Official Title: A Multicenter, International, Rollover Study of Alectinib in Patients with Anaplastic Lymphoma Kinase (ALK)-Positive or Rearranged During Transfection (RET)-Positive Cancer

NCT Number: NCT03194893

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PROTOCOL

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PROTOCOL NUMBER:	BO39694
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2017-000207-24
IND NUMBER:	111,723
TEST PRODUCT:	Alectinib (RO5424802)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Title	Approver's Name
	[redacted]

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	29 November 2019
1	24 January 2017

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol BO39694 has been amended primarily to update the management guideline of hemolytic anemia for patients treated with alectinib. Changes to the protocol, along with a rationale for each change, are summarized below:

- The table providing guidelines for the management of risks, adverse events, and laboratory abnormalities has been updated overall. This update was to add clarity on recommendations per AE CTCAE grading and to align with the current alectinib guidelines for management of risks and selected abnormalities, which have been updated according to the more mature safety profile and which includes less restrictive management of G2 adverse events or laboratory abnormalities (Section 5.1.3).
  - The update reflects use in the most recent alectinib clinical studies.
  - In addition, management guideline of hemolytic anemia for patients treated with alectinib has been updated
  - Management guidelines of bradycardia for patients treated with alectinib has been updated in line with the alectinib label.
- Hematologic findings from alectinib toxicity studies in animals have been provided to the section describing the risks associated with alectinib (Section 5.1.2.3).
- Benefit-risk assessment and guidance on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with alectinib has been added (Section 1.3, Section 4.4).
- The Medical Monitor contact information has been updated.
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1) and regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, INTERNATIONAL, ROLLOVER STUDY OF ALECTINIB IN PATIENTS WITH *ANAPLASTIC LYMPHOMA KINASE (ALK)*-POSITIVE OR *REARRANGED DURING TRANSFECTION* (*RET*)-POSITIVE CANCER**
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TEST PRODUCT:	Alectinib (RO5424802)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, INTERNATIONAL, ROLLOVER STUDY OF ALECTINIB IN PATIENTS WITH *ANAPLASTIC LYMPHOMA KINASE (ALK)*-POSITIVE OR *REARRANGED DURING TRANSFECTION* (*RET*)-POSITIVE CANCER**
PROTOCOL NUMBER:	BO39694
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2017-000207-24
IND NUMBER:	111,723
TEST PRODUCT:	Alectinib (RO5424802)
PHASE:	IIIb
INDICATION:	*Anaplastic lymphoma kinase (ALK)*-positive or *rearranged during transfection* (*RET*)-positive cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This is a rollover study for patients with *anaplastic lymphoma kinase (ALK)*-positive or *rearranged during transfection (RET)*-positive cancer treated with alectinib or crizotinib in F. Hoffmann-La Roche Ltd (Roche)–sponsored alectinib studies. Specific objectives and for the study are outlined below.

Primary Objective
• To provide continued treatment with alectinib or crizotinib as applicable to patients with *ALK*- or *RET*-positive cancer who were previously enrolled in any Roche-sponsored alectinib study and who are deriving continued clinical benefit from alectinib or crizotinib in the parent trial at the time of parent trial closure
Secondary Objective
• To assess long-term safety of alectinib therapy

Study Design

Description of Study

This is a Phase IIIb, open-label, non-randomized, multicenter, international, rollover study. Patients who are deriving clinical benefit from alectinib or crizotinib treatment during a Roche-sponsored parent trial at the time of parent trial closure and who do not have the option of being switched to a commercially available drug are eligible for this rollover study. Patients will continue alectinib or crizotinib treatment in the rollover study at the dose received at the time of parent study closure without a treatment interruption. The last dose of study drug in the parent trial will be administered on the same day as the first dose of study drug in the rollover study. Patients will continue to receive alectinib or crizotinib until no further clinical benefit is to be expected, unacceptable toxicity, availability of commercial supply, withdrawal of consent, or death, whichever occurs first.

Number of Patients

Because of the nature of the study, the total number of patients will not be estimated.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed written Informed Consent Form approved by the relevant Ethics Committee or the Institutional Review Board
- Patients enrolled in a Roche-sponsored alectinib trial who are experiencing a clinical benefit from alectinib or crizotinib treatment at the time of discontinuation from the parent trial and for whom a switch to commercial supply is not feasible
- Collected study termination data, including efficacy and safety data, as required by the parent study on the electronic Case Report Form
- Ability and willingness to comply with the protocol, in the investigator's judgment
- For women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of $<$ 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.
- For men: agreement to remain abstinent or use a contraceptive method that results in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of lack of clinical benefit in parent trial during the screening phase of this rollover study
- Permanent discontinuation of alectinib or crizotinib for any reason during the parent study or before first dose of study drug in the rollover study
- Evidence of an adverse event for which the parent protocol stipulates permanent discontinuation
- Pregnant or breastfeeding women
- Ongoing serious adverse event that has not resolved to baseline level or Grade $\leq$ 1 prior to first dose of study treatment in the rollover study
- Treatment interruption for more than 21 days due to an adverse event since the last administration of alectinib or crizotinib in the parent trial. Any ongoing adverse events that require temporary treatment interruption must be resolved to baseline grade or assessed as stable and not requiring further treatment interruption by the investigator
- Administration of strong/potent cytochrome P450 3A inhibitors or inducers within 14 days prior to the first dose of treatment on this study and while on treatment with crizotinib
- Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; these conditions should be discussed with the patient before trial entry

End of Study

The study will end when the last patient has completed the safety follow-up visit 4 weeks after the last dose of study drug.

Length of Study

Because of the nature of the study, the total length of study will not be estimated.

Outcome Measures

Safety Outcome Measures

Safety outcome measures for this study are as follows:

- *Serious and non-serious adverse events and adverse events of special interest*
- *Selected safety laboratory test measurements*

Adverse events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

Survival Outcome Measures

Date and reason for death occurring during the study will be collected. There will be no survival follow-up; hence, once a patient has permanently discontinued study drug and completed the safety follow-up visit, no further survival data will be collected.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Alectinib

The registered dose of alectinib is 600 mg (four 150-mg capsules) taken orally BID with food in the morning and in the evening. Patients should continue to receive the same dose of the study drug as they received in the parent study; guidelines provided in the parent study protocol should be followed.

Crizotinib

The registered dose of crizotinib is 250 mg (one 250-mg capsule) taken orally BID with or without food (in the morning and evening). Patients should continue to receive the same dose of the study drug as they received in the parent trial; guidelines provided in the parent study protocol should be followed.

Statistical Methods

Primary Analysis

The primary analysis population for the study is the safety analysis population defined as all patients enrolled in the study who receive at least one dose of study drug. Patients will be assigned to treatment groups as treated, and all patients who receive any dose of alectinib will be included in the alectinib treatment arm.

The primary and final analysis of the study will occur when all patients have discontinued treatment and have completed the safety follow-up visit.

No efficacy data are being collected in the study, and no hypothesis testing will be performed.

Determination of Sample Size

The purpose of this study is to provide continuous treatment with alectinib or crizotinib to patients with *ALK*- or *RET*-positive disease who are clinically benefitting from either alectinib or crizotinib in a Roche-sponsored parent study and due to approval status, reimbursement status, or local regulations do not have the option to be switched to a commercial supply at the time of parent study closure. All eligible patients from any parent study will be allowed to enter the study. No total sample size can be estimated.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
BID	twice a day
COVID-19	coronavirus disease 2019
CYP	cytochrome P450
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	Food and Drug Administration
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IxRS	interactive voice or Web-based response system
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NSCLC	non–small cell lung cancer
QD	once a day
RET	rearranged during transfection
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SLS	sodium lauryl sulfate
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON *ALK*- AND *RET*-POSITIVE CANCER

The anaplastic lymphoma kinase (ALK) was initially identified because of its involvement in anaplastic large cell lymphoma (ALCL) (Morris et al. 1994; Shiota et al. 1994). In normal human cells, ALK expression is quite rare and has been shown to be limited to some neural cells, pericytes, and endothelial cells. The exact role of the kinase in normal cells remains to be fully elucidated, but a role in neural development and differentiation has been suggested because of its significant expression in the nervous system of fetal mice and the subsequent decrease in expression during murine gestation.

