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

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

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

POST-AUTHORISATION SAFETY STUDY

PROTOCOL

Study title: A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study

Study number: Brigatinib-5007

Version number: 2.0, 17 July 2019

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

Study title: A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study

Study number: Brigatinib-5007

Version number: 2.0, 17 July 2019

Sponsor

PPD

Head of Epidemiology
Takeda Pharmaceuticals International UK
61 Aldwych, London, United Kingdom

Signature

PPD

Date: 15 July 2019

Signature (QPPV or designated person)

PPD

EU QPPV
Takeda Pharmaceuticals International Co.
Vasagatan 7, 11120, Stockholm. Sweden

PPD

PPD

PPD

Date: 18 July 2019

Investigator

Name:

Address:

Signature

Date: _____

Study Information

Title	A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study
Protocol version identifier	2.0
Date of last version of protocol	07 February 2019
EU PAS register number	Pending
Active substance	Brigatinib (ATC Code L01XE43)
Medicinal product	Alunbrig
Product reference	EMEA/H/C/004248
Procedure number	Not Applicable
Marketing authorisation holder(s)	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
Joint PASS	No
Research question and objectives	This study aims to characterise the occurrence and risk factors of early-onset pulmonary events (EOPEs) and to assess the effectiveness of the brigatinib Patient Alert Card among anaplastic lymphoma kinase-positive (ALK+) advanced non-small cell lung cancer (NSCLC) patients newly treated with brigatinib in real-world practice. The primary objective of this study is to describe the occurrence of EOPEs in ALK+ advanced NSCLC patients treated with brigatinib in real-world practice. The secondary objectives of this study are: - to describe EOPEs risk factors; - to assess the effectiveness of the Patient Alert Card as a risk minimisation measure (i.e. receipt, understanding and use of the Patient Alert Card in patients treated with brigatinib).
Country(-ies) of study	This study will be conducted in, but not limited to, the following European countries: Austria, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Sweden, and the United Kingdom. Other countries may be selected sequentially depending on product availability.

Title	A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study
Author	PPD Senior Epidemiologist Takeda Pharmaceuticals International Co.

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
MAH Contact Person	PPD Regulatory Affairs Takeda Pharmaceuticals International UK PPD

1. TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ANNEXES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALK+	Anaplastic Lymphoma Kinase-Positive
CEVA	Clinical Event Validation and Adjudication
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOPE	Early-Onset Pulmonary Event
EU	European Union
ICF	Informed Consent Form
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-Small Cell Lung Cancer
PASS	Post-Authorisation Safety Study
PQI	Product Quality Issue
QC	Quality Check
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSR	Special Situation Report
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TKI	Tyrosine Kinase Inhibitor

3. RESPONSIBLE PARTIES

The Marketing Authorisation Holder has contracted the management of this study to IQVIA.

4. ABSTRACT

Title

A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study

Rationale and Background

At the request of European Medicines Agency (EMA), this Post-Authorisation Safety Study (PASS) is being undertaken to provide real-world evidence for the characterisation of the occurrence of early-onset pulmonary events (EOPEs) in the European Union (EU) setting and the effectiveness of the brigatinib Patient Alert Card in the anaplastic lymphoma kinase-positive (ALK+) advanced non-small cell lung cancer (NSCLC) patients treated with brigatinib in Europe.

Research Question and Objectives

This study aims to characterise the occurrence and risk factors of EOPEs and to assess the effectiveness of the brigatinib Patient Alert Card among ALK+ advanced NSCLC patients newly treated with brigatinib in real-world practice.

The primary objective of this study is to describe the occurrence of EOPEs in ALK+ advanced NSCLC patients treated with brigatinib in real-world practice.

The secondary objectives of this study are:

- to describe EOPEs risk factors
- to assess the effectiveness of the Patient Alert Card as a risk minimisation measure (i.e. receipt, understanding and use of the Patient Alert Card in patients treated with brigatinib)

Study Design

This is a prospective, observational, multi-centre, cohort study of ALK+ advanced NSCLC patients treated with brigatinib in real-world practice.

Patients will participate in the study for up to 42 days (6 weeks) following brigatinib treatment initiation.

Upon study enrolment, at baseline, information will be collected on demographics, NSCLC clinical features, metastatic locations and clinical management history, prior and concurrent cancer therapies, medical history (including history of pneumonitis/interstitial lung disease, radiation pneumonitis), concurrent morbidities (including concurrent pulmonary conditions not related to lung cancer, such as chronic obstructive pulmonary disease [COPD]), and other concurrent medications.

Assessment of EOPEs

Pulmonary events occurring between Day 1 to Day 14 post treatment initiation are considered an Adverse Event of Special Interest (AESI) for this study. Their occurrence can be reported at any time during the study period. The investigator will prospectively report to the Sponsor all new or worsening pulmonary events occurring in the first 14 days after brigatinib initiation reported by the patient during any clinic visits, phone calls or other contact with the patient during Day 1-14. To help ensure no pulmonary events are missed, the investigator should also retrospectively report any pulmonary events that occurred during Day 1-14 reported by the patient at their first routine follow-up appointment (typically within 4-6 weeks after the start of brigatinib as part of standard clinical practice). An independent adjudication committee will review all reported pulmonary events to determine if they meet protocol-defined endpoint criteria of EOPEs.

Assessment of the effectiveness of the risk minimisation measure via the Patient Alert Card questionnaire

The receipt, understanding and use of the Patient Alert Card will be assessed via a phone-based interview, that will take place 30 days (or up to 42 days in case of several interview attempts) after brigatinib treatment initiation. All patients, including those with no pulmonary symptoms/events reported, will be interviewed.

In the unlikely event that the patient voluntarily reports information on pulmonary symptoms during the phone interview to the interviewer, this will be transmitted immediately to the investigator. The investigator should contact the patient, if needed, to obtain all relevant information on this pulmonary event and an independent adjudication committee will review the information as necessary.

Population

The study population is adults aged 18 years or older with ALK+ advanced (stage III or IV) NSCLC who are initiating monotherapy with brigatinib in accordance with approved indication.

This study will be conducted in, but is not limited to, the following European countries: Austria, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Sweden, and the United Kingdom. Additional countries may be selected sequentially depending on product availability.

Variables

Assessment of EOPEs

- EOPEs
    - EOPEs include dyspnoea, hypoxia, pneumonia, and interstitial lung disease/pneumonitis (this is not an exhaustive list).

- All pulmonary events, defined as AESIs, occurring in the first 14-days post initiation of brigatinib will be reported by the investigator. An independent adjudication committee will review all reports of pulmonary events and adjudicate reported cases to determine if the defined endpoint criteria for EOPE are met.

