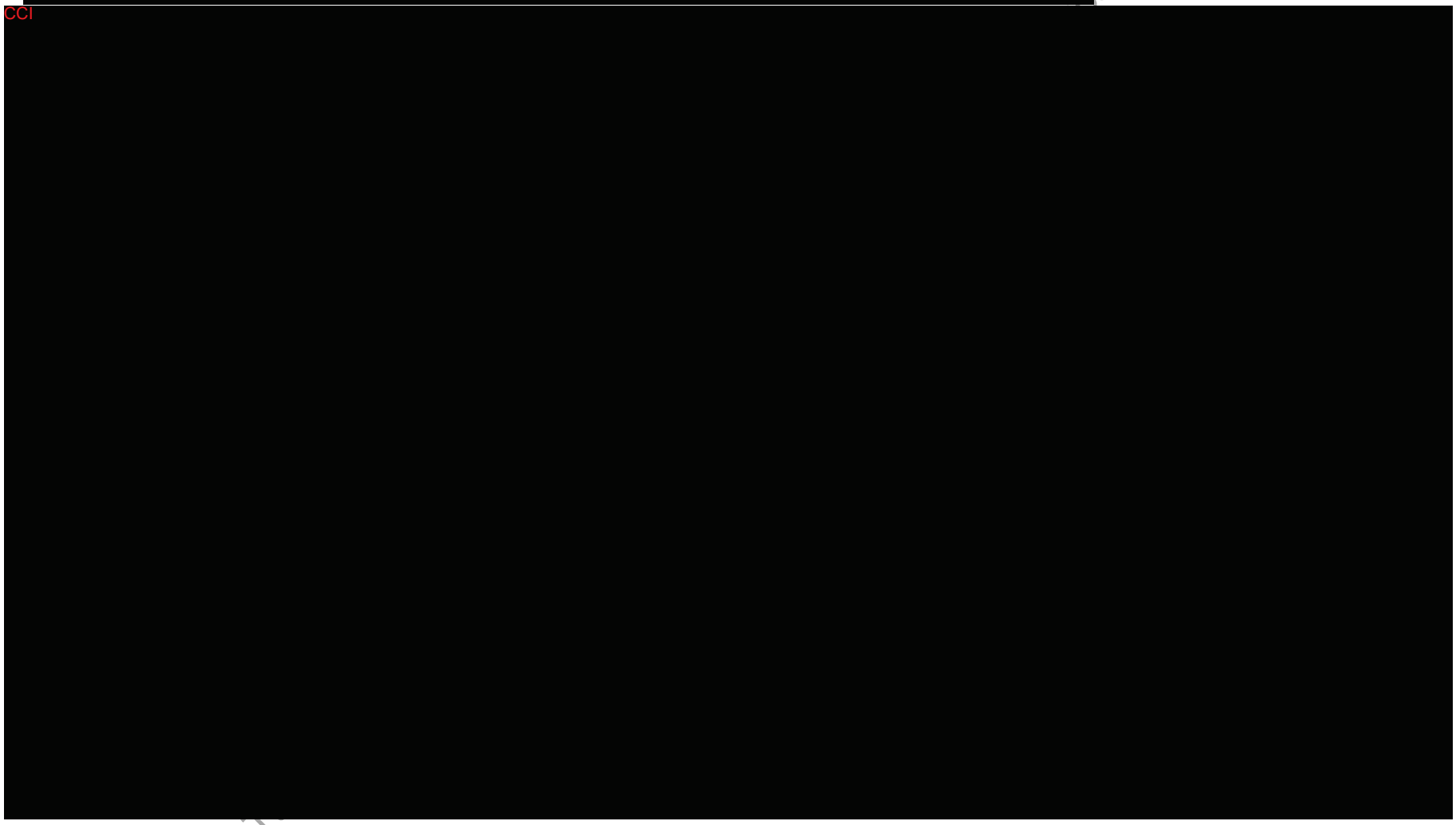

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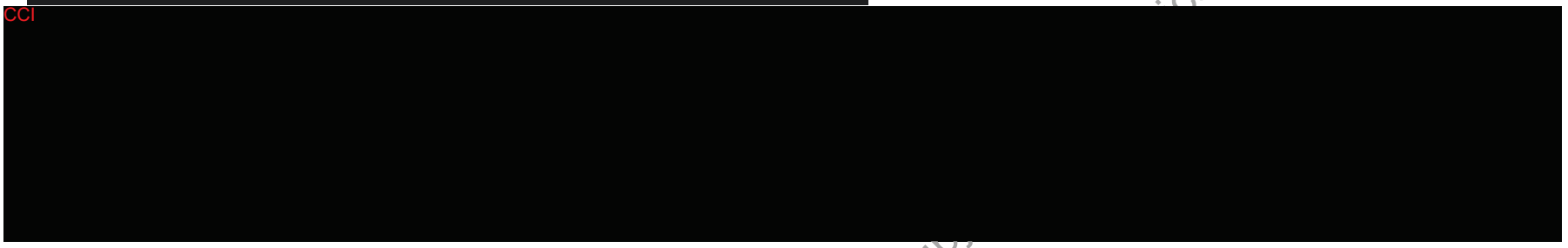