Since the identification of the erroneous expression of ALK in ALCL, additional ALK rearrangements and mutations have been identified in various malignancies such as familial cases of neuroblastoma (Mosse et al. 2008), renal cell carcinomas (Sugawara et al. 2012; Sukov et al. 2012), esophageal squamous cell carcinoma (Jazii et al. 2006; Yaakup et al. 2008), breast cancer (Lin et al. 2009), glioblastoma multiforme (Powers et al. 2002; Stoica et al. 2001), colon cancer (Lin et al. 2009), anaplastic thyroid cancer and lung cancer (Lin et al. 2009; Wang et al. 2012; Gainor and Shaw 2013). Because of the presence of ALK rearrangements and mutations in a range of malignancies and their importance in the development of non–small cell lung cancer (NSCLC), there is a possibility that ALK-meditated signaling could play a role in the development of a number of other common solid tumors as well.

For *ALK*-positive NSCLC, several targeted therapies are being tested in clinical trials and others have been approved by health authorities. The first-generation *ALK* inhibitor crizotinib (Xalkori®) is approved for first-line treatment of patients with *ALK*-positive, advanced or metastatic NSCLC. In addition, the second-generation *ALK* inhibitors alectinib (Alecensa®) and ceritinib (Zykadia™) are approved by the U.S. Food and Drug Administration (FDA) for patients who have progressed on or are intolerant of crizotinib. Brigatinib and lorlatinib are third-generation *ALK* inhibitors that are currently under development and have not yet been approved for clinical use.

The *rearranged during transfection* (*RET*) proto-oncogene encodes a receptor tyrosine kinase that belongs to the glial cell line–derived neutrotropic factor family (Knowles et al. 2006) and has an important role in cell growth and differentiation. Both gain-of-function mutations and chromosomal rearrangements leading to the formation of *RET* fusion genes can result in a ligand-independent, constitutive activation of the kinase (Takahashi et al. 1985; Zbuk and Eng 2007; Kohno et al. 2012; Takeuchi et al. 2012) and have been associated with the development of various types of human cancer (Grieco et al. 1990; Bongarzone et al. 1998; Zbuk and Eng 2007; Qi et al. 2011; Kohno et al. 2012; Lipson et al. 2012; Takeuchi et al. 2012; Wang et al. 2012; Gainor and Shaw 2013).

Mutations in *RET* have been shown to be associated with predisposition to medullary thyroid cancer (Zbuk and Eng 2007), and chromosomal rearrangements involving *RET* have been detected in sporadic and irradiation-induced papillary thyroid carcinoma (Grieco et al. 1990). *RET* fusion genes have also been identified as driver oncogenes in 2% of lung adenocarcinomas or adenosquamous carcinomas (Kohno et al. 2012; Lipson et al. 2012; Takeuchi et al. 2012; Wang et al. 2012; Gainor and Shaw 2013).

The *RET* tyrosine kinase inhibitors (TKIs) vandetanib and cabozantinib are approved by the FDA for treatment of advanced form of medullary thyroid carcinoma (Wells et al. 2012; Hart and De Boer 2013) and are currently under study for treatment of various solid tumors (Studies NCT01823068, NCT01945762, NCT01582191, NCT01934335, NCT01639508, NCT01813734, and NCT02272998).

In addition, results from studies assessing the effect of multitargeted TKIs with anti-*RET* activity, such as cabozantinib and vandetanib, for the treatment of *RET*-positive lung cancer suggest that *RET* rearrangements define a new targetable subset of NSCLC (Drilon et al. 2013; Gautschi et al. 2013; Lee et al. 2016; Seto et al. 2016).

1.2 BACKGROUND ON ALECTINIB

Alectinib is a small molecule, highly selective, potent, next-generation, oral *ALK* inhibitor with a benzo[b]carbazole scaffold, which has been shown to inhibit *ALK* as well as *RET* without showing inhibitory effects on other kinases tested, such as ROS, RON, or MET. In a kinase inhibitory assay, alectinib inhibited ALK kinase activity with IC_{50} of 1.9 nM, whereas *RET* kinase activity was inhibited at IC_{50} of 4.8 nM. The difference in effective inhibitory concentration may indicate a need for a higher dose of alectinib for effective *RET* kinase inhibition than currently approved for treatment of *ALK*-positive disease (Kodama et al. 2014).

Alectinib shows high anti-tumor activity both in vitro and in vivo against tumor cell lines with some types of *ALK* gene alteration, including NSCLC and ALCL lines harboring an *ALK* translocation and a neuroblastoma line harboring the amplified *ALK* gene (Kinoshita et al. 2011; Sakamoto et al. 2011). In addition, alectinib has been shown to have potent anti-tumor activity in *RET*-positive nonclinical models of NSCLC (Gainor and Shaw 2013).

To date, there are numerous clinical trials assessing the effect of alectinib in patients with *ALK*-positive, advanced or metastatic NSCLC. For some of these studies, results have already been published.

Based on the results of the pivotal Phase I/II study AF-001JP study, alectinib was granted full approval in Japan for treatment of patients with *ALK*-positive metastatic NSCLC in July 2014 (Seto et al. 2013). More recently, an FDA approval was granted for alectinib treatment of patients with *ALK*-positive, metastatic NSCLC who have

progressed on or are intolerant to crizotinib on the basis of the pivotal Phase I/II Study NP28761/AF-002JG (Shaw et al. 2016).

There are currently four randomized Phase III trials of alectinib being conducted with patients with *ALK*-positive NSCLC. Study JO28928 (J-ALEX), Study BO28984 (ALEX), and Study YO29449 (ALESIA) are comparing the treatment effect of alectinib versus crizotinib in the front-line setting for advanced or metastatic ALK-positive NSCLC. Study MO29750 (ALUR) is comparing alectinib versus pemetrexed or docetaxel in ALK-positive patients with NSCLC who have been previously treated with platinum-based chemotherapy and crizotinib.

Study JO28928 (J-ALEX), conducted by Chugai in Japanese patients, is an open-label study comparing the treatment effects of alectinib versus crizotinib in either treatment-naive patients or patients who had previously received a prior line of chemotherapy. In February 2016, an independent data monitoring committee recommended to stop the study early as the study met its primary endpoint at a preplanned interim analysis. The study showed that patients lived significantly longer without disease worsening (through a progression-free survival measure) when treated with alectinib than when treated with crizotinib.

The global ALEX study (BO28984) is fully recruited and still ongoing, ALUR (MO29750) started recruitment in October 2016, and ALESIA (YO29449), conducted in China, started recruitment in August 2016. No data are yet available to report for these studies.

In nonclinical studies, alectinib has been shown to inhibit *RET* kinase activity and *RET* fusion-driven cell growth by suppressing phospho-*RET*, and this inhibition in *RET*-rearranged lung cancer cells leads to suppressed viability of the cancer cells (Gainor and Shaw 2013). More recently, alectinib has demonstrated preliminary anti-tumor activity in 4 patients with advanced *RET*-rearranged NSCLC. Three of the 4 patients had received prior *RET* inhibitors (Lin et al. 2016). Alectinib has not been assessed in larger prospective clinical studies for patients with *RET*-positive NSCLC, but a study evaluating the efficacy of alectinib in patients with *RET*-positive, advanced or metastatic NSCLC, as determined by a blood-based, next-generation sequencing, circulating-tumor DNA assay, is being planned.