- Patient demographics, including age, sex and country.
- ALK+ NSCLC characteristics, including the date of the first diagnosis, stage at diagnosis, TNM status and metastatic location(s).
- Clinical management and medical/medication history:
  - History of lung diseases (including interstitial lung disease, COPD, asthma, etc.) and pulmonary symptoms/events
  - History of other medical conditions, including cardiovascular conditions and autoimmune disease
  - Previous treatment for ALK+ NSCLC, including radiotherapy, systemic anticancer therapy, and Tyrosine Kinase Inhibitors (TKIs)
  - Previous use of drugs associated with lung toxicity (including methotrexate, bleomycin, nitrofurantoin, and amiodarone)
  - Other concurrent or recent medication such as intravenous antibiotics
  - Hospitalisation, surgery, or radiotherapy in 180 days before the start of brigatinib
- Vitals/lifestyle, including body mass index, smoking status and alcohol use
- Treatment exposure of brigatinib (initial prescription details, any dose modification, reason for treatment discontinuation, and switch to another ALK-targeted TKI)

<u>Assessment of the effectiveness of the risk minimisation measure via the Patient Alert Card questionnaire</u>

- Did the patient receive the Patient Alert Card?
- Did the patient read the Patient Alert Card?
- Did the patient understand the Patient Alert Card?
- Did the patient visit any healthcare professionals during 30 days after starting brigatinib (hospitalisations, emergency room visits, visits to general practitioners or any other healthcare professionals)?
  - If yes, how many times? If for a hospital stay, for how long?

- Was the hospital stay, emergency room visit or healthcare professional visit because of pulmonary symptoms/events?
- Did the patient inform the healthcare professionals that they were taking brigatinib?
- Did the patient show the Patient Alert Card to the healthcare professionals?
- Did the healthcare professionals read the Patient Alert Card?

Data Sources

Primary data collection:

- The investigators will collect information on baseline variables at study initiation.
- The investigators will collect information on pulmonary events occurring during the first 14 days post treatment initiation.
- Patients will report via a phone interview whether they received, understood and used the Patient Alert Card.

Study Size

This study plans to enrol 120 patients treated with brigatinib. The sample size is based on the number of available patients with ALK+ advanced NSCLC who have progressed on from or are intolerant to crizotinib and likely to initiate brigatinib during the period of this study. The study is sufficiently powered to determine an incidence rate of 6.4% (8 confirmed cases of EPOE) with a precision of ± 4.4%.

If the number of confirmed cases of EOPE in this study is fewer than 8, recruitment may continue until 180 patients are recruited or 8 cases of EOPE have been confirmed by the independent adjudication committee or reaching 19 February 2024, whichever occurs first.

Data Analyses

Assessment of EOPEs

Descriptive statistics will comprise the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables; as well as number and percent for categorical variables. The distributions of key variables will be summarized by descriptive statistics for all patients treated with brigatinib, as well as for the subgroups, defined by the number of previous lines of ALK-targeted TKI treatment or by duration from the date of previous TKI discontinuation to the date of brigatinib initiation.

For the assessment of EOPE occurrence, the 14-day incidence of EOPEs will be calculated for the study cohort and subgroups. The incidence is calculated as the number of patients with an adjudicated EOPE, divided by the number of patients at risk.

Logistic regression modelling will be used to identify potential risk factors for EOPEs, with magnitude of risk for each risk factor quantified using odds ratio estimates.

Assessment of the effectiveness of risk minimisation scheme via the Patient Alert Card questionnaire

Data will be analysed using descriptive statistics. Frequency distributions of responses to each question from the questionnaire will be presented. Success of the risk minimisation measure will be quantified according to the proportion of positive (for Patient Alert Card receipt and use) or correct answers (for Patient Alert Card understanding) given by the patient.

Milestones

Anticipated date for recruitment of the first patient into the study is dependent on several factors, including date of drug reimbursement, date of commercial availability of brigatinib within participating countries, and granting of study approvals by ethics committees and national agencies. The anticipated recruitment timelines shown below are based on conservative assumptions, and actual dates of achieving recruitment milestones may be in advance of these dates.

Milestone	Planned date
First Patient In	Q2 2020
Last Patient In	Q1 2024
Last Patient Out	Q1 2024
Database Lock	Q2 2024
Study report to EMA	Q4 2024

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
0 (Version 1.0)				Initial draft protocol
1 (Version 2.0)		Multiple sections		Update following EMA/PRAC review of protocol

6. MILESTONES

Milestone	Planned date	Actual date	Comments
First Patient In	Q2 2020		
Last Patient In	Q1 2024		
Last Patient Out	Q1 2024		
Database Lock	Q2 2024		
Study Report to EMA	Q4 2024		

7. RATIONALE AND BACKGROUND

7.1 Background

7.1.1 Non-Small Cell Lung Cancer

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 European Union (EU). In the EU, lung cancer is ranked as the fourth most-frequent cancer; approximately 313,000 new cases were diagnosed in 2012, with 268,000 deaths reported in the year 2012 (1).

NSCLC is the most prevalent histologic class of lung cancer, accounting for nearly 85% of all lung cancers (3-5). Most patients with lung cancers are diagnosed at advanced stages and at higher risks for metastasis. In England in 2014, half of the lung cancers were diagnosed at stage IV, and approximately 70% of the patients had advanced lung cancer (stage III and IV) (6). The prognosis in patients with advanced lung cancer is very poor. One-year survival for patients with metastatic lung cancer was only 15% for men and 19% for women (7).

NSCLC is further subdivided by tumour oncogenic profile into several subtypes, such as ALK-rearranged NSCLC (commonly called ALK+ NSCLC). Estimates of the frequency of ALK rearrangement in the overall population of NSCLC patients range from 2% to 7% (8-9), representing approximately 5,800 to 20,000 ALK-rearranged NSCLC patients in the EU in 2016. ALK rearrangements are more common among patients with adenocarcinoma histology, never or light smokers, women, and younger patients (10-12).

Several ALK-targeted TKIs (i.e., ALK inhibitors) have been approved to treat ALK+ advanced NSCLC in the EU, including crizotinib, alectinib, and ceritinib. Recent clinical studies have demonstrated that patients with locally advanced or metastatic ALK+ NSCLC have a better prognosis when treated with the ALK inhibitors than with chemotherapy.

7.1.2 Brigatinib

Brigatinib is a novel TKI that targets ALK, c-ros oncogene 1, and insulin-like growth factor 1 receptor. Among these, brigatinib is most active against ALK. Brigatinib inhibits autophosphorylation of ALK and ALK mediated phosphorylation of the downstream signalling protein STAT3 in *in vitro* and in *in vivo* assays.

In 2018, the European Commission granted marketing authorization for ALUNBRIG® (brigatinib) as a monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib (13).

The efficacy and safety of brigatinib have been demonstrated in a Phase II randomized, open-label study (ClinicalTrials.gov number, NCT02094573) (14, 15). This study enrolled 222 patients with crizotinib-refractory ALK+ NSCLC and randomized patients to receive either

brigatinib 90 mg once daily or brigatinib 180 mg once daily with a 7-day lead-in at 90 mg. Both brigatinib regimens of 90 mg once daily and 180 mg once daily showed substantial antitumor activity with an objective response rate of 51% and 56% as assessed by independent review committee, respectively. Brigatinib was associated with a median progression-free survival of 9.2 and 16.7 months at 90 mg once daily and 180 mg once daily, respectively (15). Among ALK+ NSCLC patients with measurable brain metastases at baseline, brigatinib 180 mg once daily yielded a better objective response rate (61%) than brigatinib 90 mg once daily (43%). The safety of brigatinib was acceptable in both dose groups (15). The most common any grade treatment-emergent adverse events were nausea, diarrhoea, headache, and cough (14). Fourteen of 219 (6%) patients overall had pulmonary adverse reactions with early-onset (all grades). Seven (3%) patients had grade ≥3 events, all of whom permanently discontinued brigatinib after the pulmonary event (14). Nevertheless, in the Phase III trial (ClinicalTrials.gov number, NCT02737501) in which 275 patients with ALK+ advanced NSCLC were randomized to receive either brigatinib 180 mg once daily or crizotinib 250 mg twice daily as the front-line therapy, the first interim analysis showed a lower incidence of early-onset interstitial lung disease/pneumonitis of any grade (3%) in patients who received brigatinib (16).