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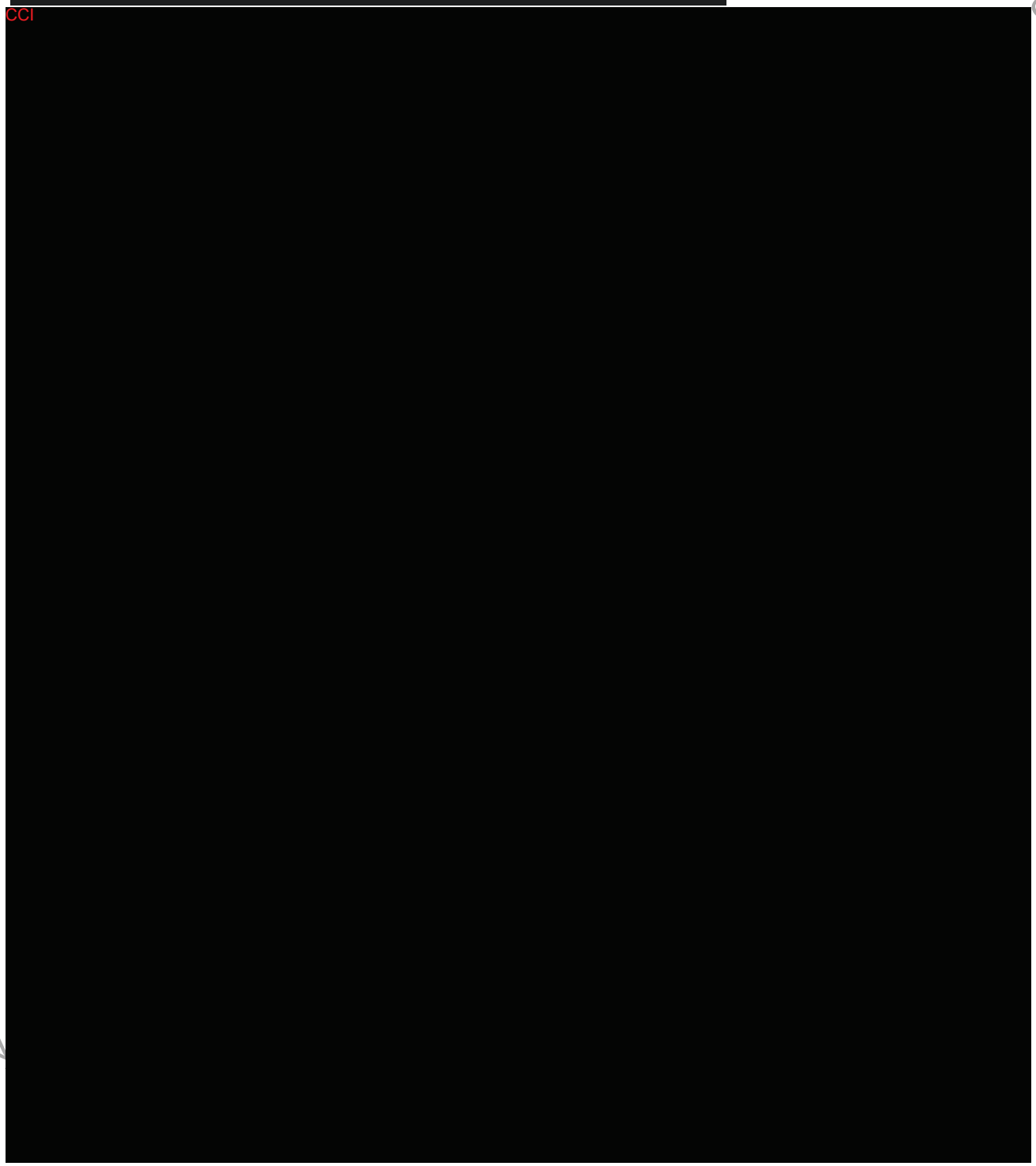