Refer to the Alectinib Investigator's Brochure for additional details on nonclinical and clinical studies and to the respective parent protocols for additional background information on alectinib usage within respective trials.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

In Japan, alectinib is approved for treatment of *ALK* fusion gene-positive, unresectable, recurrent or advanced NSCLC, independent of prior treatments. In the United States, Israel, Canada, Hong Kong, South Korea, and Kuwait, alectinib is approved for treatment of patients with advanced *ALK*-positive NSCLC who have progressed on or

are intolerant to crizotinib treatment. Thus, depending on approval status, reimbursement status, and local regulations, patients may not have the option of receiving a commercially available drug at the end of the parent study.

This is an open-label, multicenter, non-randomized study to provide access to alectinib or crizotinib treatment to eligible patients who were previously enrolled and treated in an alectinib study (referred to as the parent study) without meeting the protocol criteria for study treatment discontinuation and who are still deriving clinical benefit from the respective treatment as assessed by the treating investigator. This study, referred to as the rollover study, allows continued treatment of patients with *ALK*- or *RET*-positive cancer for whom a switch to a commercially available drug is not feasible, with their parent study protocol-specified treatment upon termination of the respective parent study.

This rollover study is designed to ensure an optimal benefit–risk ratio. The rollover protocol includes the following measures to manage the risks:

- The Sponsor will assess each study carefully before declaring it a "qualifying" parent study and enrolling its eligible patients into this rollover study. For example, a study that is prematurely stopped for safety issues related to alectinib would not become a parent study.
- Alectinib and crizotinib treatment for each patient will remain as specified in the parent study, taking into consideration protocol-mandated dose modifications. The starting dose of alectinib or crizotinib given in the rollover study will be the same as last dose received on parent study.
- Clear guidance is provided on interruption and discontinuation for alectinib and crizotinib in case a patient develops severe side effects, also taking into account side effects experienced during treatment in the parent study.
- Patients enrolled in the rollover study will undergo safety monitoring during the study; all adverse events will be documented and selected, periodic safety laboratory tests will be performed.
- The Sponsor will collect long-term safety data on alectinib and crizotinib treatment arms in accordance with local regulations.

These patients have limited alternative treatment options and may potentially benefit from continued treatment with alectinib or crizotinib according to parent study protocol. Therefore, the potential benefits of participating in this rollover study outweigh the potential associated risks.

1.3.1 *COVID-19 Benefit–Risk Assessment*

No changes related to coronavirus disease 2019 (COVID-19) have been made to this protocol.

In the setting of the COVID-19 pandemic, patients with certain comorbidities, including those with cancer, are a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how anti-cancer therapies such as chemotherapy or targeted therapy affect the incidence or severity of SARS-CoV-2 infections. Based on their safety profiles and mechanisms of action, it is not anticipated that the medicinal products used in this study will increase the risk of infection with SARS-CoV-2. Other clinical trials with the medicinal products used in this study have been ongoing during this pandemic and, although the numbers are small, patients have not shown any increased risk of developing COVID-19 symptoms.

1.3.2 *COVID-19 Vaccine Benefit–Risk Assessment*

Based on the published mechanism of action of the COVID-19 vaccines and the known mechanism of action of alectinib, there is no scientific rationale to expect that COVID-19 vaccines will affect the efficacy of alectinib and crizotinib. Based on a specific benefit-risk assessment, taking into account the available relevant information, the approved non-live COVID-19 vaccines may and should be administered in patients who are in the study, as long as there is no other contraindication (e.g., known hypersensitivity to a vaccine component).

Investigators should share with patients' primary healthcare provider's relevant information regarding any potential effect of respective study drugs on the response to COVID-19 vaccination, as applicable. Also, patients should contact the investigators or site staff, when they are invited to receive a COVID-19 vaccine deployed in their region. The decision to vaccinate a patient should be based on a patient's SARS-CoV-2 infection/complication risk, general health condition, severity of underlying malignancy, and regional epidemiology of SARS-CoV-19 exposure. COVID-19 vaccines should be administered in accordance with their respective prescribing information and applicable immunization guidelines.

After COVID-19 vaccination, one should continue to observe the applicable epidemiologic/public health and hygiene measures, during the pandemic, along with per protocol safety measures and assessments, in order to minimize the risk, but also to appropriately identify and assess potential adverse reactions (e.g., nausea, diarrhea, myalgia) possibly shared by vaccines and study drugs.

2. OBJECTIVES

This is a rollover study for patients with *ALK*-positive or *RET*-positive cancer treated with alectinib or crizotinib in F. Hoffmann-La Roche Ltd (Roche)–sponsored alectinib studies. Specific objectives for the rollover study are outlined below (see Table 1).

Table 1 Objectives

Primary Objective
• To provide continued treatment with alectinib or crizotinib as applicable to patients with *ALK*- or *RET*-positive cancer who were previously enrolled in any Roche-sponsored alectinib study and who are deriving continued clinical benefit from alectinib or crizotinib in the parent trial at the time of parent trial closure
Secondary Objective
• To assess long-term safety of alectinib therapy

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase IIIb, open-label, non-randomized, multicenter, international rollover study. Patients who are deriving clinical benefit from alectinib or crizotinib treatment during a Roche-sponsored parent trial at the time of parent trial closure and who do not have the option of being switched to a commercially available drug are eligible for this rollover study. Patients will continue alectinib or crizotinib treatment in the rollover study at the dose received at the time of parent study closure without a treatment interruption. The last dose of study drug in the parent trial will be administered on the same day as the first dose of study drug in the rollover study. Patients will continue to receive alectinib or crizotinib until no further clinical benefit is to be expected, unacceptable toxicity, availability of commercial supply, withdrawal of consent, or death, whichever occurs first.

The current protocol is to be used together with the approved parent study protocol from which patients are transitioned. Alectinib and crizotinib will be provided by the Sponsor.

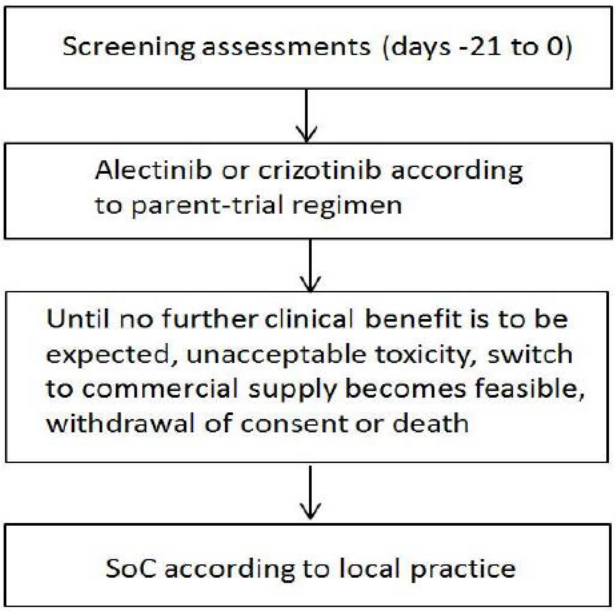
Safety parameters will be collected on the study according to the schedule of activities (see Appendix 1) and Section 5. Disease assessments should be performed according to local practice and will not be captured on the electronic Case Report Form (eCRF). If clinically indicated, local therapy (e.g., stereotactic radiotherapy or surgery) can be provided during the study as long as treatment is interrupted according to the protocol (see Section 4.4.1).

Patients who discontinue treatment will be followed for safety assessments 4 weeks after permanent discontinuation of study drug. Subsequently, patients will be discontinued from the study and will receive standard-of-care treatment according to local practice. The date of death will be collected if it occurs while the patient is enrolled in the study. No survival follow-up data will be collected for patients after study discontinuation.

Safety will be monitored by the collection of all adverse events (non-serious adverse events, serious adverse events, and adverse events of special interest; see Sections 5.2.2 and 5.2.3) on the dedicated eCRF. Specific safety laboratory assessments (see Section 4.5.6) will be collected at every visit and reported on dedicated eCRF pages. Vital signs, ECGs, and other laboratory assessments not included in the periodic safety monitoring should be performed according to local practice and should only be reported on the eCRF if they are relevant for a reported adverse event.