7.2 Study Rationale

Interstitial lung disease/pneumonitis is a known adverse drug reaction to medications that target ALK+ NSCLC, including crizotinib (17), ceritinib (18), alectinib (19) and brigatinib (13). In addition to interstitial lung disease/pneumonitis, several other respiratory AEs, such as cough, dyspnoea, and hypoxia occurred during clinical trials within approximately 7 days of starting brigatinib (median time to onset: 2 days). This group of respiratory symptoms/events occurring shortly after initiating brigatinib therapy have been termed EOPEs. Symptoms of these pulmonary adverse events can be confused with symptoms of the underlying lung cancer and other lung diseases in ALK+ advanced NSCLC patients. Thus, it is challenging to ascertain causality for EOPEs. The contribution of brigatinib to these events is not always certain but cannot be excluded.

As part of European risk minimisation activities, patients initiating treatment with brigatinib are provided with a Patient Alert Card by the healthcare professionals who prescribe brigatinib. The Patient Alert Card is intended to be shared by the patient with other healthcare professionals (outside of the oncology/lung team that are treating the patient) to alert them of the possibility of EOPEs.

This Post-Authorisation Safety Study (PASS) is being undertaken to further investigate EOPEs in ALK+ advanced NSCLC patients, treated with brigatinib in Europe in standard routine practice, and to assess the effectiveness of the Patient Alert Card as a risk minimisation measure.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to characterise the occurrence and risk factors of EOPEs and to assess the effectiveness of the brigatinib Patient Alert Card among ALK+ advanced NSCLC patients newly treated with brigatinib in real-world practice.

The primary objective of this study is to describe the occurrence of EOPEs in ALK+ advanced NSCLC patients treated with brigatinib in real-world practice.

The secondary objectives of this study are:

- to describe EOPE risk factors;
- to assess the effectiveness of the Patient Alert Card as a risk minimisation measure (i.e. receipt, understanding and use of the Patient Alert Card in patients treated with brigatinib).

9. RESEARCH METHODS

9.1 Study Design

This is a non-interventional, prospective, observational, multi-centre, single-arm cohort design study.

All patients receive standard of care, and all clinical management decisions including choice of the treatment regimen, are independent of participation in the study. The study has no additional diagnostics, procedures, or clinic visits, other than what a patient would receive as part of the routine standard of care. Brigatinib will be provided according to routine local practice.

Each participating investigator recruits consecutive patients under their care with ALK+ advanced NSCLC, for whom a decision has already been made to initiate or switch to brigatinib. Patients are enrolled after the decision to initiate or switch to brigatinib but prior to the start of brigatinib treatment.

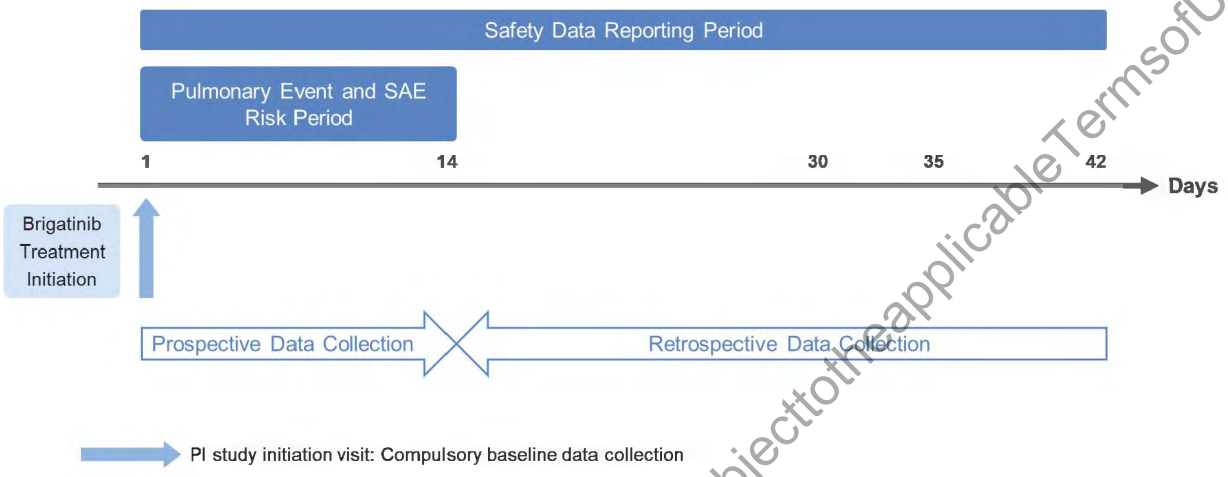
Following recruitment and completion of informed consent, the investigator will collect baseline information on patient's demographics, NSCLC clinical characteristics, medical history (including history of pneumonitis/interstitial lung disease, radiation pneumonitis), prior and concurrent cancer therapies, recent or concurrent morbidities (including pulmonary conditions not related to lung cancer, such as chronic obstructive pulmonary disease [COPD]) and concurrent medications.

Each patient will participate in the study for up to 42 days after starting brigatinib. Figure 1 describes the data collection for pulmonary events and serious adverse events (SAEs). Figure 2 describes the data collection for Patient Alert Card receipt, understanding and use.

Pulmonary events occurring between Day 1 to Day 14 post treatment initiation are considered as AESIs in this study. Their occurrence can be reported at any time during the study period. The investigator will prospectively report to the Sponsor all new or worsening pulmonary events occurring in the first 14 days after brigatinib initiation reported by the patient during any clinic visits, phone calls or other contact with the patient during Day 1-14. To help ensure no pulmonary events are missed, the investigator should also retrospectively report any pulmonary events that occurred during Day 1-14 reported by the patient at their first routine follow-up appointment (typically within 4-6 weeks after the start of brigatinib as part of standard clinical practice).