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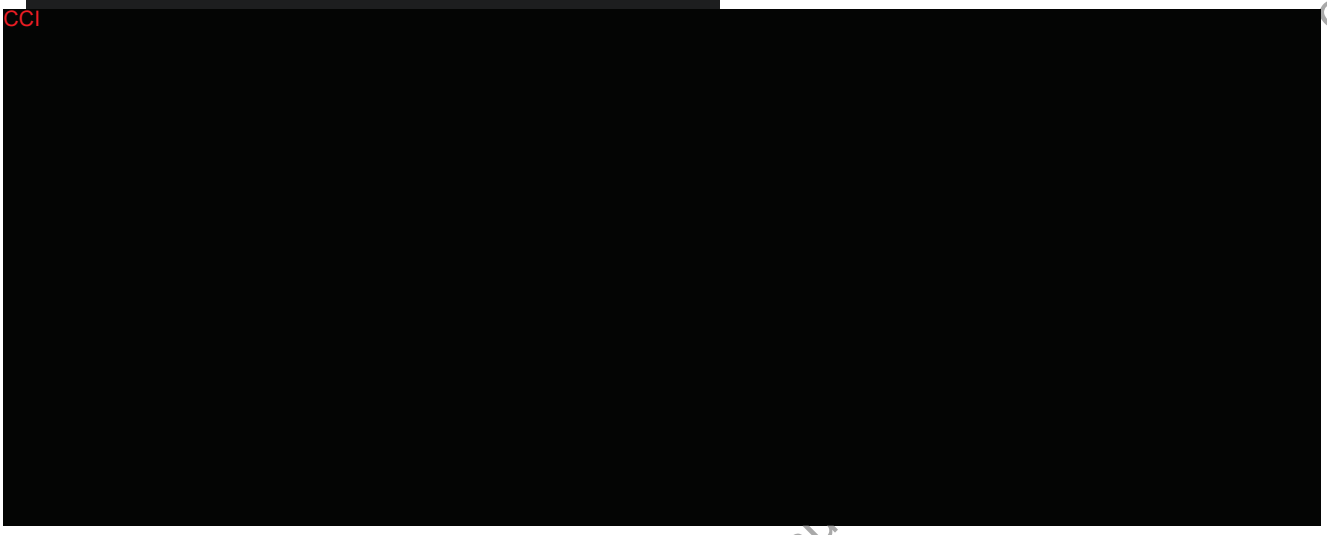

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