A summary of the study design is shown in Figure 1. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



SOC = standard of care

3.2 END OF STUDY AND LENGTH OF STUDY

The study will end when the last patient has completed the safety follow-up visit 4 weeks after the last dose of study drug. Because of the nature of the study, the total length of study will not be estimated.

3.3 RATIONALE FOR STUDY DESIGN

This study is designed to provide continuous treatment with alectinib or crizotinib to patients with *ALK*- or *RET*-positive disease who are clinically benefitting from either alectinib or crizotinib in a Roche-sponsored alectinib trial and who do not have the option to be switched to a commercial supply at the time of the parent study closure because of lack of approval or reimbursement status or local regulations.

For patients who continue to derive clinical benefit from treatment, the study allows continuous treatment and safety follow-up under one protocol. This is more efficient than requiring multiple and separate extension studies for each of the parent studies and facilitates the pooling of long-term safety data for all patients across parent studies.

3.3.1 Rationale for Alectinib and Crizotinib Doses

The study is designed so that the parent protocol continues to guide medication regimen, dose(s), and treatment management to allow within-patient continuity and minimize disruptions to patient treatment so that patients have the best chance of sustaining benefit and tolerability.

Patients on the parent trials receiving crizotinib as comparator treatment will be provided with the same option for continued treatment on this study.

3.3.2 Rationale for Patient Population

This study is intended to provide patients with *ALK*- or *RET*-positive cancer who have been clinically benefitting from alectinib or crizotinib on Roche-sponsored parent trials with continued treatment upon closure of the parent trials in regions where alectinib is either not commercially available or patients cannot receive the drug via commercial supply. Patients receiving alectinib or crizotinib from sources other than Roche-sponsored trials are not eligible for this study.

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

Safety outcome measures for this study are as follows:

- Serious and non-serious adverse events and adverse events of special interest
- Selected safety laboratory test measurements

Adverse events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

3.4.2 Survival Outcome Measures

Date and reason for death occurring during the study will be collected. There will be no survival follow-up; hence, once a patient has permanently discontinued study drug and completed the safety follow-up visit, no further survival data will be collected.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with *ALK*- or *RET*-positive cancer who are clinically benefitting from alectinib or crizotinib treatment in the parent study and who, in the investigator's opinion, may benefit from continued study treatment.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed written Informed Consent Form approved by the relevant Ethics Committee (EC) or the Institutional Review Board (IRB)
- Patients enrolled in a Roche-sponsored alectinib trial who are experiencing a clinical benefit from alectinib or crizotinib treatment at the time of discontinuation from the parent trial and for whom a switch to commercial supply is not feasible
- Collected study termination data, including efficacy and safety data, as required by the parent study on the eCRF
- Ability and willingness to comply with the protocol, in the investigator's judgment
- For women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of $<$ 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.
- For men: agreement to remain abstinent or use a contraceptive method that results in a failure rate of $<$ 1% per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of lack of clinical benefit in parent trial during the screening phase of this rollover study
- Permanent discontinuation of alectinib or crizotinib for any reason during the parent study or before first dose of study drug in the rollover study
- Evidence of an adverse event for which the parent protocol stipulates permanent discontinuation
- Pregnant or breastfeeding women
- Ongoing serious adverse event that has not resolved to baseline level or Grade $\leq$ 1 prior to first dose of study treatment in the rollover study
- Treatment interruption for more than 21 days due to an adverse event since the last administration of alectinib or crizotinib in the parent trial. Any ongoing adverse events that require temporary treatment interruption must be resolved to baseline

grade or assessed as stable and not requiring further treatment interruption by the investigator

- Administration of strong/potent cytochrome P450 (CYP) 3A inhibitors or inducers within 14 days prior to the first dose of treatment on this study and while on treatment with crizotinib
- Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; these conditions should be discussed with the patient before trial entry

4.2 METHOD OF TREATMENT ASSIGNMENT

Patients will receive the same study drug at the same dose and schedule and according to the same administration guidelines as they received at the time of discontinuation from the parent trial. In order to ensure continuous treatment, the study completion visit for the parent protocol will serve as the baseline visit for the rollover study. Study treatment will be provided by the Sponsor. Drug pack number allocations will be performed and managed by an interactive voice or Web-based response system (IxRS); each investigational site will acknowledge receipt of investigational medicinal products (IMPs) using the IxRS system.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Alectinib

Alectinib comes in a hard-capsule dosage form containing the following active ingredient: 9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloride.

Each capsule contains 150 mg of alectinib (as free base), lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate (SLS), magnesium stearate, and carboxymethylcellulose calcium encapsulated in a capsule shell consisting of hypromellose, carrageenan, potassium chloride, titanium dioxide, and carnauba wax.

Alectinib capsules should be stored in accordance with the storage instructions on the label.

The registered dose of alectinib is 600 mg twice a day (BID). Alectinib capsules should be administered orally with food in the morning and evening.

The formulation contains SLS as an excipient. This excipient is known to be potentially associated with gastrointestinal (GI) adverse events, such as nausea, vomiting, diarrhea, and abdominal pain.

For further details, see the Alectinib Investigator's Brochure.

4.3.1.2 Crizotinib

Crizotinib comes in a hard-capsule dosage form. Each capsule contains 200 mg or 250 mg crizotinib. Crizotinib hard capsules should be stored in accordance with the storage instructions on the label. Crizotinib capsules should be administered orally BID. For further details, see the local prescribing information for crizotinib (XALKORI U.S. Package Insert [USPI]; XALKORI Summary of Product Characteristics [SmPC]).

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Alectinib

The registered dose of alectinib is 600 mg (four 150-mg capsules) taken orally BID with food in the morning and in the evening. Patients should continue to receive the same dose of the study drug as they received in the parent study; guidelines provided in the parent study protocol should be followed.

If a patient misses a dose, it can be taken within 6 hours of the scheduled time. If the time is greater than 6 hours or if the patient vomits the dose, the patient should wait until the next scheduled time and take the next scheduled dose. Patients should not take two doses at the same time to make up for a missed dose.

Guidelines for dosage modifications and treatment interruptions or discontinuation due to specified adverse events are provided in Section 5.1.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Crizotinib

The registered dose of crizotinib is 250 mg (one 250-mg capsule) taken orally BID with or without food (in the morning and evening). Patients should continue to receive the same dose of the study drug as they received in the parent trial; guidelines provided in the parent study protocol should be followed.

If a dose is missed, then it should be taken as soon as the patient remembers unless it is fewer than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after a dose of crizotinib, the next dose should be taken as scheduled.

If dose reduction is necessary, then the dose of crizotinib should be reduced to 200 mg BID. If further dose reduction is necessary, then the dose should be modified to 250 mg taken once a day (QD).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.

Any overdose or incorrect administration of crizotinib should be noted on the Crizotinib Administration eCRF. Adverse events associated with an overdose or incorrect administration of crizotinib should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

IMPs required for completion of this study (alectinib and crizotinib) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Provision of Care

The sponsor does not intend to provide alectinib or crizotinib to patients upon early withdrawal or after completion of this rollover study.

4.4 CONCOMITANT THERAPY

Approved COVID-19 vaccines and treatments (including those with emergency use authorizations) are permitted:

- *Details of any COVID-19 vaccination received before study enrollment should be captured in the medical history section, at screening, whereas details regarding the COVID-19 vaccine received during the study should be recorded in the concomitant medication section.*

4.4.1 Therapies to Be Used with Caution

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the first dose of study drug to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

All therapy and/or medication administered to manage serious adverse events should be recorded on the Adverse Event eCRF.

Caution should be exercised if local therapy (e.g., stereotactic radiotherapy or surgery) is provided according to local practice during alectinib treatment:

- In case of radiation or surgery, procedures may start within 24 hours of the last dose of alectinib, unless, in the judgment of the investigator, patient safety will require a longer washout period prior to therapy. Dosing of alectinib may resume with the resolution of any radiation toxicity to Grade $\leq$1.