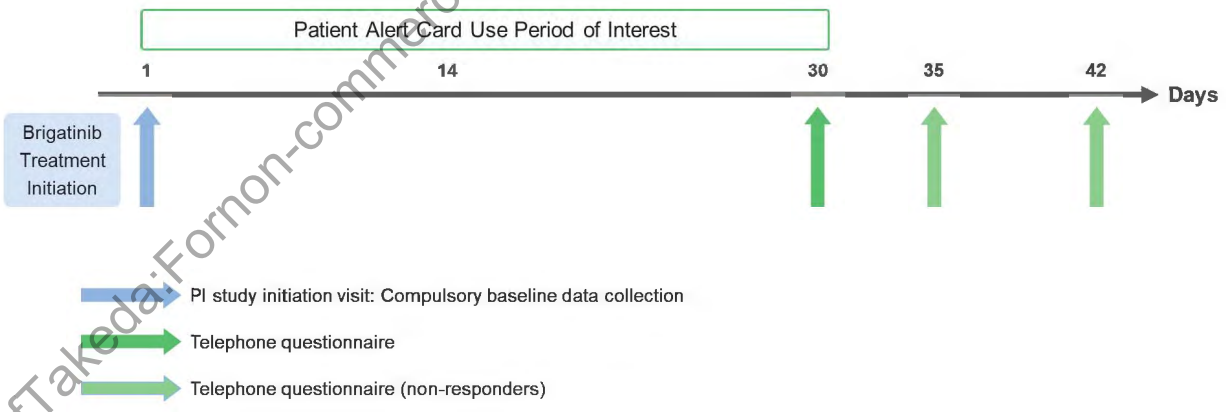
All participating patients, including those with no pulmonary events reported, will be asked to participate in a telephone interview to collect information on the receipt, understanding and use of the brigatinib Patient Alert Card in the 30 days after brigatinib initiation. The interview will use a closed-ended questionnaire and be administrated by trained interviewers in local language. The interview will be timed to be around Day 30 after brigatinib initiation. In case of failure to interview the patient, two further attempts to contact the patients will be timed for around Day 35 and Day 42 after brigatinib initiation.

Figure 1 Study design for pulmonary events and serious adverse events



PI = principal investigator; SAE = serious adverse event

Figure 2 Study design for Patient Alert Card receipt, understanding and use



PI = principal investigator

9.2 Setting

9.2.1 Study Population

The study population is adults aged 18 years or older with ALK+ advanced (stage III or IV) NSCLC who are initiating monotherapy with brigatinib in accordance with approved indication.

This study will be conducted in, but not limited to, the following European countries: Austria, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Sweden, and the United Kingdom. Additional countries may be selected sequentially depending on product availability.

9.2.2 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study. A patient must meet all of the following criteria to be eligible for recruitment in the study.

1. Signed informed consent by the patient or a legally acceptable representative, obtained before any study-related activities are undertaken.
2. Age ≥ 18 years.
3. Male and female patients.
4. Patients with ALK+ advanced (stage III or IV) NSCLC as determined by the healthcare professional who prescribes brigatinib.
5. Initiating monotherapy with brigatinib as per approved label.
6. Patients should be recruited on or before the day of the first dose of brigatinib.
7. Signed release form, by the patient or a legally acceptable representative, permitting abstraction of the patient's medical records at baseline and during participation in the study.

9.2.3 Exclusion Criteria

A patient who meets any of the following criteria is not eligible for recruitment in the study.

1. The patient is currently participating in or did participate in any interventional clinical trial within the previous 6 months in which treatment regimen and/or monitoring is dictated by a protocol.
2. Patients who received treatment with brigatinib previously.
3. Patients who will receive brigatinib in combination with any systemic anticancer therapy.

4. Pregnant and lactating women and women of child-bearing potential using hormonal contraception.

9.2.4 Selection of Study Sites

Oncologists and pulmonologists in participating countries treating ALK+ NSCLC patients, and who use brigatinib in their routine clinical care, and are interested in participating as investigators will be considered for inclusion, subject to fulfilling minimum site selection criteria, until site and patient recruitment targets are met.

As ALK+ NSCLC is a rare type of lung cancer, it is anticipated that 30-50 sites will be required, each recruiting 2-3 ALK+ NSCLC patients, to reach the sample size target of 120 patients. Additional sites may be added if recruitment is low. To avoid over-representation of any one country, the number of sites per country will be approximately proportional to the national population.

9.2.5 Recruitment of Patients

Study sites will recruit participants from patients attending their clinics. The decision to initiate or switch a patient to brigatinib is independent of participation in the study. Patients are recruited to the study only after the healthcare professional/patient has decided to proceed with brigatinib.

9.2.6 Patient Follow-Up

Patient follow-up is based on routine clinical practice. Information on pulmonary events reported by the patient during any clinic visit, phone calls or other contacts with the patient during Day 1-14 will be prospectively collected and reported by the investigator.

To help ensure no pulmonary events are missed, the investigator should also retrospectively collect any pulmonary events that occurred during Day 1-14 reported by the patient at the first routine follow-up appointment (typically 4-6 weeks after start of brigatinib as part of routine clinical practice).

For patients who develop a pulmonary event within 14 days after initiation of brigatinib, the investigator will follow-up to collect data on the outcome of the event, even if this extends beyond the end of the study period.

All patients, irrespective of pulmonary event occurrence status, will be contacted around 30 days after brigatinib initiation to complete the Patient Alert Card questionnaire. The patients will be contacted again up to 2 times in case of non-response, around Day 35 and around Day 42.

Patient follow-up in the EOPE component of the study will cease at the earliest of any of the following:

- First routine follow-up appointment after Day 14 (typically within 4-6 weeks after the start of brigatinib therapy as part of standard clinical practice)

- Patient lost to follow-up
- Patient withdrawal from study
- Patient death
- Patient enters another NSCLC clinical trial

Patient follow-up in the Patient Alert Card assessment component of the study will cease at the earliest of any of the following:

- Completion of Patient Alert Card questionnaire
- End of the 42-day study period
- Patient lost to follow-up
- Patient withdrawal from study
- Patient death
- Patient enters another NSCLC clinical trial

9.2.7 Patient Withdrawal from the Study

Patients may discontinue participation in the study at any time. Withdrawal will not affect their medical care or access to treatment. This study protocol allows investigators to modify or discontinue a patient's TKI therapy during the overall 42-day study period without having to withdraw the patients from the study.

All information already collected as part of the study will be retained for analyses. No further efforts will be made to obtain or record additional information regarding the patient and outcomes after study withdrawal. The primary reason for study withdrawal should be recorded in the electronic case report form (eCRF). Patients who withdraw from the study will not be replaced.

9.2.8 Patient Death

If a patient death occurs during the 14 days post brigatinib initiation, the investigator must complete a SAE report form, and use best effort to obtain information on date, cause and causality assessment of death.

9.3 Variables

9.3.1 Exposure Variable

- Brigatinib line of therapy
- Treatment exposure:
    - prescribed daily dose of brigatinib

- dose escalation from 90 mg once daily to 180 mg once daily, if applicable
- dose modification, if applicable
- if treatment discontinuation: reason for treatment discontinuation or switch (including switch to another ALK-targeted TKI with information on which TKI)

9.3.2 Outcome Variable

Assessment of EOPEs

The primary outcome variable of this study is the occurrence of adjudicated EOPEs occurring within 14 days after the initiation of brigatinib. EOPEs include dyspnoea, hypoxia, pneumonia, and interstitial lung disease/pneumonitis (this is not an exhaustive list). Their occurrence can be reported at any time during the study period. The investigator will prospectively collect all new or worsening pulmonary events occurring during Day 1-14 after initiation of brigatinib reported by the patient during any clinic visits, phone calls or other contact with the patient during Day 1-14. To help ensure no pulmonary events are missed, the investigator should also retrospectively report any pulmonary events that occurred during Day 1-14 reported by the patient at their first routine follow-up appointment (typically within 4-6 weeks after start of brigatinib as part of standard clinical practice).