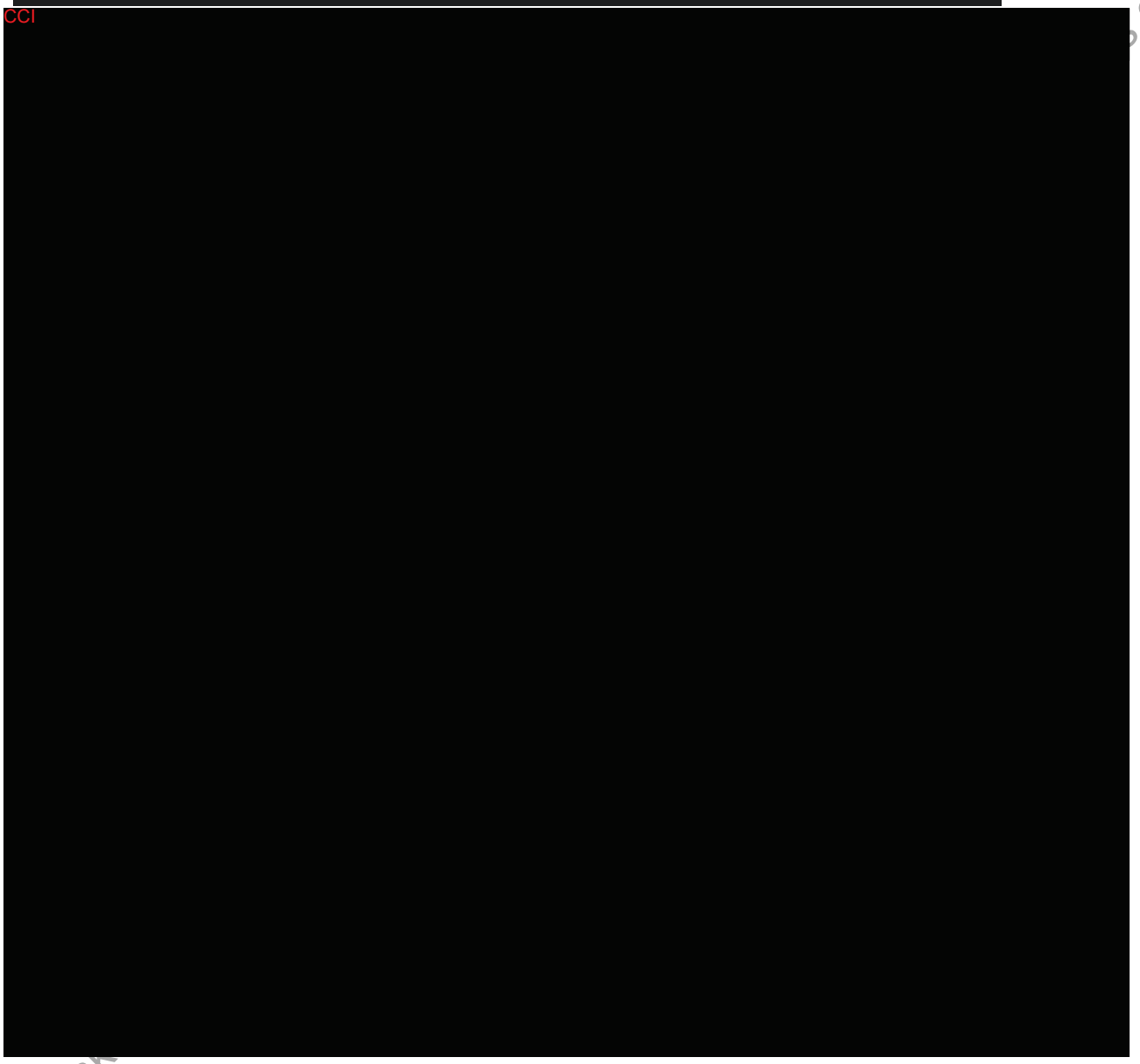

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