Caution should be exercised when the following are co-administered with alectinib:

- Medications that are substrates of P-gp transporter or breast cancer resistance–protein transporter. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration cannot be avoided, it is recommended that drug levels and/or signs for toxicity are carefully monitored (see Appendix 2).

Caution should be exercised when the following are co-administered with crizotinib:

- Drugs that are predominantly metabolized by CYP3A. Crizotinib has been shown to be a moderate inhibitor of CYP3A. Dose reduction may be needed for co-administered drugs that are predominantly metabolized by CYP3A in patients receiving crizotinib. Concurrent use of CYP3A substrates with narrow therapeutic indices should be avoided (see Appendix 2).
- Medicinal products that are substrates of P-gp. On the basis of an in vitro study, crizotinib is predicted to inhibit intestinal P-gp. Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, and pravastatin) may increase their therapeutic effect and adverse reactions (see Appendix 2). Close clinical surveillance is recommended when crizotinib is administered with these medicinal products.
- Other agents known to cause bradycardia. Bradycardia has been reported during clinical studies; therefore, avoid using crizotinib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible.
- Medicinal products that are predominantly metabolized by pregnane X receptor and constitutive androstane receptor-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). In vitro studies in human hepatocytes indicated that crizotinib may induce pregnane X receptor and constitutive androstane receptor-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). However, there was no observed induction in vivo when crizotinib was co-administered with the CYP3A probe substrate midazolam. Of note, the effectiveness of concomitant administration of oral contraceptives may be altered.
- Drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz). In vitro studies indicated that crizotinib is an inhibitor of CYP2B6. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz).

4.4.2 Prohibited Therapy

Use of the following therapies (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) is prohibited during the study unless otherwise specified below. Exceptions to restrictions of the concomitant therapies listed below may be made if the rationale is discussed and documented by the investigator and the Sponsor's clinical pharmacologist.

- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid–binding resins during study treatment
- Systemic chemotherapy
- Additional investigational drug

Only for patients treated with crizotinib:

- Potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St. John's wort [*Hypericum perforatum*]) during treatment with study drugs (see Appendix 2)
- Potent inhibitors of CYP3A (e.g., ketoconazole) during treatment with study drug (see Appendix 2)
- Any concomitant medications known to affect QT interval duration, including but not limited to the following drugs during treatment through the end of the study: amiodarone, cisapride, clarithromycin, methadone, and quinidine

The list of medications provided above is not necessarily comprehensive. The investigator should consult the prescribing information as well as the Internet references provided below for any concomitant medication when determining whether a certain medication strongly inhibits or induces CYP3A. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

4.4.3 Prohibited Food

Consumption of Seville oranges, grapefruit, or grapefruit juice should be avoided during treatment with crizotinib as these contain a potent CYP3A inhibitor and may increase plasma concentration of crizotinib.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before entering the study. The investigator will maintain a *detailed* record of all patients screened and to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Demographic Data and Baseline Characteristics

Demographic data will include age, sex, and self-reported race/ethnicity. Baseline characteristics will include reproductive status.

Adverse events that are ongoing at the time of parent study closure will be captured as baseline conditions and any treatment for these events will be captured as concomitant treatment.

4.5.3 Physical Examinations

Symptom-directed physical examinations should be performed if clinically indicated according to local practice. Abnormal changes should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Symptom-directed collection of vital signs should be performed if clinically indicated according to local practice. Abnormal changes should be recorded in patient notes. Clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

Tumor and response evaluations will be performed according to local practice and will not be reported in the eCRF.

4.5.6 Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- ALT, AST, total bilirubin, alkaline phosphatase (ALP), blood creatinine phosphokinase
- Pregnancy test: All women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile will have a urine pregnancy test at screening, a maximum of 3 days prior to first dose of study drug on this

rollover study. Urine pregnancy tests will be performed at any time during the study, as per investigator's discretion. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test

Other safety laboratory assessments should be performed as per local clinical practice.

4.5.7 Electrocardiograms

ECGs should be performed according to local practice. In the case of abnormal findings that are associated with or diagnostic for an adverse event, an unscheduled ECG assessment should be reported on the eCRF.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- If study drug becomes commercially available and accessible to patients outside the study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Inability to tolerate study drug on the basis of the investigator's judgment

See the guidelines for managing adverse events and for comprehensive guidance on study drug discontinuation in Section 5.1.3.

Patients who discontinue study drug prematurely will be asked to return to the clinic for safety follow-up assessment as per study schedule (see Appendix 1). The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Collection of Adverse Events

Any adverse events occurring during the screening period but prior to the first dose of study treatment in this rollover protocol will be assessed and reported as per parent trial guidelines and be captured on the adverse event reports of the parent trial. After the first dose of study treatment and until the safety follow-up visit (4 weeks after the last dose of study treatment), all adverse events regardless of seriousness, causality, assessment, or actions taken with study drug reported by the investigator or designated medically qualified study site personnel will be collected as described below. At each visit, the investigator or designated medically qualified study personnel will ask the patient if any untoward medical event has occurred since the last visit. It is the investigator's responsibility to record all adverse events in the source patient's medical records.

All adverse events will be reported on the standard Adverse Event/Serious Adverse Event eCRF.

5.1.2 Adverse Events Relating to *ALK* Inhibitors and/or the TKI Class and Alectinib Data

Events described in Sections 5.1.2.1–5.1.2.10 will be closely monitored and represent selected adverse events for this study.

For more details regarding the alectinib safety profile, see the Alectinib Investigator's Brochure.

5.1.2.1 Interstitial Lung Disease

TKIs, including the *ALK* inhibitor crizotinib, have been associated with the occurrence of treatment-related interstitial lung disease (including fatalities).

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.2 Hepatotoxicity

Hepatobiliary findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib, and findings in the 13-week studies were similar to those of the 4-week studies. The findings were at or close to clinically relevant exposures. Hepatobiliary effects included increased hepatic ALP, direct bilirubin, gamma-glutamyl transferase and liver weight, vacuolation, degeneration, and necrosis of bile duct epithelium, inflammatory cell infiltration in Glisson's sheath, enlargement and focal necrosis of hepatocytes, and enlargement of Kupffer cells.

Abnormal hepatobiliary laboratory test values, such as increased ALT, AST, or bilirubin levels, have been observed after alectinib administration. AST, ALT, and total bilirubin levels temporarily increased in the initial stages of treatment and then improved. In patients with Grade 3 or 4 AST/ALT elevations, documented drug-induced liver injury by liver biopsy was reported with uncommon frequency in alectinib pivotal clinical trials. Concurrent elevations in ALT or AST $\geq 3 \times$ upper limit of normal (ULN) and total bilirubin $\geq 2 \times$ ULN with normal ALP occurred with uncommon frequency in patients treated in alectinib clinical trials.

Abnormal liver function tests and drug-induced hepatotoxicity, including cases with fatal outcome, have been reported in patients treated with other tyrosine kinase *ALK* inhibitor drugs.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.3 Anemia

Hematologic findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib. *The findings were at or close to clinically relevant exposures. Changes in RBC morphology (e.g., poikilocytosis, red cell fragmentation) and in other erythroid parameters (e.g., reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume) were seen with alectinib in these studies. However, the changes on the erythroid system were considered to be of little toxicological significance because they were slight (0.94- to 1.3- fold vs. baseline), considered reversible, and did not exacerbate with prolonged treatment with alectinib.*

Cases of anemia*, including hemolytic anemia,* have been reported in patients treated with alectinib; the majority of the events were Grade 1 or 2.

See Section 5.1.3 for *anemia (including hemolytic anemia) adverse events* management and follow-up guidelines.

5.1.2.4 Gastrointestinal Disorders

Gastrointestinal disorders, such as nausea, vomiting, constipation, and diarrhea, have been reported with alectinib. Similar GI disorders have been observed with other TKIs, including ALK inhibitor crizotinib.