On the report form, the investigator is asked to provide the diagnosis and description of the pulmonary events (with grade), and to provide any relevant clinical information, including laboratory results, imaging tests (reports and copies of images), and histopathology results. Pulmonary events, as reported by the investigator, will be coded to the Medical Dictionary for Regulatory Affairs (MedDRA) Preferred Terms. An independent adjudication committee will review the reports of all pulmonary events together with supporting source documents, and categorise these events as cases of EOPE or not, based on the following definition:

The adjudication criteria of EOPE:

1. Presence of a temporal relationship (defined as signs/symptoms beginning within the first 14 days following brigatinib initiation).
2. The case had evidence of a pneumonitis-like process (e.g., hypoxia or dyspnoea along with supportive imaging or pathology findings, such as ground glass opacities on computed tomography/x-ray, or diffuse alveolar damage on histopathology).
3. Determination that other aetiology was unlikely (e.g., infectious, tumour).

Where incomplete information is provided, the investigator will be contacted to obtain all relevant information.

Assessment of the effectiveness of the risk minimisation scheme via the Patient Alert Card questionnaire

The secondary outcome variable of this study is whether the Patient Alert Card was successful. The data will be collected from the patient via a questionnaire. The risk

minimisation measure will be considered successful if at least a 75% success rate is reached in 2 out of the 3 criteria listed below.

Criteria 1: Did the patient receive the Patient Alert Card?

- Criteria 1 will be considered successful if 75% of patients answer 'yes'.

Criteria 2: Did the patient read the Patient Alert Card?

- Criteria 2 will be considered successful if 75% of patients answer 'yes'.

Criteria 3: Did the patient understand the Patient Alert Card?

- Criteria 3 will be considered successful if 75% of patients answer correctly to the following questions:
    - Why was Alunbrig given to the patient?
        - To slow down the growth and spread of lung cancer? (CORRECT)
        - To slow down the growth and spread of pancreatic cancer? (WRONG)
        - To slow down the growth and spread of bone cancer? (WRONG)
    - When experiencing difficulty breathing, should the patient:
        - Ignore the symptoms as they are normal? (WRONG)
        - Call his/her doctor straight away? (CORRECT)
        - Call his/her doctor after 3 days? (WRONG)
    - You cannot experience high temperature (fever) when taking Alunbrig
        - True (WRONG)
        - False (CORRECT)
    - You can expect pulmonary adverse reactions associated with Alunbrig to occur within the first 7 days of starting the treatment?
        - True (CORRECT)
        - False (WRONG)

Data on the use of the Patient Alert Card will be collected from the patient via these questions:

- Did the patient go to the hospital (at least one overnight stay) / visit the emergency room / a general practitioner / visit the oncologist / lung specialist / any doctor other than general practitioners or other healthcare professionals (other than the oncology / lung team) in the 30 days after starting brigatinib?
    - If yes, how many times?
    - If hospitalised, for how long?

- Was the hospitalisation / emergency room visit / doctor visit because of pulmonary symptoms / events?
- Did the patient inform the healthcare professional that he/she was taking brigatinib?
- Did the patient show the Patient Alert Card to the healthcare professional?
- Did the healthcare professional read the Patient Alert Card?

9.3.3 Risk Factors and Other Variables

Baseline data

- Demographic data: age, sex, and country
- Lifestyle data: smoking status (current smoking: yes/no; ever smoked: yes/no, pack-years), alcohol use, and body mass index
- Clinical history of lung cancer:
  - Initial and metastatic diagnosis date of ALK+ NSCLC
  - Lung cancer stage or TNM status at initial diagnosis
  - Lung cancer stage or TNM at the time of initiating brigatinib
  - Current metastatic location(s)
  - Current cancer related symptoms
  - All previous lung cancer treatment
    - Surgery: date and types
    - Radiotherapy: date, types (e.g., stereotactic body radiation therapy or others), anatomic locations, and concomitant use with chemotherapy
    - Systemic anticancer therapy, TKI, and other therapies: anticancer agent names and start/end dates
  - Time since discontinuation of the last TKI
- Pulmonary history:
  - History of interstitial lung disease/pneumonitis any time prior to initiation of brigatinib
    - Cause of interstitial lung disease/pneumonitis: drug-related, radiation, or other causes.
  - Pulmonary condition or disease in 180 days prior to brigatinib initiation, including diagnosis date, laboratory test date and test results (if available):
    - Dyspnoea

- Hypoxia
- Pneumonia
- Pulmonary embolism
- COPD
- Asthma
- Chronic bronchitis
- Other pulmonary disease

- Other medical history in 180 days prior to brigatinib initiation, such as:
  - Heart and vascular disease: chronic heart disease, pulmonary heart disease, ischemic heart disease, and cerebrovascular disease.
  - Gastroesophageal reflux disease
  - Autoimmune diseases: scleroderma, rheumatoid arthritis, lupus, and Sjogren's syndrome
- Medication in 180 days prior to brigatinib initiation
  - Use of drugs with known lung toxicity, including start/stop dates, dose, frequency and route of administration:
    - Chemotherapy: methotrexate, cyclophosphamide, and bleomycin
    - Heart medications: amiodarone and propranolol
    - Antibiotics: nitrofurantoin and ethambutol
    - Anti-inflammatory drugs: rituximab, sulfasalazine, and TNF-alpha blockers
  - Use of intravenous antibiotics
- Concurrent medication to brigatinib initiation
  - Use of drugs with known lung toxicity, including start date, dose, frequency and route of administration:
    - Chemotherapy: methotrexate, cyclophosphamide, and bleomycin
    - Heart medications: amiodarone and propranolol
    - Antibiotics: nitrofurantoin and ethambutol
    - Anti-inflammatory drugs: rituximab, sulfasalazine, and TNF-alpha blockers
  - Use of intravenous antibiotics
- Other hospitalisation, surgery, or radiotherapy in 180 days prior to brigatinib initiation

9.4 Data Sources

9.4.1 Assessment of EOPEs

The investigators will provide information on baseline variables and any pulmonary events occurring during Day 1-14. Information on pulmonary events will be recorded by the investigator in the eCRF within 1 working day of their awareness of the pulmonary event.

9.4.2 The Patient Alert Card Questionnaire

Patients will be administered the Patient Alert Card questionnaire by phone around Day 30. Non-responders will be re-contacted around Day 35, and if necessary around Day 42 to complete the questionnaire.

9.5 Study Size

The purpose of this study is to provide additional real-world data on pulmonary safety to supplement the data generated from the Phase II trial upon which marketing approval was granted. This study plans to enrol 120 patients initiating brigatinib. The sample size is not based on statistical power consideration but on the anticipated number of available patients with advanced or metastatic ALK+ NSCLC who have progressed or were intolerant to crizotinib and initiate brigatinib. There are multiple competing clinical trials in this patient population, and given this environment, it is unlikely to recruit a larger number of patients and conduct a better powered study.