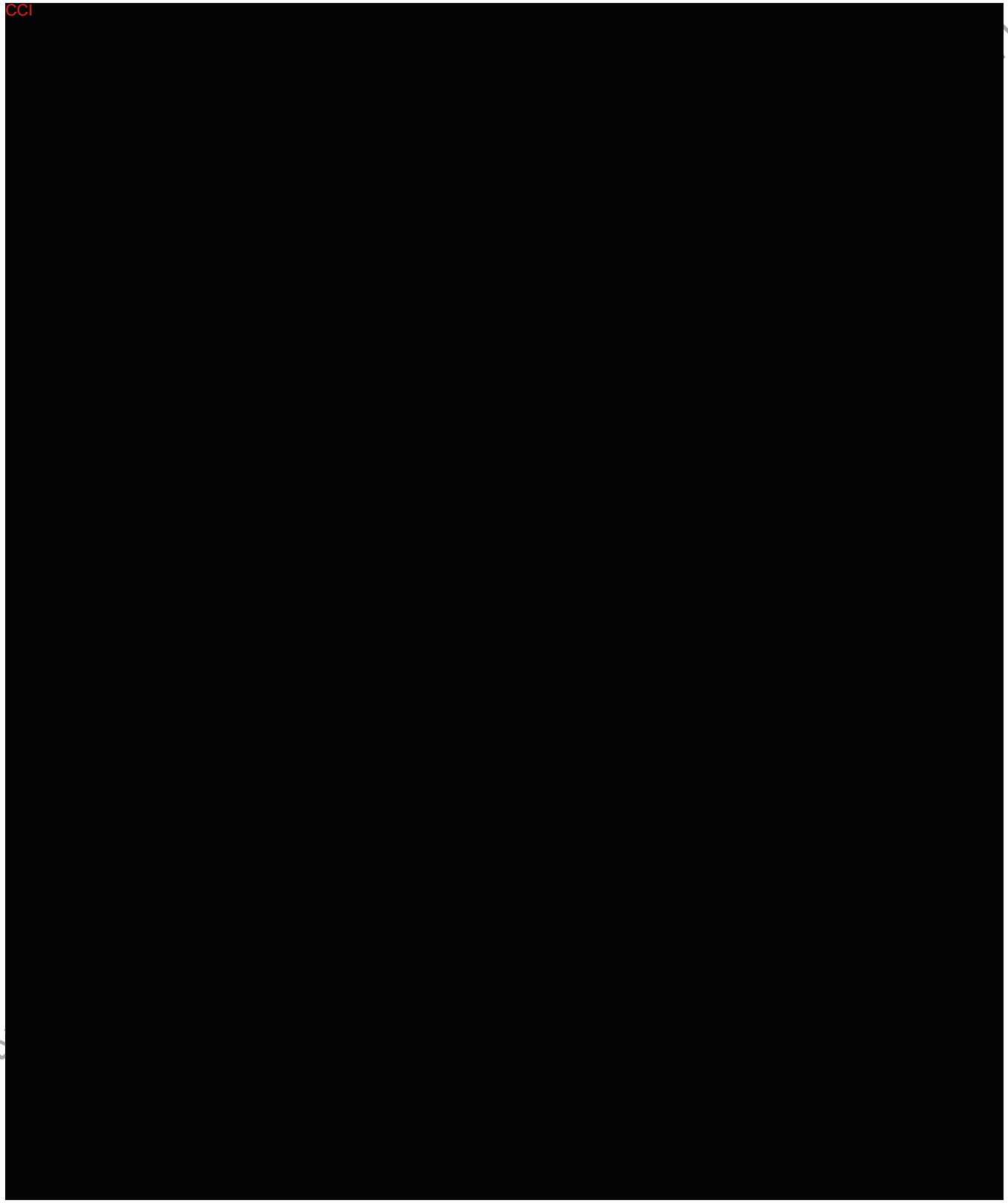

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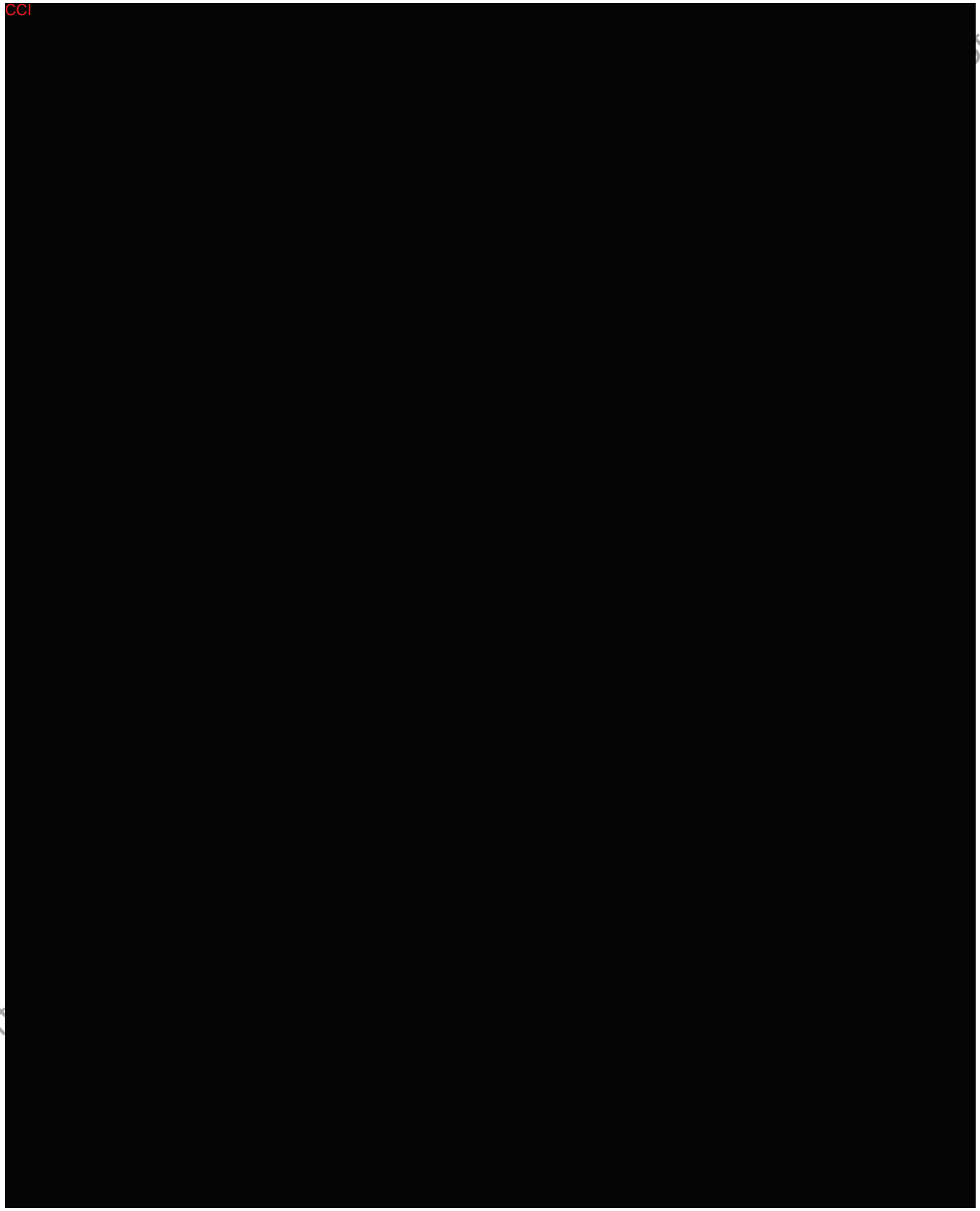