Sodium lauryl sulfate is a surfactant excipient in the clinical formulation at a concentration of 50% (weight-to-weight percentage SLS to active pharmaceutical ingredient). This excipient is a known GI irritant and may be associated with GI adverse events including nausea, vomiting, diarrhea, and abdominal pain. Of note, GI tract toxicity as the safety determinant of SLS is not because of systemic toxicity but as a consequence of local irritation to the GI tract. In general, when mixed with diet, higher levels of SLS are tolerated versus gavage administrations.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.5 Skin Disorders

Results of an in vitro phototoxicity study indicated that alectinib may have phototoxic potential.

Skin rash has been reported with majority of TKIs, including those targeting the *ALK* receptor (Hartmann et al. 2009).

Cases of skin rash and photosensitivity have been reported with alectinib and were generally Grade 1 or 2.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.6 Vision Disorders

In the rat quantitative whole-body autoradiography study, tissue radioactivity disappeared over time, following a time course comparable to that of plasma radioactivity, except for melanin-containing tissues such as uveal tract of eyes, which had much higher and more sustained exposure in pigmented rats. This finding is consistent with what is commonly observed for lipophilic basic drugs.

Vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters, have been reported with several TKIs, including *ALK* inhibitor crizotinib (Shaw et al. 2013).

Vision disorders, such as dry eye, blepharitis, conjunctivitis, blurred vision, and impaired vision, have been reported with alectinib and were generally Grade 1 or 2.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.7 Edema

Most TKIs, including *ALK* inhibitor crizotinib, have been associated with edema. Events of edema have been reported with alectinib (mostly Grade 1 or 2).

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.8 Bradycardia

In a monkey telemetry study, there were no effects on the ECG, any of the other cardiovascular parameters, or body temperature at doses up to 15 mg/kg (mean maximum concentration: 279 ng/mL).

In a preliminary non–Good Laboratory Practice telemetry study in conscious cynomolgus monkeys, a slight hypotensive effect (approximately 10 mmHg) was seen when alectinib was administered at 20 mg/kg and 60 mg/kg orally with no effects on ECG or heart rate. The hypotensive effect of alectinib observed in monkeys was considered likely to be caused by vasodilatation induced by L-type Ca^{2+} channel inhibition.

Events of bradycardia have been reported with alectinib. Preliminary heart rate data (based on ECG and pulse measurements) from the ongoing alectinib clinical trials show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. In patients treated with other *ALK* inhibitors (crizotinib and ceritinib), bradycardia adverse events, as well as decreases in heart rate based on ECG and pulse measurements, have also been reported (XALKORI USPI; ZYKADIA USPI).

In case of bradycardia, concomitant medications must be evaluated to identify those that are known to cause bradycardia, as well as anti-hypertensive medications, and discontinuation or dose reduction of these concomitant medications must be considered.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.9 Abnormal Renal Function

In the 2-week, non-human primate study at a dose of 60 mg/kg alectinib, an increase in creatinine was observed, but no changes were observed in histopathology. In all other non-human primate studies, no changes in creatinine were observed.

Serum creatinine increases have been reported with alectinib treatment and were generally Grades 1 and 2.

See Section 5.1.3 for management and follow-up guidelines.

5.1.2.10 Severe Myalgia and CPK Elevations

Postmarketing experience with some TKIs includes reports of myopathy and rhabdomyolysis (Hohenegger 2012).

Blood CPK increases, generally Grades 1 and 2 events and muscular adverse events, have been reported with alectinib treatment. Grade 3 myalgia and CPK elevations have been reported with alectinib treatment and were reversible upon dose reduction and interruption.

See Section 5.1.3 for management and follow-up guidelines.

5.1.3 Management of Specific Adverse Events with Alectinib

Table 2 Guidelines for Management of Specific Adverse Events with Alectinib

Event	Action to Be Taken
Interstitial lung disease	• Patients should be monitored for pulmonary symptoms indicative of *interstitial lung disease*/pneumonitis. • *Regardless of relatedness to alectinib, s*tudy drug should be permanently discontinued in patients diagnosed with interstitial lung disease *of any grade*.
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4 and Section 5.3.5.6. • At any time during study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible. *Regardless of relatedness to alectinib, the grade-dependent rules for dose interruptions and dose modification outlined in the last section of this table must be followed.* *In addition, s*tudy drug treatment has to be permanently discontinued if any of the following occurs: First observation of ALT or AST > 8 × ULN ALT or AST > 5 × ULN for more than 2 weeks First observation of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN First observation of ALT or AST > 3 × ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [> 5%]). • Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found. • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria.
GI tract adverse events (e.g., nausea, vomiting, and diarrhea)	The events are expected to be minimized by taking study drug with a meal. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. *In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.*

Table 2 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)

Event	Action to Be Taken
Skin disorder adverse events (e.g., phototoxicity and rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least *7* days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sunscreen and lip balm of at least SPF 50 to help protect against potential sunburn *during this period.* *In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.*
Vision disorders	Investigators should consider referring patients for an ophthalmologic evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity and should advise patients to exercise caution when driving or operating machinery because the risk of developing a vision disorder. *In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.*
Edema	Physical examinations should be performed routinely in accordance with local clinical practice. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. *In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.*
Abnormal kidney function adverse events	Kidney function laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4. • If, at any time during the study treatment, eGFR decreases by > 50% of the baseline visit value, the patient must be carefully monitored. All of the underlying factors that may have acutely affected serum creatinine levels must be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate). • Any eGFR decrease of > 50% of the baseline visit value requires repeat testing. • *For Grade 1 and Grade 2 AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.* • *For Grade 3 AEs related to alectinib, temporarily interrupt alectinib until laboratory value recovers to Grade 1 or baseline, then resume at reduced dose.* • *For Grade 4 AEs related to alectinib, permanently discontinue study drug.*

Table 2 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)

Event	Action to Be Taken
Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4. • Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms. • *In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table*
Hemolytic anemia	*If hemoglobin concentration is <10 g/dl (Grade ≥2) and hemolytic anemia is suspected, withhold alectinib and initiate appropriate laboratory testing, in accordance with local clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (refer to the general dose modification Table 3) upon resolution with improvement of hemoglobin to Grade ≤1 or baseline, or permanently discontinue alectinib.* *In case of anemia of non-hemolytic mechanism, assessed as related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.*
Bradycardia [b]	*Grade 2 or Grade 3* • *Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to Grade ≤1 (asymptomatic) bradycardia or to a heart rate of ≥60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products.* • *If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 (asymptomatic) bradycardia, or to a heart rate of ≥60 bpm.* *If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.* *Grade 4* • *Permanently discontinue if no contributing concomitant medicinal product is identified.* • *If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated.* *Permanently discontinue in case of recurrence.*

Table 2 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)

Event	Action to Be Taken
All AEs related [a] to alectinib (unless otherwise specified in this table) ***or*** *Hepatotoxicity AEs (irrespective of relatedness)*	• *Grade 4:* – *Temporarily interrupt alectinib for a maximum of 21 days, after which drug must be permanently withdrawn. If improvement to Grade ≤1 or baseline does not occur within 3 weeks, permanently discontinue alectinib.* – *First episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule BID).* – *Second episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule BID).* – *Third episode: Permanently discontinue alectinib.* • *Grade 3:* – *Temporarily interrupt alectinib for a maximum of 21 days, after which drug must be permanently withdrawn.* – *First episode: If improvement to Grade ≤1 or baseline within 10 days, alectinib may be restarted at the original dose or with dose reduced by 150 mg (1 capsule BID) as per investigator discretion. If improvement occurs after 10 days but within 21 days, then decrease the current dose of alectinib by 150 mg (1 capsule BID).* – *Second episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule BID).* – *Third episode: Permanently discontinue alectinib.* • *Grade 2:* – *To be managed at the investigator's discretion. Please note that alectinib cannot be interrupted for more than 21 days and cannot be dose reduced below 300 mg BID.* • *Grade 1: no action required*

AE =adverse event; ALP =alkaline phosphatase; BID =twice a day; eGFR =estimated glomerular filtration rate; GI =gastrointestinal; ULN =upper limit of normal.