The Phase II registration trial of brigatinib showed an approximately 6.4% incidence for EOPEs in patients who progressed on crizotinib. Thus, it is expected to observe 8 cases of EOPE among 120 patients treated with brigatinib. Table 1 presents the expected number of events and 95% confidence intervals for a range of incidence estimates, based on a sample of 120 patients treated with brigatinib and an alpha of 5%.

Table 1 Expected number of EOPEs and 95% confidence interval in a sample of 120 patients treated with brigatinib

EOPE Incidence	Expected Number of EOPEs	Expected 95% Confidence Interval of EOPE Incidence
3%	3.6	0-6.1%
5%	6.0	1.1-8.9%
6.4%	**7.7**	**2.0-10.8%**
7%	8.4	2.4-11.6%
9%	10.8	3.9-14.1%

EOPEs: early onset pulmonary events

It is important that an adequate number of EOPE cases are observed in this study to enable EOPE to be characterised. If the observed EOPE cases in this study are fewer than 8 confirmed cases, patient recruitment may continue until 180 patients are recruited, or 8 cases

of EOPE have been confirmed by the independent adjudication committee, or reaching 19 February 2024, whichever occurs first.

9.6 Data Management

All data collected in this study will be stored in accordance with local laws and regulatory requirements.

Electronic data collection will be performed using eCRFs. Sites will enter data into the electronic data capture (EDC) system. The system used for capturing patients' data complies with industry standards and regulatory expectations for software developers and service providers within the global regulatory environment (United States [US] 21 CFR Part 11, EU Commission Directive 2005/28/EC). The platform is a secure, easy to use and reliable web-based EDC platform for the collection and reporting of clinical data. Patients will be identified using a study identification number assigned to them when they enrol in the study. The investigator and site staff will receive training on recording the data on the eCRFs using the EDC system. Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with the study's data entry guidelines. The Investigator is responsible for ensuring that accurate data are entered into the eCRFs in a timely manner. Online logic checks will be built into the system, so that missing or illogical data are not submitted. If inconsistent data persist, queries may be issued electronically to the study site and answered electronically by site staff. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the investigator's approval of any data changes in the eCRF will be recorded.

The investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on patient data, and a password that together will represent a traditional handwritten signature.

All submitted eCRFs will be checked for missing information and queries will be generated to prevent the occurrence of most missing data, with special focus on completeness of pulmonary events and drug exposure. All reported events will be coded, using MedDRA Version 22.0 or later. Drug exposures will be coded to the World Health Organization Drug Dictionary. A computer assisted telephone interview will be administered to the patients using a platform complying with the exact same requirements described above for eCRF. Patient personal contact information will be stored separately from patient medical information.

9.7 Data Analysis

An overview of statistical analyses is provided below. Further details on analyses, including complete analytical specifications and rules to handle missing data will be described in the

statistical analysis plan (SAP). The SAP will be prepared for any analysis and will be finalized and approved prior to database lock.

All the analysis will be performed using SAS 9.4 or higher statistical software (SAS Institute Inc., Cary, North Carolina, USA).

9.7.1 Assessment of EOPEs

The data analyses of this study begin with a description of the study population by patient demographics, cancer characteristics, pulmonary conditions, the baseline variables listed in Section 9.3.3, and clinical management for the adjudicated cases of EOPE. Descriptive statistics will comprise the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables; as well as number and percent for categorical variables. Descriptive analysis will be performed for all the patients treated with brigatinib, as well as for the following subgroups:

- Subgroups defined by the number of previous lines of TKI therapy
- Subgroups defined by duration from the date of previous TKI discontinuation to the date of brigatinib initiation
- Subgroups of patients who developed EOPEs in 14 days after brigatinib initiation

The 14-day incidence of EOPEs will be calculated for all patients treated with brigatinib and the subgroups. The incidence is calculated as the number of patients with an adjudicated EOPE divided by the number of patients at risk.

The 42-day study duration is relatively short for loss to follow-up, and a small number of patients who are censored before the end of follow-up is expected. If necessary, more sophisticated statistical methods to deal with competing risks will be implemented to calculate the incidence.

The association of potential risk factors with EOPEs will be evaluated by univariable logistic regression models and will be quantified using odds ratios with 95% confidence intervals. Given an anticipated small number of EOPEs observed in this study, the multivariable model may not be applicable. If applicable, variables that are strongly associated with EOPEs in the univariable models will be entered into the multivariable model. Backwards eliminations will be employed to remove all non-significant variables.

9.7.2 The Patient Alert Card Questionnaire

The analysis of the Patient Alert Card questionnaire will be descriptive in nature, to evaluate the effectiveness of the Patient Alert Card in patients treated with brigatinib. The data will be reported as descriptive statistics for the survey administration, study population, and survey questions. Frequency distributions of responses to each question (the number of respondents who give each answer or response option to each question or response option) will be presented. Analysis will provide information on:

- The receipt of the Patient Alert Card
- Whether the Patient Alert Card was read
- Whether the Patient Alert Card was understood
- Whether the Patient Alert Card was used (using healthcare utilisation data)

The data to be described will include:

- Number of the Patient Alert Card questionnaires performed
- Number of the Patient Alert Card questionnaires non-response calls
- Analyses may be stratified by variables of interest, including but not limited to:
  - Age
  - Sex
  - Country

9.8 Quality Control

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure the collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, eCRF pages, and on the use of the EDC system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse reactions, SAEs, and other information.

Monitoring will be performed to ensure that informed consent forms (ICFs) have been completed for all enrolled patients. Subsequently, escalated monitoring may be performed at selected sites as needed, according to the study Monitoring Plan. At monitoring visits, the progress of the study and any procedural or data issues will be discussed with the investigator and/or site staff. The investigator will make patient source documents available for review and will permit the Sponsor, representatives of the Sponsor, Independent Ethics Committee (IEC), or regulatory authorities to inspect the facilities and original records relevant to this study. The investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions as necessary.

9.9 Limitations of the Research Methods

9.9.1 Sample Size

ALK+ NSCLC is a rare disease and only a small number of patients in Europe are treated with brigatinib. The study will need to recruit 120 patients to observe 8 cases of EOPE. If the number of confirmed EOPE cases is fewer than 8 cases, patient recruitment may continue until 180 patients are recruited or 8 cases of EOPE have been confirmed by the independent adjudication committee or reaching 19 February 2024, whichever occurs first. A larger study

is not possible because of the small number of patients being treated with brigatinib. Although limited by a small sample size, this study will provide valuable real-world information about brigatinib safety regarding EOPE incidence and potential risk factors.

Given a small number of patients in the study and a small number of EOPE cases anticipated, the estimated incidence is likely to be imprecise with a wide confidence interval. The small number of cases is also likely to impact the risk factor analysis. However, the number of events should be sufficient for univariate analyses.

9.9.2 Selection Bias

In order to minimise selection bias, the investigators will attempt to consecutively enrol all patients who consent and meet the inclusion/exclusion criteria, regardless of health status or other considerations. Nonetheless, it is acknowledged that due to the low prevalence of the disease and the probable small number of events of interest that will be observed, a limitation will remain in the interpretation of data related to the significance of the values obtained.