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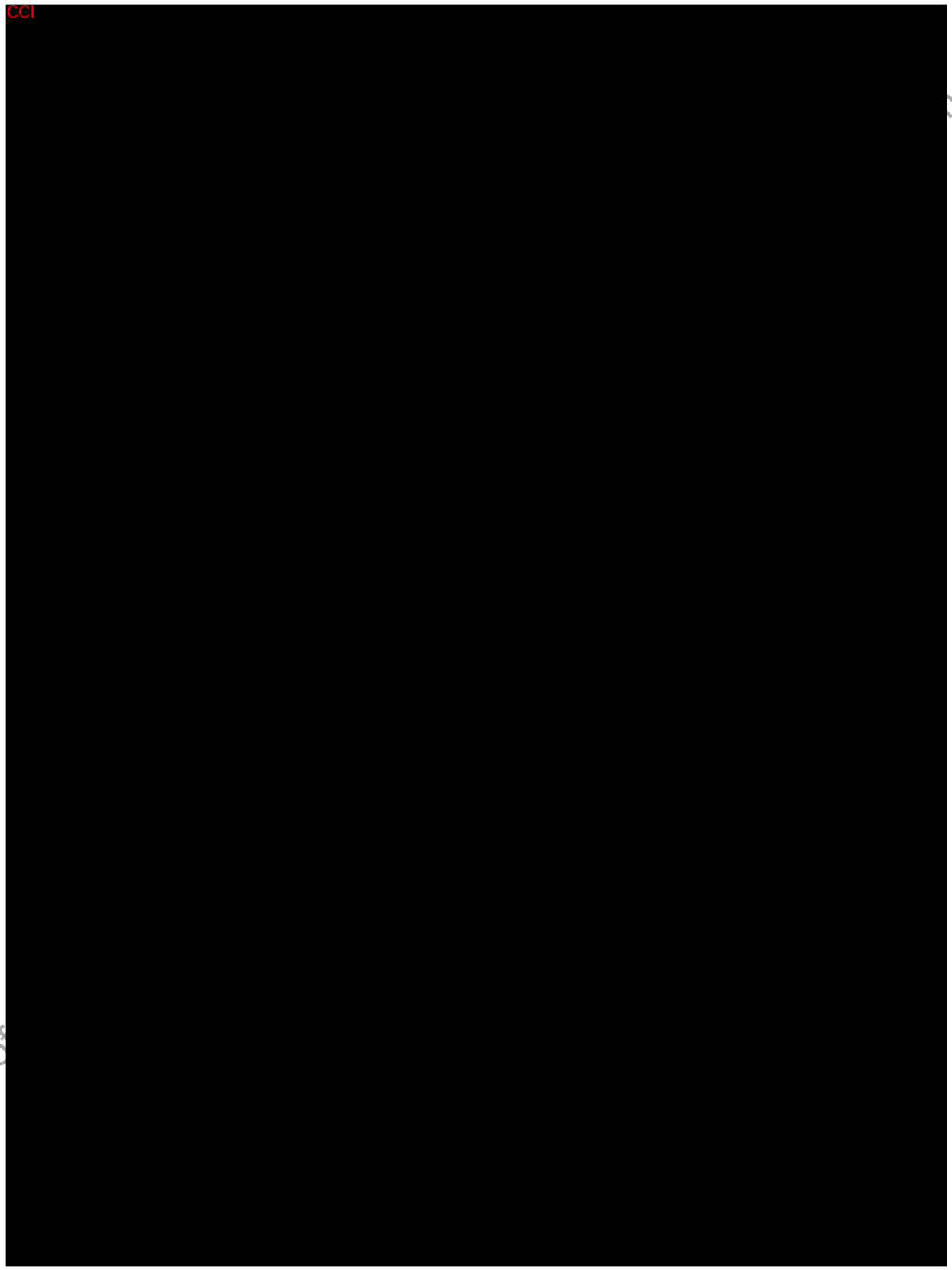