Notes: Diarrhea, nausea, and vomiting should be handled with best supportive care first before considering dose modification. Preexisting pleural effusion will not be considered as an adverse event. If patients are receiving a starting dose different from the registered 600-mg BID dose, the parent protocol should be referred to in regards to study drug modifications.

[a] *To determine whether event should be assessed as related or unrelated, see Section 5.3.4.*

[b] *Heart rate less than 60 bpm.*

Table 3 *Alectinib Dose Modification*

Dose Reduction Schedule	*Dose Level*
Dose	*600 mg twice daily*
First dose reduction	*450 mg twice daily*
Second dose reduction	*300 mg twice daily*

5.1.4 Safety of Crizotinib and Management of Adverse Events

A dosing interruption and/or dose reduction may be required on the basis of an individual's safety and tolerability. If a dose reduction is necessary, then the dose of crizotinib should be reduced to 200 mg BID. If a further dose reduction is necessary, then the dose should be modified to 250 mg QD on the basis of the individual's safety and tolerability (XALKORI USPI; XALKORI SmPC). For more details on dose reduction and permanent discontinuation for hematologic and non-hematologic toxicities, refer to the latest XALKORI USPI, Crizotinib SmPC, or local prescribing information.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest and performing protocol-specified safety laboratory assessments that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE, v4.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)

- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug** on this rollover study, all adverse events should be reported on the parent trial in accordance with parent trial reporting conventions.

After initiation of study drug on this rollover study, all adverse events will be reported until 4 weeks after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to study drug treatment (see Section 5.6). Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time-points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the ALK- or *RET*-positive cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths during the study, regardless of relationship to study drug, must

be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after study completion will not be captured in the eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. These would include adverse events that are ongoing at the time of discontinuation from parent trial. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A baseline condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of *ALK*- or *RET*-Positive Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data should contribute to the disease assessments for the patient, which will be performed according to local practice and will not be collected in the eCRF. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

Medical Monitor Contact Information for all sites

Medical Monitor: [redacted], *M.D.*
Mobile Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study treatment in this rollover study, all new adverse events should assessed and reported as per parent trial guidelines and be captured on the adverse event pages for the parent trial. Adverse events reported on the parent trial that are ongoing at the time of first dose of study drug on this rollover study will be captured as baseline medical conditions on the eCRF.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 4 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special *Situations* Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the

study or within 3 months after the last dose of study drug. A *Clinical Trial* Pregnancy Report*ing Form* should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and *send* to Roche Safety Risk Management *either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators*. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study drug. *The* investigator *should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee* immediately (i.e., no more than 24 hours after learning of the pregnancy)*, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.* Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the *Clinical Trial* Pregnancy Report*ing Form* with additional information on the *pregnant partner and the* course and outcome of the pregnancy *as it becomes available*. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, reporting instructions provided in Section 5.4.3.1 should be followed.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 4 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Alectinib Investigator's Brochure
- SmPC (European Union) for crizotinib

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis population for the study is the safety analysis population defined as all patients enrolled in the study who receive at least one dose of study drug. Patients will be assigned to treatment groups as treated, and all patients who receive any dose of alectinib will be included in the alectinib treatment arm.

The primary and final analysis of the study will occur when all patients have discontinued treatment and have completed the safety follow-up visit.

No efficacy data are being collected in the study, and no hypothesis testing will be performed.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to provide continuous treatment with alectinib or crizotinib to patients with *ALK*- or *RET*-positive disease who are clinically benefitting from either alectinib or crizotinib in a Roche-sponsored parent study and due to approval status, reimbursement status, or local regulations do not have the option to be switched to a commercial supply at the time of parent study closure. All eligible patients from any parent study will be allowed to enter the study. No total sample size can be estimated.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, and reasons for discontinuation from study treatment will be summarized by treatment arm for all patients, including a summary of the number of patients enrolled from each parent study. Violations of inclusion and exclusion criteria, on the basis of information captured on the eCRF, will be reported and summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS AND CONDITIONS

Demographic and baseline characteristics (including age, sex, race, and reproductive status) and baseline conditions will be summarized using means, standard deviations,

medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 SAFETY ANALYSES

The following safety parameters will be summarized in tables by treatment arm:

- Adverse events, including adverse events leading to dose modifications or interruptions, study drug withdrawal, and death
- Severe, serious, and selected adverse events
- Deaths
- Laboratory parameters recorded on the eCRF

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and summarized by mapped term and appropriate thesaurus level. All adverse events and required laboratory parameters will be assessed according to the NCI CTCAE v4.0 grading system. For adverse events, the most extreme severity will be used for reporting. Adverse events will be described by individual listings and by body system, as well as by severity. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

Laboratory values will be summarized by treatment arm including summary tables for the shifts in grades from baseline to the worst grade observed during treatment.

Study drug administration will be summarized by duration and cumulative dose (based on the treatment received under this protocol only, not including the parent study treatment period).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the initial study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and

approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability (HIPAA) Act of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Enrollment will occur through an IxRS. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

ALECENSA® U.S. Package Insert, Hoffmann-La Roche Ltd, 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208434s000lbl.pdf.

Bongarzone I, Vigneri P, Mariani L, et al. RET/NTRK1 rearrangements in thyroid gland tumors of the papillary carcinoma family: correlation with clinicopathological features. Clin Cancer Res 1998;4:223–8.

Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013;3:630–5. doi:10.1158/2159-8290.CD-13-0035. Epub 26 March 2013.

Gainor J, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncol 2013;18,865–75. doi:10.1634/theoncologist.2013-0095. Epub 28 June 2013.

Gautschi O, Zander T, Keller FA, et al. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. J Thoracic Oncol 2013:8:e43–4. doi:10.1097/JTO.0b013e31828a4d07.

Grieco M, Santoro M, Berlingieri MT, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. Cell 1990;60:557–63.

Hart CD, De Boer RH. Profile of cabozantinib and its potential in the treatment of advanced medullary thyroid cancer. Onco Targets Ther 2013;6:1–7. doi:10.2147/OTT.S27671. Epub 3 January 2013.

Hartmann JT, Haap M, Kopp HG, et al. Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. Curr Drug Metab 2009;10:470–81.

Hohenegger M. Drug induced rhabdomyolysis. Curr Opin Pharmacol 2012;12:335–9. doi:10.1016/j.coph.2012.04.002. Epub 5 May 2012.

Jazii FR, Najafi Z, Malekzadeh R, et al. Identification of squamous cell carcinoma associated protoeins by proteomics and loss of beta tropomyosin expression in esophageal cancer. World J Gastroenterol 2006;12:7104–12.

Kinoshita K, Kobayashi T, Asoh K, et al. 9-Substituted 6, 6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazoles as highly selective and potent anaplastic lymphoma kinase inhibitors. J Med Chem 2011;54:6286–94. doi:10.1021/jm200652u. Epub 25 August 2011.

Knowles PP, Murray-Rust J, Kjaer S, et al. Structure and chemical inhibition of the RET tyrosine kinase domain. J Biol Chem 2006;281:33577–87. Epub 23 August 2006.

Kodama T, Tsukaguchi T, Satoh Y, et al. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. Mol Cancer Ther 2014;13:2910–8. doi:10.1158/1535-7163.MCT-14-0274. Epub 27 October 2014.

Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med 2012;18:375–7. doi:10.1038/nm.2644.

Lee SH, Lee JK, Ahn MJ, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement [abstract]. J Clin Oncol 2016;34(suppl);abstr 9013.

Lin E, Li L, Guan Y, et al. Exon array profiling detects EML4-ALK fusion in breast, colorectal, and non-small cell lung cancers. Mol Cancer Res 2009;7:1466–76. doi:10.1158/1541-7786.MCR-08-0522. Epub 8 September 2009.

Lin JJ, Kennedy E, Sequist LV, et al. Clinical activity of alectinib in advanced RET-rearranged non–small cell lung cancer. J Thoracic Oncol 2016;11:2027–32. doi:10.1016/j.jtho.2016.08.126. Epub 17 August 2016.

Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012;18;382–4. doi:10.1038/nm.2673.

Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994;263:1281–4.

Mossé YP, Laudenslager M, Longo L, et al. Identification of ALK as a major familial neuroblastoma predisposition gene. Nature 2008;455:930–5. doi:10.1038/nature07261. Epub 24 August 2008.

Powers C, Aigner A, Stoica GE, et al. Pleiotrophin signaling through anaplastic lymphoma kinase is rate-limiting for glioblastoma growth. J Biol Chem 2002;277:14153–8. Epub 23 January 2002.

Qi XP, Ma JM, Du ZF, et al. RET germline mutations identified by exome sequencing in a Chinese multiple endocrine neoplasia type 2A/familial medullary thyroid carcinoma family. PLoS One 2011;6:e20353. doi:10.1371/journal.pone.0020353. Epub 31 May 2011.

Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH542802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell 2011;19:679–90. doi:10.1016/j.ccr.2011.04.004.

Seto T, Kiura K, Nishio M, et al. CH542802 (RO542802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. Lancet Oncol 2013;14:590–8. doi:10.1016/S1470-2045(13)70142-6. Epub 30 April 2013.

Seto T, Yoh K, Satouchi M, et al. A phase II open-label single-arm study of vandetanib in patients with advanced *RET*-rearranged non-small cell lung cancer (NSCLC): Luret study [abstract]. J Clin Oncol 2016;34(suppl):abstr 9012.

Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-postive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17:234–42.

Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385–94. doi:10.1056/NEJMoa1214886. Epub 1 June 2013.

Shiota M, Fujimoto J, Semba T, et al. Hyperphosphorylation of a novel 80 kDa protein-tyrosine kinase similar to Ltk in a human Ki-1 lymphoma cell line, AMS3. Oncogene 1994;9:1567–74. doi:10.1016/S1470-2045(15)00488-X. Epub 19 December 2015.

Stoica GE, Kuo A, Aigner A, et al. Identification of anaplastic lymphoma kinase as a receptor for the growth factor pleiotrophin. J Biol Chem 2001;276:16772–9. Epub 8 February 2001.

Sugawara E, Togashi Y, Kuroda N, et al. Identification of anaplastic lymphoma kinase fusion in renal cancer: large-scale immunohistochemical screening by the intercalated antibody-enhanced polymer method. Cancer 2012;118:4427–36. doi:10.1002/cncr.27391. Epub 17 January 2012.

Sukov WR, Hodge JC, Lohse CM, et al. ALK alterations in adult renal cell carcinoma: frequency, clinicopathologic features and outcome in large series of consecutively treated patients. Mod Pathol 2012;25:1516–25. doi:10.1038/modpathol.2012.107. Epub 29 June 2012.

Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 1985;42:581–8.

Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med 2012;18:378–81. doi:10.1038/nm.2658.

Wang R, Hu H, Pan Y, et al. RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. J Clin Oncol 2012;30:4352–9. doi:10.1200/JCO.2012.44.1477. Epub 13 November 2012.

Wells Jr SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134–41. doi:10.1200/JCO.2011.35.5040. Epub 24 October 2011.

XALKORI U.S. Package Insert, Pfizer Inc. 2012 [cited 20 January 2014]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s002lbl.pdf.

XALKORI Summary of Product Characteristics, Pfizer Inc. 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002489/WC500134759.pdf

Yaakup H, Sagap I, and Fadilah SA. Primary oesophageal Ki(CD30)-positive ALK+ anaplastic large cell lymphoma of T-cell phenotype. Singapore Med J 2008;49:e289–92.

Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. Nat Rev Cancer 2007;7:35–45. Epub 14 December 2006.

ZYKADIA™ U.S. Package Insert, Novartis Pharmaceuticals Corporation, 2015. Available from: http://www.pharma.us.novartis.com/product/pi/pdf/zykadia.pdf.

Appendix 1
Schedule of Activities

	Screening [a]		Treatment Period			Treatment Discontinuation	Safety Follow-Up	Unscheduled Visits [b]
Assessments	Days –21 to 1	Days –3 to 1	Visit 1 Baseline (Day 1) [c]	Visit 2 (Week 4) ±3 Days	Visits 3 and beyond (Every 12 Weeks) ±7 Days		28±7 Days after Last Dose of Study Drug	
Informed consent	x							
Confirmation of eligibility		x						
Demographics and baseline characteristics [d]	x							
CRF, CRTN, and protocol number of parent trial	x							
Urine pregnancy test		x [e]	To be repeated as necessary					x
Adverse events [f, g]			x	x	x	x	x	
Selected safety laboratory parameters [h]		x [e]		x	x	x	x	x
Vital signs [i]			To be reported if clinically significant and/or if associated with an adverse event					
Drug dispensing and accountability			x	x	x	x [j]		
Hematology [i]			To be reported if clinically significant and/or if associated with an adverse event					
Biochemistry except selected safety parameters [i]			To be reported if clinically significant and/or if associated with an adverse event					
ECG [i]			To be reported if clinically significant and/or if associated with an adverse event					
Baseline conditions [k]	x							
Survival [l]			x	x	x	x	x	

ALP = alkaline phosphatase; CRF = Case Report Form; CRTN = clinical research task number; eCRF = electronic Case Report Form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] All screening assessments should be completed prior to the first dose on the rollover study.

[b] Unscheduled visit pages will be available for reporting of pregnancy test results, hematology, biochemistry, vital signs, and ECG.

[c] Study drug discontinuation and study completion visits for the parent trial should be performed on the same day as the baseline visit for the rollover study.

[d] Date of birth, sex, race/ethnicity and reproductive status.

[e] Results of laboratory screening assessments and pregnancy test should be reported on baseline visit eCRF page.

[f] Graded according to NCI CTCAE v4.0.

[g] Any adverse event occurring during the screening period but prior to the first dose of study drug administered on this rollover study should be reported within the parent trial according to parent trial reporting conventions.

[h] ALT, AST, total bilirubin, ALP, and blood CPK.

[i] According to local practice.

[j] Accountability only.

[k] Baseline conditions include adverse events with an onset date during the parent trial and that are unresolved at the time of first dose of study drug in the rollover study.

[l] Date and cause of death occurring during the study to be captured.

Appendix 2
List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters

This representative list is not intended to be an exhaustive list. Each patient's concomitant medications should be carefully considered by the investigator with regard to the risk-benefit for the particular patient and appropriate monitoring, including any concomitant medication, dose adjustment, or therapeutic alternatives, which should be determined by the investigator caring for the patient.

CYP3A Potent Inducers	CYP3A Potent Inhibitors
avasimibe, barbiturates, carbamazepine, efavirenz, ethosuximide, garlic supplements, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentine, St. John's wort, troglitazone	aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, verapamil, voriconazole
P-gp	
Substrates	**Inducers**
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan	avasimibe, carbmazepine, phenytoin, rifampin, St John's wort, tipranavir

This information in this appendix is adapted from Levien and Baker 2003[1], Zhang et al. 2011[2], and Food and Drug Administration (FDA) Guidance on Drug–Drug Interactions.

[1] Levien TL, Baker DE. Cytochrome P450 drug interactions. Therapeutic Research Center Pharmacist's Letter/Prescriber's Letter [resource on the Internet]. 2003 [cited day month year]. Available from: www.pharmacistsletter.com and www.prescribersletter.com.

[2] Zhang L, Huang SM, Lesko LJ. Transporter-mediated drug-drug interactions. Clin Pharmacol Ther 2011;89:481–4. doi: 10.1038/clpt.2010.359.

Appendix 2
List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters (cont.)

Also see:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Potent inhibitors of CYP3A are those considered to be "strong CYP3A inhibitors" previously shown to result in a ≥ 5-fold increase in the AUC of a concomitantly. These are based on the available published literature and, thus, are not considered exhaustive or inclusive. See FDA Guidance on Drug–Drug Interactions for further detail.