9.9.3 Information Bias

The quality and completeness of pulmonary event reports can vary between the investigators. Information bias will be minimised by providing appropriate training on the required components and supporting information needed for pulmonary events, and by providing training on how this should be recorded in the eCRF page.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Informed Consent

Before any protocol-specified assessments are carried out, the investigator or designee will explain details of the protocol and study procedures to patients and/or their legally acceptable representative. Patients will be informed that they are free to withdraw from the study at any time.

Each patient, or legally acceptable representative, must sign an ICF, approved by the IEC, indicating their consent to participate. ICFs and assent forms will conform to the requirements of International Conference on Harmonisation E6 4.8, Principles of Good Clinical Practices. The original signed ICFs must remain in the patient's file in the clinic. Each patient will receive a copy of the signed ICF.

Each patient enrolled in the study, or a legally acceptable representative, must also sign a medical records release form permitting abstraction of medical data for entry in the study EDC system. Individual patient data included in the study database will be treated in compliance with all applicable laws and regulations regarding privacy protection.

10.2 Independent Ethics Committee Approval

Investigators will be required to obtain approval from the appropriate IEC, and will be responsible for maintaining all related documents, before enrolment of any patient into the study. The investigator is responsible for informing the IEC of the completion of the study and should provide any required study status and/or safety report(s).

10.3 Adherence to the Protocol

The study must be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the patient requires intervention. Any significant deviation from the protocol must be reported immediately to the Sponsor and the IEC.

10.4 Protocol Amendment

Any amendment to the protocol will be created by the Sponsor, and subsequently submitted by the site to the IEC and appropriate regulatory authority for approval. If the protocol amendment substantially alters the study design or increases the potential risk of discomfort to the patients, written consent for continued participation in the study must be obtained.

10.5 Retention of Patient Records

When the study is completed, the investigator must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigator will notify the Sponsor prior to moving or destroying any study documents.

10.6 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

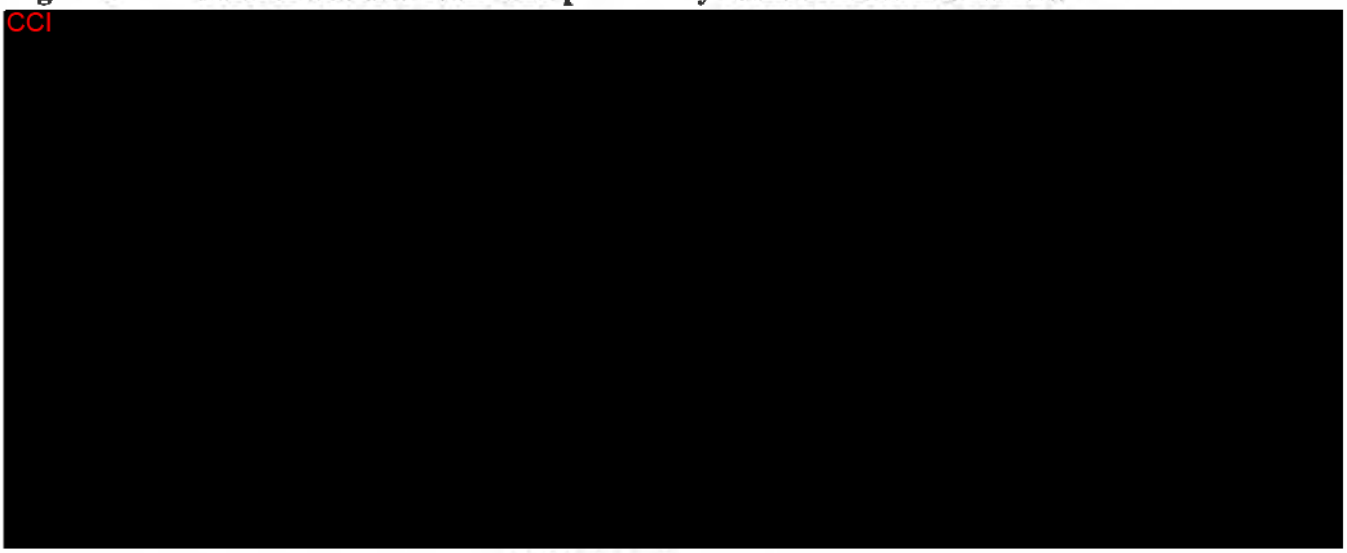
Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IEC, or local regulatory agency.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

SAEs (including all deaths) and pulmonary events, defined as AESIs in this study, occurring during the first 14 days after brigatinib initiation, will be collected for all participating patients, regardless of their relationship with brigatinib and reported to the Sponsor. Details of data collection and management are described below in Figure 3.

Given the high burden of morbidity in ALK+ advanced NSCLC patients, other non-serious AEs occurring during Day 1-14 will not be systematically collected in this study. Similarly, any SAE or AE occurring from Day 15 onwards will not be systematically collected in this study. However, the investigators may report these events to the local Takeda Pharmacovigilance department or national pharmacovigilance reporting system. These will be treated as spontaneous reports and independent of the study.

Figure 3 Serious adverse event and pulmonary event collection workflow



AE: adverse event; CEVA: Clinical Event Validation and Adjudication; EDC: electronic capture system; QC: quality control; SAE: serious adverse event.

Note: The study does not require the systematic collection and recording of other non-serious AEs.

11.1 Definitions

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to the discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

11.1.2 Serious Adverse Events

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

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above (examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that does not require an inpatient hospitalisation).

11.1.3 Adverse Events of Special Interest

An AESI is an AE (serious or non-serious) that is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate.

11.1.4 Adverse Drug Reaction

An adverse drug reaction is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

11.1.5 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labelling, or design of the product.

11.1.6 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Occupational exposure
- Use outside the terms of the marketing authorisation, also known as "off-label"
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

11.1.7 Relationship of an AE to Studied Drug(s)

- Related (Yes): An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), and for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also have contributed.
- Not related (No): An AE that does not follow a reasonable temporal sequence from the administration of the medication, vaccine or device and/or that can reasonably be explained by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments.

The assessment of the relationship of an AE to the studied drug(s) should be based on the investigator's consideration of all available information about the event, including temporal

relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative aetiology (e.g., underlying illness, concurrent conditions, concomitant treatments).

11.2 Collection and Recording of SAEs and Pulmonary Events

Collection and recording of SAEs and pulmonary events will commence once the study participant has provided informed consent. The investigator should notify Takeda within 1 working day of becoming aware of a pulmonary event and/or any other SAE. This is typically achieved by the investigator completing the eCRF adverse event report pages.

The investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information and will notify Takeda within 1 working day of obtaining the additional information.

11.3 Collection and Recording of Other Non-Serious Adverse Events, Special Situation Reports and Product Quality Issues

The study does not require the systematic collection and recording of other non-serious AEs, SSRs or PQIs. However, investigators may report these spontaneously to national pharmacovigilance centres or to Takeda's local pharmacovigilance office, in accordance with national law or regulations. These events will be treated as spontaneous events and independent of the study.

11.4 Reporting of Adverse Drug Reactions by Investigators to Local Agencies and Ethics Committees

If required by national law or regulation, the investigator shall report serious adverse drug reactions suspected of being related to brigatinib to the applicable local authorities and IEC within the timelines required by such law or regulation. The investigator shall maintain records of all such submissions. The Sponsor is responsible for reporting of adverse events to National Regulatory Agencies in accordance with European and national requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Sponsor and/or designee will prepare progress reports as required by the competent authority. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

The study protocol and synopsis of findings will be entered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register of studies (encepp.eu/encepp/studiesDatabase.jsp), and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines will be followed.