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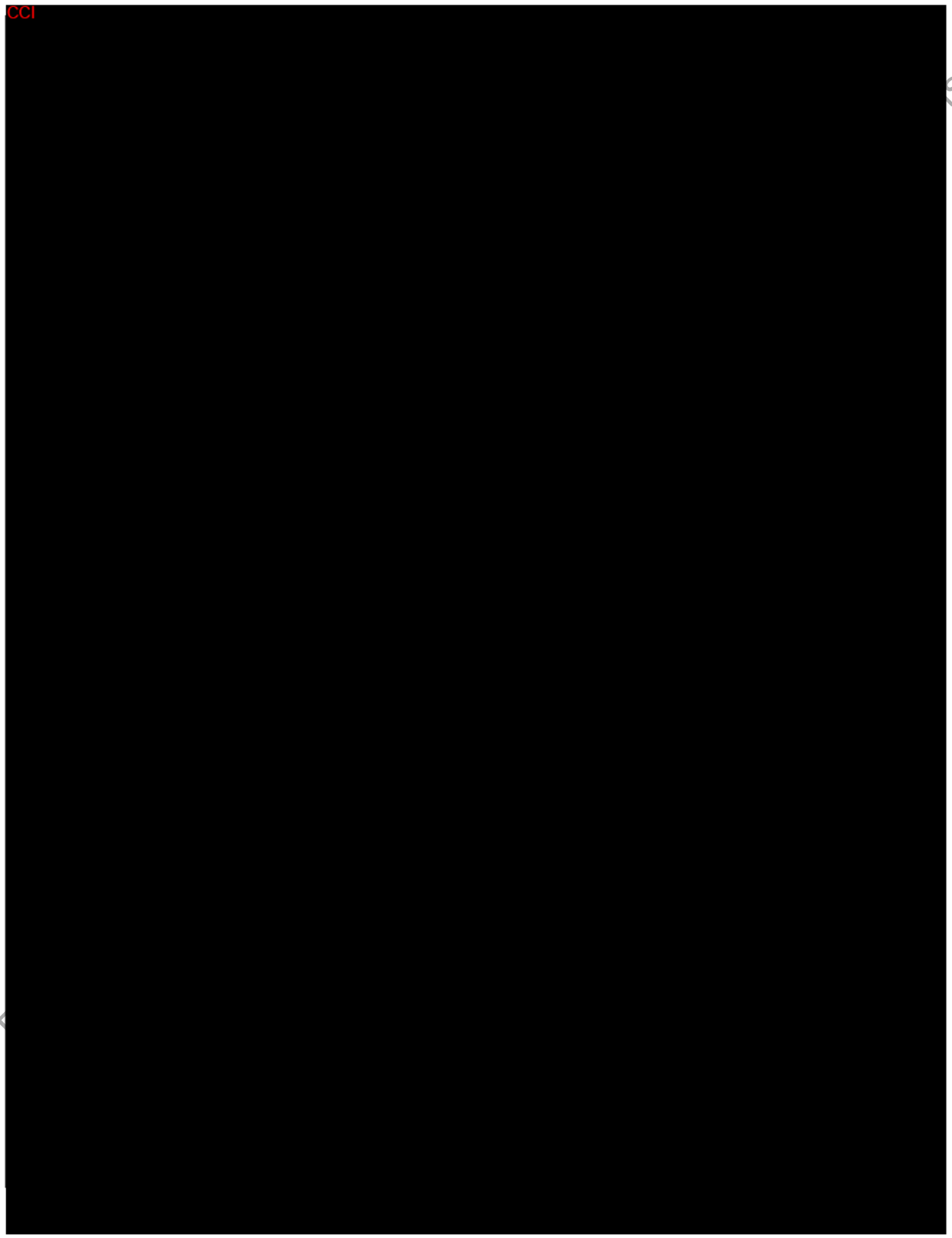

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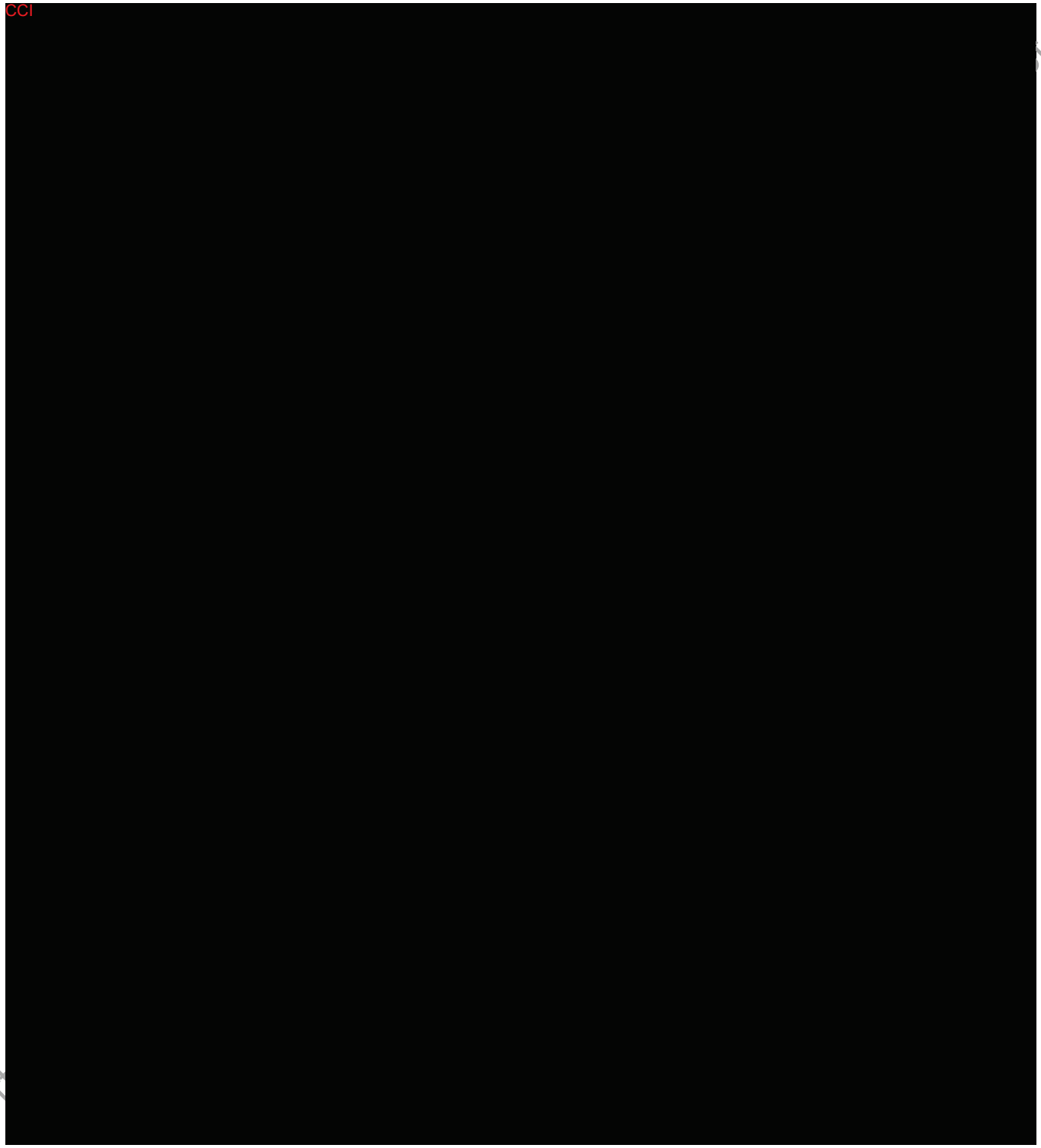

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