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of Takeda Pharmaceutical Company Limited.

13. REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 31 January 2019.
2. Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E. and Forman, D., 2011. Global cancer statistics. CA: a cancer journal for clinicians, 61(2), pp.69-90.
3. National Comprehensive Cancer Network [NCCN] Guidelines version 3.2016 NSCLC
4. Reck, M., Popat, S., Reinmuth, N., De Ruysscher, D., Kerr, K.M. and Peters, S., 2014. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology, 25(suppl_3), pp.iii27-iii39.
5. Novello, S., Barlesi, F., Califano, R., Cufer, T., Ekman, S., Levra, M.G., Kerr, K., Popat, S., Reck, M., Senan, S. and Simo, G.V., 2016. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 27(suppl_5), pp.v1-v27.
6. Cancer Research UK, Lung cancer incidence by stage at diagnosis. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence, accessed on 31 January 2019.
7. Office for National Statistics, 2016. Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015, accessed on 31 January 2019.
8. Kwak, E.L., Bang, Y.J., Camidge, D.R., Shaw, A.T., Solomon, B., Maki, R.G., Ou, S.H.I., Dezube, B.J., Jänne, P.A., Costa, D.B. and Varella-Garcia, M., 2010. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. New England Journal of Medicine, 363(18), pp.1693-1703.
9. Wong, D.W.S., Leung, E.L.H., So, K.K.T., Tam, I.Y.S., Sihoe, A.D.L., Cheng, L.C., Ho, K.K., Au, J.S.K., Chung, L.P., Pik Wong, M. and University of Hong Kong Lung Cancer Study Group, 2009. The EML4- ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild- type EGFR and KRAS. Cancer, 115(8), pp.1723-1733.
10. Shaw, A.T., Yeap, B.Y., Mino-Kenudson, M., Digumarthy, S.R., Costa, D.B., Heist, R.S., Solomon, B., Stubbs, H., Admane, S., McDermott, U. and Settleman, J., 2009.

Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK. Journal of clinical oncology, 27(26), p.4247.

11. Takahashi, T., Sonobe, M., Kobayashi, M., Yoshizawa, A., Menju, T., Nakayama, E., Mino, N., Iwakiri, S., Sato, K., Miyahara, R. and Okubo, K., 2010. Clinicopathologic features of non-small-cell lung cancer with EML4–ALK fusion gene. Annals of surgical oncology, 17(3), pp.889-897.
12. Camidge, D.R. and Doebele, R.C., 2012. Treating ALK-positive lung cancer—early successes and future challenges. Nature reviews Clinical oncology, 9(5), p.268.
13. Brigatinib Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/9691, accessed 31 January 2019.
14. Kim, D.W., Tiseo, M., Ahn, M.J., Reckamp, K.L., Hansen, K.H., Kim, S.W., Huber, R.M., West, H.L., Groen, H.J., Hochmair, M.J. and Leighl, N.B., 2017. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol, 35(22), pp.2490-2498.
15. Huber, R.M., Kim, D.W., Ahn, M.J., Langer, C.J., Tiseo, M., West, H., Groen, H.J., Reckamp, K.L., Hochmair, M.J., Leighl, N.B. and Holmskov Hansen, K., 2018. Brigatinib (BRG) in crizotinib (CRZ)-refractory ALK+ non–small cell lung cancer (NSCLC): Efficacy updates and exploratory analysis of CNS ORR and overall ORR by baseline (BL) brain lesion status. J Clin Oncol, 36(15_suppl), 9061-9061.
16. Camidge, D.R., Kim, H.R., Ahn, M.J., Yang, J.C.H., Han, J.Y., Lee, J.S., Hochmair, M.J., Li, J.Y.C., Chang, G.C., Lee, K.H. and Gridelli, C., 2018. Brigatinib versus crizotinib in ALK-positive non–small-cell lung cancer. New England Journal of Medicine, 379(21), pp.2027-2039.
17. Crizotinib Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/2857/smpc, accessed 31 January 2019.
18. Ceritinib Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/zykadia-epar-product-information_en.pdf , accessed 31 January 2019
19. Alectinib Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/alecensa-epar-product-information_en.pdf, accessed on 31 January 2019.

ANNEXES

Annex 1 List of stand-alone documents

None.

Annex 2 ENCePP Checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Study title: A Cohort Study to Describe the Occurrence of Early-Onset Pulmonary Events in Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Treated with Brigatinib: A Post-Authorisation Safety Study

Study reference number: Brigatinib-5007

SECTION 1: MILESTONES	**YES**	**NO**	**N/A**	**SECTION NUMBER**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

SECTION 2: RESEARCH QUESTION	**YES**	**NO**	**N/A**	**SECTION NUMBER**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1; 7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7.2
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

SECTION 3: STUDY DESIGN		**YES**	**NO**	**N/A**	**SECTION NUMBER**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1; 9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

SECTION 4: SOURCE AND STUDY POPULATIONS		**YES**	**NO**	**N/A**	**SECTION NUMBER**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	6
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

SECTION 5: EXPOSURE DEFINITION AND MEASUREMENT	**YES**	**NO**	**N/A**	**SECTION NUMBER**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

SECTION 6: OUTCOME DEFINITION AND MEASUREMENT		**YES**	**NO**	**N/A**	**SECTION NUMBER**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2
6.4	Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

SECTION 7: BIAS		**YES**	**NO**	**N/A**	**SECTION NUMBER**
7.1	Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
	7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2	Does the protocol address:				
	7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
	7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3	Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3

Comments:

This study is to describe patient characteristics and risk factors of early-onset pulmonary events in patients who receive brigatinib. The study variables are reported by the investigators.

SECTION 8: EFFECT MODIFICATION	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Not Applicable

SECTION 9: DATA SOURCES		**YES**	**NO**	**N/A**	**SECTION NUMBER**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
	9.3.3 Covariates?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

All the study variables are reported by the investigator and there is no coding system needed for exposure and covariates. For the outcome, the reports of pulmonary events will be coded in the MedDRA Preferred Terms.

SECTION 10: ANALYSIS PLAN	**YES**	**NO**	**N/A**	**SECTION NUMBER**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

SECTION 11: DATA MANAGEMENT AND QUALITY CONTROL	**YES**	**NO**	**N/A**	**SECTION NUMBER**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

SECTION 12: LIMITATIONS	**YES**	**NO**	**N/A**	**SECTION NUMBER**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

This study is to describe patient characteristics and identify risk factors of early-onset pulmonary events in patients who receive brigatinib.

SECTION 13: ETHICAL ISSUES	**YES**	**NO**	**N/A**	**SECTION NUMBER**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

SECTION 14: AMENDMENTS AND DEVIATIONS	**YES**	**NO**	**N/A**	**SECTION NUMBER**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

SECTION 15: PLANS FOR COMMUNICATION OF STUDY RESULTS	**YES**	**NO**	**N/A**	**SECTION NUMBER**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:
