# PROTOCOL

| | |
|---|---|
| **TITLE:** | **AN OPEN-LABEL, ONE TREATMENT, FOUR GROUP, PARALLEL GROUP STUDY TO INVESTIGATE THE EFFECT OF IMPAIRED HEPATIC FUNCTION ON THE PHARMACOKINETICS OF ENTRECTINIB IN VOLUNTEERS WITH DIFFERENT LEVELS OF HEPATIC FUNCTION** |
| **PROTOCOL NUMBER:** | GP41174 |
| **VERSION NUMBER:** | 2 |
| **EUDRACT NUMBER:** | 2019-003065-17 |
| **IND NUMBER:** | 120500 |
| **NCT NUMBER:** | NCT04226833 |
| **TEST PRODUCT:** | Entrectinib (RO7102122, formerly RXDX-101) |
| **MEDICAL MONITOR:** | Harald Zeuner |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | See electronic date stamp below |

## PROTOCOL AMENDMENT APPROVAL

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## PROTOCOL HISTORY

| Protocol | |
|---|---|
| **Version** | **Date Final** |
| 1 | 28 August 2019 |

## PROTOCOL AMENDMENT, VERSION 2:
## RATIONALE

Protocol GP41174 has been amended to update safety data to align with most recent Entrectinib Investigator's Brochure (Version 9, Addendum 1). Changes to the protocol, along with a rationale for each change, are summarized below:

- Inclusion of the safety risks has been added to list of less common risks for entrectinib and the information has been put in tabular form (Section 1.1.4):

| **Less Common** (occurs in 1%–10% of patients) |
|---|
| • Difficulty swallowing<br>• Bone fracture<br>• Fainting due to drop in blood pressure<br>• Weakness of the heart muscle causing decreased pumping of blood, which may cause breathing difficulty, reduced kidney function, and fluid accumulation<br>• Electrocardiogram (ECG) QT prolonged, which may mean heart is not working normally |

- The protocol has been updated to specify that women of child-bearing potential are required to remain abstinent or use a highly effective method of contraception throughout the study and for 5 weeks after last study treatment. Men with female partners of child-bearing potential must agree to remain abstinent or use barrier contraception throughout the study and for 3 months after the last study treatment. Men whose female partners are pregnant must also use barrier contraception throughout the study to avoid potential exposure of the fetus to the study drug (Sections 1.2.2 and 4.4.2).
- Information has been added to clarify that re-screening is not allowed (Section 3.1).
- Information about future use of screening samples has been added (Section 4.5.5).

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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Sponsor Representative's Name (print)

Sponsor Representative's Signature

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**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.

## PROTOCOL SYNOPSIS

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| **EUDRACT NUMBER:** | 2019-003065-17 |
| **IND NUMBER:** | 120500 |
| **NCT NUMBER:** | NCT04226833 |
| **TEST PRODUCT:** | Entrectinib (RO7102122, formerly RXDX-101) |
| **PHASE:** | Phase I |
| **INDICATION:** | Volunteers with impaired hepatic function |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

## OBJECTIVES AND ENDPOINTS

| | Objectives | Endpoints |
|---|---|---|
| Primary | To investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib | The geometric mean ratio and associated 90% confidence intervals of total and unbound entrectinib and M5 $AUC_{inf}$ and $C_{max}$ parameters between groups of volunteers with reduced hepatic function and a control group of volunteers with normal hepatic function. Duplicate analyses will be performed for groups based on Child-Pugh and NCI-ODWG classifications. |
| | To explore the relationship between entrectinib pharmacokinetic parameters and measures of hepatic function | Linear or nonlinear models or regression analyses of the relationship between entrectinib pharmacokinetic parameters (e.g. $C_{max}$ and $AUC_{inf}$) and selected hepatic function parameters (e.g., Child-Pugh scores, albumin, bilirubin, or aspartate aminotransferase concentrations, prothrombin time) |
| Secondary | To explore the safety and tolerability of a single 100 mg oral dose of entrectinib in groups of volunteers with reduced hepatic function and a control group of volunteers with normal hepatic function | Incidence and severity of AEs, incidence of abnormalities in laboratory safety tests, 12-lead ECGs, vital sign measurements |

## OVERALL DESIGN

### Study Design

This is a non-randomized, open-label, one treatment, four group, parallel group study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function. Volunteers with mild, moderate or severe hepatic impairment (‘Mild’, ‘Moderate’ and ‘Severe’ groups), and control volunteers with normal hepatic function (‘Normal’ group) will each receive a single 100 mg dose of entrectinib after consumption of a standardized meal.

Volunteers with reduced hepatic function will be assigned to a functional category based on assessments at the Screening visit. Each individual will be categorized according to the Child Pugh system for classifying hepatic impairment and also according to the National Cancer Institute organ dysfunction working group (NCI-ODWG) system. Sufficient volunteers will be enrolled to ensure that at least six individuals are recruited in each hepatic function group for both classification systems.

Recruitment will be staggered to allow review of pharmacokinetic and safety data from at least three volunteers with mild hepatic impairment and three volunteers with moderate hepatic impairment (Child-Pugh classification system) before volunteers with severely impaired hepatic

function are enrolled. Recruitment of volunteers with severely impaired hepatic function will only proceed if there is agreement between the Sponsor and the Investigator that data from this group are necessary to fulfil the objectives of the study and that dosing is not anticipated to present an unacceptable risk to those individuals.

The control group of volunteers with normal hepatic function will be enrolled after the full complement of volunteers with hepatic dysfunction has been dosed. The Normal group will be matched with the hepatically impaired volunteers with respect to sex, age and weight. The control group will include volunteers within the range of the hepatically impaired volunteers (extremes covered as far as possible), with approximately 50% of volunteers on each side of the median.

The study treatments will be administered orally as 1 x 100 mg F06 capsule, and given with approximately 240 mL of water within 30 minutes of consumption of a standardized meal.

Blood samples for measurement of plasma concentrations of entrectinib and its active metabolite M5 will be collected before and at intervals up to 144 hr after study drug dosing. In addition, samples will be taken for ex vivo measurement of plasma protein binding. Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

**Length of Study**
The total duration of the study for each enrolled volunteer (screening through to end of study) will be up to 7 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug
- One treatment period
- Safety follow-up: $11$ to $13$ days after $first$ study drug administration

Study participants will be resident in the study centre from Day -1 until at least Day 3, although the timing of admission and discharge is at the discretion of the Investigator and individuals may remain resident until Day 7. Volunteers will also have ambulatory study centre visits at Screening and Follow-up, and Days 4, 5 and 7 as appropriate.

**PARTICIPANT POPULATION**

**Inclusion Criteria:**
Volunteers must fulfill the following inclusion criteria to be eligible for participation in the study:

All volunteers

1. Male or female
2. Aged 18 to 75 years of age, inclusive, at screening.
3. A body mass index (BMI) between 18.0 and 38.0 kg/m$^2$, and weighing at least 50 kg, at screening.
4. Agreement to comply with measures to prevent pregnancy and restrictions on sperm donation.
5. Able and willing to give written informed consent and to comply with study protocol and study restrictions.

Additional criteria for volunteers with normal hepatic function:

6. Normal hepatic function and no history of clinically significant hepatic dysfunction.

7. Healthy for age-group in the opinion of the Investigator. Assessment of health status is based on a detailed medical history, physical examination, vital signs and 12-lead ECG assessment, and laboratory safety test results. Concurrent chronic disorders such as hypertension and diabetes are permissible providing they are stable and adequately controlled.

Additional criteria for volunteers with hepatic impairment

8. Mild, moderate or severe hepatic dysfunction (i.e. Child-Pugh A, B or C, NCI-ODWG Mild, Moderate or Severe) arising from cirrhosis of the liver as the result of parenchymal liver disease. Cirrhosis should be documented by relevant laboratory test results and medical history, including confirmation of the diagnosis by liver biopsy, hepatic ultrasound, computerized tomography scan or magnetic resonance imaging scan.

9. Stable hepatic function. Stable hepatic function is defined as no recent (i.e. within the preceding 14 days) clinically significant change in disease status according to the Investigator's clinical judgment (e.g., no worsening of clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin by more than 50%).

**Exclusion Criteria:**
Participants are not eligible for the study if any of the following criteria are met:

All volunteers

1. Transjugular intrahepatic portosystemic shunt or other porta-caval shunt.

2. A history of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers within the three months preceding screening.

3. Recent history (i.e. within the last 6 months prior to screening) or signs of severe hepatic encephalopathy (e.g., a portal systemic encephalopathy score >2).

4. Advanced ascites or ascites which require emptying and albumin supplementation, as judged by the Investigator

5. Hepatocellular carcinoma, acute liver disease (e.g., caused by an infection or drug toxicity) or serum ALT or AST at screening not consistent with stable disease in the opinion of the Investigator.

6. Recipient of a liver transplant.

7. Uncontrolled hypertension, defined as systolic blood pressure $>$ 160 mmHg and/or diastolic blood pressure $\geq$ 105 mmHg, considered clinically significant by the Investigator.

8. Clinically significant impairment of renal function, defined as a creatinine clearance of <60 mL/min estimated from serum creatinine concentrations using *Cockcroft-Gault equation*.

9. A history of gastrointestinal surgery (e.g. gastric bypass) or other gastrointestinal disorder (e.g. malabsorption syndrome) that might affect absorption of medicines from the gastrointestinal tract. Cholecystectomy is permissible.

10. Clinically significant change in health status, as judged by the Investigator, or any major illness within the four weeks before screening, or clinically significant acute infection or febrile illness within the 14 days before screening.

11. Apart from hepatic dysfunction, any other ongoing condition or disease, or laboratory test result, that the Investigator considers would render the participant unsuitable for the study, place the volunteer at undue risk, interfere with the ability of the volunteer to complete the study (e.g. short life expectancy), or confound interpretation of study data. Concurrent chronic disorders such as hypertension and diabetes are permissible providing they are stable and adequately controlled.

12. Women who are pregnant or lactating.

13. Heart-rate corrected QT interval (QTcF) >480 msec or the presence of any other abnormal ECG finding, which, in the Investigator's opinion, is clinically significant.

14. Use of moderate or potent inhibitors or inducers of cytochrome P450 3A4 enzyme within the 28 days before screening.

15. Participation in any other clinical study involving an investigational medicinal product or device within 28 days before screening.

16. A positive test result for human immunodeficiency virus (HIV).

17. Recent history (i.e. within the last 6 months prior to screening) of alcoholism, drug abuse, or drug addiction, or a positive test for alcohol or drugs of abuse. Alcohol consumption not exceeding 21 units for men and 14 units for women per week (1 unit equals 250 mL of beer, 75 mL of wine, or 25 mL of spirits) is permitted, although volunteers should not consume alcohol in the 48 hours preceding study center visits or during the period of in-patient confinement.

18. Known history of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds or other excipients in the entrectinib formulation.

19. Donation or loss of over 500 mL of blood within the three months before screening.

**NUMBER OF PARTICIPANTS**

It is planned that approximately 24 volunteers will be enrolled, with a target of six in each hepatic function group. The actual number enrolled will be determined by the Sponsor during the study from review of emerging data to ensure that at least six individuals are recruited in each hepatic function group for both classification systems, i.e. additional volunteers will be recruited if differences between the two categorization systems mean that there are fewer than six evaluable individuals in any hepatic function analysis group. Volunteers who withdraw from the study before Day 7 may also be replaced to ensure that at least six volunteers in each group have evaluable pharmacokinetic data.

No formal sample size calculations were performed. Six volunteers per group is consistent with recommendations in US and European regulatory guidelines [3, 4]. Based on the observed variability in entrectinib exposure parameters in previous clinical studies (e.g. $AUC_{inf}$ CV% 9-34%

from F06 capsules in healthy volunteers under fed conditions) six volunteers per group is considered appropriate to estimate the magnitude of the effect of hepatic impairment on entrectinib pharmacokinetic parameters.

**PERMITTED AND PROHIBITED CONCOMITANT MEDICATIONS**

Concurrent administration of drugs used to manage hepatic dysfunction and related disorders are permitted providing there has been no alteration to the treatment regimen within one week preceding screening and the dosing regimen is not anticipated to change during the study. Similarly, other medications for chronic conditions (e.g. diabetes, hypertension) are permitted providing the volunteer has been on a stable dose and dosing regimen for at least one month preceding screening. However, the following categories of medication are specifically prohibited:

- Moderate or potent inhibitors or inducers of CYP3A enzymes.

Volunteers should not consume grapefruit or Seville oranges during the study. During periods of in-patient residency volunteers will also be required to refrain from smoking, abstain from consumption of alcohol, and follow restrictions on consumption of food and beverages containing caffeine/xanthines, according to standard practices for the study center.

Women of child-bearing potential will be required to remain abstinent or use a highly effective method of contraception throughout the study *and for 5 weeks after the last study treatment. Women must refrain from donating eggs during this same period.* Men with female partners of child-bearing potential *must agree to remain abstinent or* use barrier contraception throughout the study *and for 3 months after the last study treatment. Men whose female partners are pregnant must also use barrier contraception throughout the study to avoid potential exposure of the fetus to the study drug.* All men must also refrain from donating sperm during the study *and for 3 months after the last study treatment.*

**STATISTICAL ANALYSIS**

Plasma concentrations of entrectinib and its active metabolite M5, and derived plasma pharmacokinetic parameters, will be listed and summarized by group using descriptive statistics. Individual and mean concentration versus time profiles will be plotted. Separate summaries will be presented for groups categorized according to the Child Pugh and NCI-ODWG system for classifying hepatic function. In effect there may be eight analysis groups (i.e. Normal Child-Pugh, Normal NCI-ODWG, Mild Child-Pugh, Mild NCI-ODWG, Moderate Child-Pugh, Moderate NCI-ODWG, Severe Child-Pugh, and Severe NCI-ODWG).

The following pharmacokinetic parameters will be derived using standard non-compartmental methods:

- $C_{max}$: Maximum observed plasma concentration
- $AUC_{last}$: Area under the plasma entrectinib concentration-time curve from time 0 to the last measurable concentration.
- $AUC_{inf}$: Area under the plasma entrectinib concentration-time curve from time 0 extrapolated to infinity.
- $T_{max}$: Time of maximum observed plasma concentration
- $\lambda_z$: Apparent terminal elimination rate constant
- $t_{1/2}$: Apparent terminal elimination half-life
- M:P ratio: Molecular weight-adjusted metabolite to parent ratio based on $AUC_{inf}$
- CL/F: Apparent oral clearance (entrectinib only)
- V/F: Apparent volume of distribution (entrectinib only)
- $f_u$: Fraction of drug unbound in plasma

The fractions of entrectinib and M5 unbound in plasma ($f_u$) will be determined by ex vivo protein binding assay and used to calculate exposure parameters adjusted for protein binding (i.e., unbound $C_{max}$, unbound $AUC_{inf}$).

An analysis of variance (ANOVA) will be used to estimate the effect of hepatic impairment on log-transformed total and unbound entrectinib and M5 exposure parameters and will include the factor hepatic impairment (i.e. mild, moderate and severe, and none). Estimates of geometric mean ratios on the original scale, together with the corresponding 90% confidence intervals (CIs), will be derived for the comparisons between each hepatic impairment group and the control group with normal hepatic function. Duplicate analyses will be performed for groups based on Child-Pugh and NCI-ODWG classifications.

The relationship between entrectinib pharmacokinetic parameters (e.g. $C_{max}$ and $AUC_{inf}$) and measures of hepatic function (e.g., Child-Pugh scores, albumin, bilirubin, or AST concentrations, prothrombin time etc.) will be explored using linear or non-linear models or regression analyses, as appropriate.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| ANOVA | analysis of variance |
| BMI | body mass index |
| CI | confidence interval |
| CNS | central nervous system |
| CRO | contract research organization |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DBP | diastolic blood pressure |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| HDL-C | High density lipoprotein-cholesterol |
| hERG | human ether-à go-go-related gene |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| LC-MS/MS | liquid chromatography tandem mass spectrometry |
| LDL-C | Low density lipoprotein-cholesterol |
| MRI | magnetic resonance imaging |
| NCI | National Cancer Institute |
| ODWG | organ dysfunction working group |
| P-gp | P-glycoprotein |

| Abbreviation | Definition |
|---|---|
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RBC | red blood cell |
| SI | Système international (d'unités), [International System of Units] |
| SBP | systolic blood pressure |
| UGT | UDP-glucuroyltransferase |
| ULN | upper limit of normal |
| US | United States of America |
| WBC | white blood cell |

# 1. BACKGROUND

Entrectinib (RO7102122, formerly known as RXDX-101) is a potent and selective inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK receptor tyrosine kinases. These kinases are overexpressed or dysregulated in a number of types of cancer with constitutive activity, making the growth of the cancer cells dependent on or "addicted" to the abnormal kinases [5, 6]. Therefore, these kinases represent attractive targets for anticancer therapy and approval is currently being sought for use of entrectinib in adults and children for oncology indications.

Refer to the Investigator's Brochure (IB) for detailed background information on entrectinib and for details on nonclinical and clinical studies.

## 1.1 BACKGROUND ON ENTRECTINIB

### 1.1.1 Pharmacology

Entrectinib selectively inhibits TRKA/B/C, ROS1, and ALK tyrosine kinases at low nanomolar concentrations in vitro, and is highly potent in inhibiting proliferation of tumor cell lines dependent on the expression of these kinases. Treatment of mice bearing different xenograft (TRKA- or ALK-dependent) or allograph (ROS1 dependent) tumors with 60 mg/kg entrectinib twice daily showed potent growth inhibition of TRKA-dependent tumors and even complete regression of ROS1- and ALK-dependent tumors.

### 1.1.2 Toxicology and Safety Pharmacology

In in vivo toxicology studies, adverse findings were observed in the skin, liver, central nervous system (CNS), and hemolymphopoietic system of both rats and dogs, while gastrointestinal toxicity was also observed in dogs. These effects were dose- and exposure-dependent, and exhibited reversibility. Central and peripheral neurologic events were common, consistent with penetration of entrectinib into the CNS and the role of TRK receptors in neuronal development and maintenance; signs included incoordination, decreased activity, staggering, abnormal gait, tremors, hypoactivity, and depression. In Good Laboratory Practices repeat-dose studies, no observed adverse effect levels were 7.5 mg/kg/day in rats and 15 mg/kg/day in dogs.

Entrectinib inhibited human ether-à go-go-related gene (hERG) tail current in vitro with a half-maximal inhibitory concentration of 0.6 μM as free drug (approximating to 120 μM after correction for plasma protein binding in humans). In in vivo preclinical studies, moderate but reversible prolongation of the QT interval corrected for heart rate (QTc) was noted on electrocardiograms (ECGs) at high doses in dogs.

Entrectinib was not mutagenic or clastogenic in in vitro or in vivo genotoxicity studies. There was no evidence of adverse effects on reproductive organs in repeat-dose toxicology studies. In an embryo-fetal developmental study, oral administration of entrectinib to pregnant rats during organogenesis caused developmental abnormalities at dose levels that also caused maternal toxicity.

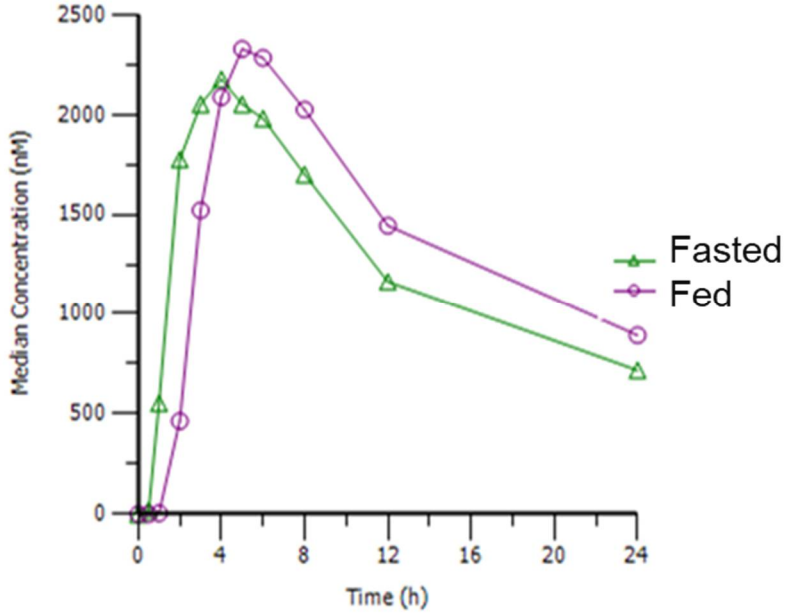
Entrectinib is not phototoxic based on results from an in vivo rat study. However, microscopic findings in rats of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at high doses were considered entrectinib-related.

### 1.1.3 Pharmacokinetics

Entrectinib is readily absorbed following oral administration with reasonable oral bioavailability (31% to 76% in preclinical species) and with peak concentrations typically occurring approximately 4 hours after dosing with immediate release capsules (Figure 1). Entrectinib exposure is dose proportional, with no significant dose- or time-dependency. The terminal half-life of entrectinib is approximately 20 to 30 hours.

Food has no clinically relevant effect on entrectinib oral bioavailability from capsule formulations (Figure 1).

**Figure 1: Median entrectinib plasma concentration versus time profile following a single 600 mg dose to healthy volunteers under fed or fasted conditions**




Source: Study RXDX-101-154 CSR Figure 14.3.

Entrectinib is highly protein bound (≥99%) and has a high apparent volume of distribution (approximately 600 L), indicating extensive distribution into body tissues. Data also suggest that entrectinib crosses the blood/brain barrier.

Entrectinib is primarily cleared by metabolism, with the majority of a dose being recovered as metabolites in feces and very little elimination of parent drug or metabolites via the kidney. Based on in vitro incubations, cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for the biotransformation of entrectinib, with lesser contributions

from other CYPs and Phase II enzymes. The M5 metabolite (formed by demethylation) is a major circulating metabolite and is also pharmacologically active.

In in vitro and in vivo drug-drug interaction studies entrectinib was a weak inhibitor of CYP3A enzyme activity. Although in vitro studies suggest entrectinib is a poor P-glycoprotein (P-gp) substrate and has weak inhibitory effects on selected drug transporters, clinically relevant interactions are not anticipated in vivo.

### 1.1.4 Clinical Program

The clinical program to date includes 10 completed healthy volunteer and 5 patient studies: approximately 300 healthy volunteers and approximately 400 patients have received one or more doses of entrectinib. In patients with NTRK, ROS1, or ALK fusion-positive locally advanced or metastatic extracranial solid tumors, antitumor activity has been broadly observed among TRK, ROS1, and ALK inhibitor-naïve patients treated with entrectinib, including patients with CNS involvement. Based upon particularly compelling clinical safety and efficacy data and an assessment of unmet medical need, entrectinib development has focused on 2 patient populations, NTRK fusion-positive solid tumors and ROS1 fusion-positive non-small cell lung cancer.

*The treatment-related AEs in* the four main entrectinib studies in oncology patients *are described in Table 1:*

### *Table 1 Treatment-Related AEs Experienced in Four Main Entrectinib Studies*

| ***Common*** *(occurs in more than 10% of patients)* |
|---|
| • *Feeling weak or lack of energy*<br>• *Swelling or fluid retention of the face, arms, or legs, or a part of the body*<br>• *Pain (including back pain, neck pain, muscle or bone pain in chest, muscle or bone pain, pain in arms or legs)*<br>• *Fever*<br>• *Constipation*<br>• *Diarrhea*<br>• *Nausea*<br>• *Vomiting*<br>• *Abdominal pain*<br>• *Taste alteration*<br>• *Dizziness (including a sense of spinning, dizziness when changing position)*<br>• *Abnormal sensation of touch (including burning or prickling sensation, increase or decrease in sensitivity of skin)*<br>• *Cognitive disorders (difficulty with memory, learning, and judgment, including confusion, disturbance in attention, hallucination, and mental status changes)*<br>• *Effects on nerves that control arms and legs resulting in weakness*<br>• *Headache*<br>• *Loss of muscle control and balance*<br>• *Shortness of breath*<br>• *Cough*<br>• *Decrease in red blood cells, which may result in symptoms such as tiredness, weakness, or shortness of breath*<br>• *Decrease in neutrophils (a type of white blood cell), which may affect your body's ability to fight infection*<br>• *Weight increased*<br>• *Decreased appetite*<br>• *Dehydration*<br>• *Increased level of creatinine in blood, which may mean kidneys are not working normally*<br>• *Joint pain*<br>• *Muscle pain*<br>• *Muscle weakness*<br>• *Increased level of aspartate aminotransferase, which may mean liver is not working normally*<br>• *Increased level of alanine aminotransferase, which may mean liver is not working normally*<br>• *Lung infection, including bronchitis, upper or lower respiratory tract infection, and pneumonia*<br>• *Urinary tract infection*<br>• *Blurred vision*<br>• *Rash, including rash that may be red, itchy, with small bumps on skin*<br>• *Decreased blood pressure* |

**Table 1 Treatment-Related AEs Experienced in Four Main Entrectinib Studies (cont.)**

| ***Less Common*** *(occurs in 1% –10% of patients)* |
|---|
| • *Difficulty swallowing*<br>• *Bone fracture*<br>• *Fainting due to drop in blood pressure*<br>• *Weakness of the heart muscle causing decreased pumping of blood, which may cause breathing difficulty, reduced kidney function, and fluid accumulation*<br>• *Electrocardiogram (ECG) QT prolonged, which may mean heart is not working normally* |

All AEs were reversible with dose modifications, and there was no evidence of cumulative toxicity, clinically significant hepatic toxicity, or clinically significant QTc prolongation. In single-dose clinical pharmacology studies, entrectinib doses up to 800 mg have been administered to healthy volunteers without significant *serious or severe* safety findings.

## 1.2 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

### 1.2.1 Study Rationale

In vitro studies indicate that the clearance of entrectinib is predominantly through hepatic metabolism, and that entrectinib is primarily metabolized by cytochrome P450 3A4 (CYP3A4) with minor contributions from several other cytochrome P450 enzymes and UDP-glucuroyltransferase 1A4 (UGT1A4). Furthermore, co-administration of a strong CYP3A4 inhibitor (itraconazole), increased entrectinib total exposure by approximately 5-fold while co-administration of a strong inducer (rifampin) decreased entrectinib total exposures by approximately 77%. Thus the results indicate that entrectinib is a sensitive substrate of CYP3A4 and hence impairment of liver function has the potential to alter exposure of entrectinib and its major active metabolite M5. As entrectinib is likely to be administered to patients with hepatic dysfunction, a pharmacokinetic study in individuals with reduced hepatic function is required according to US and European regulatory guidelines [3, 4]. The aim of this study is therefore to quantify the effect of hepatic impairment on the pharmacokinetics of entrectinib and thereby underwrite dosing recommendations for use of entrectinib in patients with reduced hepatic function.

### 1.2.2 Benefit-Risk Assessment

There will be no therapeutic benefit for the volunteers participating in the study.

The risks of participation are primarily those associated with adverse reactions to the study drug, although there may also be some discomfort from collection of blood samples and other study procedures. The tolerability profile of entrectinib from administration of single doses up to 800 mg to healthy subjects has been characterized from previous clinical studies. There have been few AEs following entrectinib dosing in

previous clinical studies in healthy volunteers and no specific safety concerns have been identified about the use of 100 mg entrectinib in volunteers with impaired hepatic function in this study. Of the risks identified in the IB, none require specific monitoring or risk mitigation procedures. Potential drug-drug interactions with other medications are addressed by restrictions on concomitant medication use. Potential risks to a developing fetus from entrectinib exposure in utero are addressed by exclusion of pregnant females from the study and the requirement for all participants to use *highly* effective contraception throughout the study. *In addition, woman need to use highly effective contraception for 5 weeks after cessation of entrectinib treatment and men with female partners of childbearing potential or female partners who are pregnant need to use highly effective contraception for 3 months after last study treatment.*

Overall, no significant safety concerns have been identified about the use of 100 mg entrectinib in volunteers with impaired hepatic function. All volunteers will be resident in the study center and remain under medical supervision following study drug administration and will undergo a standard battery of safety assessments. Hence, the risks to participants in this study are considered acceptable.

# 2. OBJECTIVES AND ENDPOINTS

## 2.1 PRIMARY OBJECTIVES

The primary objectives of the study are to:

- To investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib
- To explore the relationship between entrectinib pharmacokinetic parameters and measures of hepatic function

## 2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to:

- To explore the safety and tolerability of a single 100 mg oral dose of entrectinib in groups of volunteers with reduced hepatic function and a control group of volunteers with normal hepatic function

## 2.3 ENDPOINTS

The primary endpoints of the study are:

- The geometric mean ratio and associated 90% confidence intervals of total and unbound entrectinib and M5 $C_{max}$ and $AUC_{inf}$ parameters between groups of volunteers with reduced hepatic function and a control group of volunteers with normal hepatic function.

Duplicate analyses will be performed for groups based on Child-Pugh and NCI-ODWG classifications.

- Linear or nonlinear models or regression analyses of the relationship between entrectinib pharmacokinetic parameters (e.g. $C_{max}$ and $AUC_{inf}$) and selected hepatic function parameters (e.g., Child-Pugh scores, albumin, bilirubin, or aspartate aminotransferase [AST] concentrations, prothrombin time).

Secondary endpoints of the study are:

- Incidence and severity of AEs, incidence of abnormalities in laboratory safety tests, 12-lead ECGs, vital sign measurements

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

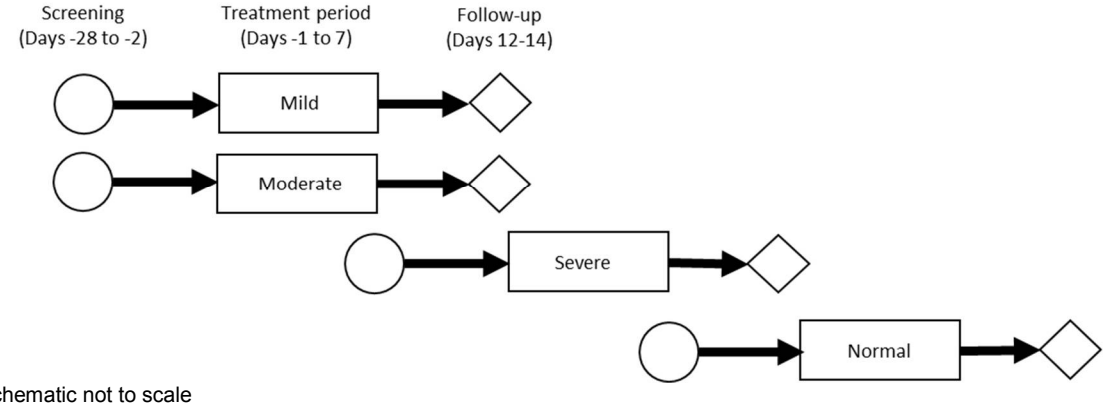
This is a non-randomized, open-label, one treatment, four group, parallel group study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function. Volunteers with mild, moderate or severe hepatic impairment ('Mild', 'Moderate' and 'Severe' groups), and control volunteers with normal hepatic function ('Normal' group) will each receive a single 100 mg dose of entrectinib after consumption of a standardized meal. A representation of the study design is provided in Figure 2.

Volunteers with reduced hepatic function will be assigned to a functional category based on assessments at the Screening visit. Each individual will be categorized according to the Child Pugh system for classifying hepatic impairment (Table 3) and also according to the National Cancer Institute (NCI) organ dysfunction working group (NCI-ODWG) system (Table 4). Sufficient volunteers will be enrolled to ensure that at least six individuals are recruited in each hepatic function group for both classification systems (see Section 6.1 ).

Recruitment will be staggered to allow review of pharmacokinetic and safety data from at least three volunteers in each of the Mild and Moderate groups before volunteers are enrolled into the Severe group. Recruitment of the Severe group will only proceed if there is agreement between the Sponsor and the Investigator that data from this group are necessary to fulfill the objectives of the study and that dosing is not anticipated to present an unacceptable risk to those individuals.

The control group of volunteers with normal hepatic function will be enrolled after the full complement of volunteers with hepatic dysfunction has been dosed. The Normal group will be matched with the hepatically impaired volunteers with respect to sex, age and weight. The control group will include volunteers within the range of the hepatically impaired volunteers (extremes covered as far as possible), with approximately 50% of volunteers on each side of the median.

**Figure 2: Overview of study design**




Schematic not to scale

The study treatment will be administered orally as 1 x 100 mg F06 capsule, and given with approximately 240 mL of water within 30 minutes after consumption of a standardized meal.

Blood samples for measurement of plasma concentrations entrectinib and its active metabolite M5 will be collected before and at intervals up to 144 hr after study drug dosing. In addition, samples will be taken for ex vivo measurement of plasma protein binding. Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

Study participants will be resident in the study center from Day -1 until at least Day 3, although the timing of admission and discharge is at the discretion of the Investigator and individuals may remain resident until Day 7. Volunteers will also have ambulatory study center visits at Screening and Follow-up, and Days 4, 5 and 7 as appropriate.

*Patients who do not meet the criteria for participation in this study (screen failure) cannot be re-screened. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).*

## 3.2 END OF STUDY AND LENGTH OF STUDY

The total duration of the study for each enrolled volunteer (screening through to end of study) is expected to be approximately 8 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug
- One treatment period
- Safety follow-up: *11* to *13* days after *first* study drug administration

The end of study is defined as the date of the last scheduled study procedure for the last participating volunteer. In addition, the Sponsor may decide to terminate the study at any time.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Entrectinib Dose and Schedule

A single 100 mg dose will be administered to each participant. The recommended dose of entrectinib for cancer patients is 600 mg once daily and single doses of entrectinib up to 800 mg have been administered to healthy volunteers in previous clinical pharmacology studies without notable safety or tolerability findings. A lower dose of entrectinib has been chosen for this study because of the anticipated effect of hepatic impairment on entrectinib pharmacokinetics. Although first pass clearance of entrectinib appears negligible and it is not anticipated that peak exposure from a single dose will be significantly altered by hepatic dysfunction, any reduction in systemic clearance has the potential to markedly increase total exposure. Selection of a low dose allows the same dose to be used in all categories of hepatic function without compromising individual safety, while still permitting full characterization of entrectinib and M5 pharmacokinetics in all groups.

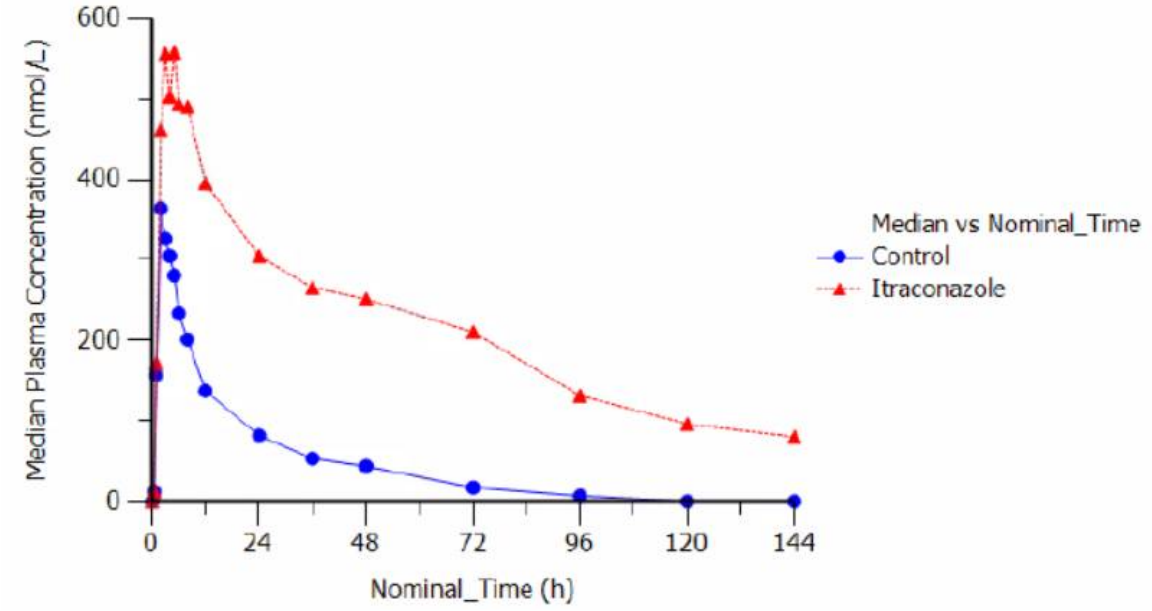
It is anticipated that severe impairment of liver function will lead to an increase in entrectinib exposure comparable to the magnitude of the drug-drug interaction observed when a potent CYP3A4 inhibitor is co-administered with entrectinib (Study RXDX-101-12. Figure 3 and Table 2). When a single 100 mg dose of entrectinib was co-administered with the potent CYP3A4 inhibitor itraconazole, entrectinib total exposure was increased approximately 500% but remained similar to that from a single 600 mg entrectinib dose administered alone (e.g. Figure 1).

**Table 2: Entrectinib and M5 pharmacokinetic parameters following administration of a single 100 mg dose of entrectinib with and without co-administration of itraconazole (Study RXDX-101-12)**

| | Parameter | 100 mg entrectinib alone (n=10) | 100 mg entrectinib plus itraconazole (n=9) | Ratio between treatment means (90% CI) |
|---|---|---|---|---|
| Entrectinib | $C_{max}$ (nM) | 358 (35%) | 615 (17%) | 1.73 (1.37, 2.18) |
| | $T_{max}$ (hr) | 2.0 (1.0-3.0) | 5.0 (2.0-8.0) | |
| | $AUC_{inf}$ (nM.hr) | 6190 (50%) | 36100 (17%) | 6.04 (4.54, 8.04) |
| | $t_{1/2}$ (hr) | 20.2 (17%) | 49.8 (22%) | |
| M5 | $C_{max}$ (nM) | 52.3 (37%) | 31.5 (42%) | 0.44 (0.35, 0.56) |
| | $T_{max}$ (hr) | 5.0 (3.0-5.0) | 6.00 (5.0-48.0) | |
| | $AUC_{inf}$ (nM.hr) | 1710 (30%) | 4310 (30%) | 0.23 (0.18, 0.29) |
| | $t_{1/2}$ (hr) | 40.8 (22%) | 88.0 (32%) | |

Source: Study RXDX-101-12 CSR Tables 7, 13.1 and 13.2
Geometric mean (CV%) for $C_{max}$, $AUC_{inf}$, and $t_{1/2}$, median (minimum-maximum) for $T_{max}$.

**Figure 3: Median entrectinib plasma concentration vs. time profiles following administration of a single 100 mg dose of entrectinib with and without co-administration of itraconazole (Study RXDX-101-12)**




Source: Study RXDX-101-12 CSR Figure 13.1

Study drug administration will be with food. Typically, pharmacokinetic studies are conducted while fasted but many hepatically impaired patients are diabetic and would thus be unable to comply with a standard fasting regimen. Giving entrectinib with food also matches dosing instructions for patients in pivotal and supportive clinical trials, which recommend administering entrectinib within 30 minutes following a meal.

### 3.3.2 Rationale for Patient Population

The study will recruit volunteers with impaired hepatic function arising from liver cirrhosis and matched controls with normal hepatic function. Hepatic function will be assessed using two widely accepted functional categorization systems (Child Pugh, see Table 3; NCI-ODWG, see Table 4). Cirrhosis is to be confirmed by independent diagnostic procedures. The two categorization systems will be used in parallel because, while regulatory guidelines on assessment of the effect of hepatic impairment on drug pharmacokinetics recommend use of Child Pugh categorization [3, 4], entrectinib is intended for use in oncology indications and the NCI-ODWG system is considered most relevant for prescribers.

### 3.3.3 Rationale for Study Design

The aim of the study is to estimate the effect of hepatic impairment on the pharmacokinetics of entrectinib with the intention of underwriting recommendations for the safe use of entrectinib in patients with hepatic dysfunction. This will be achieved by comparison of entrectinib single dose pharmacokinetic parameters between groups of volunteers with reduced hepatic function and a demographically matched control group

of healthy volunteers with normal hepatic function. The study design follows the principles described in regulatory guidelines for investigating the effects of hepatic impairment on investigational compounds [3, 4]. Two designs are suggested in regulatory guidelines: a 'full' study design including volunteers with normal hepatic function (control) and mild, moderate and severe hepatic impairment, and a 'reduced' study design including volunteers with normal hepatic function (control) and moderate hepatic impairment. A ‘full’ study design has been selected because the intended indications for entrectinib make it likely to be used in patients with significant hepatic dysfunction.

A single dose design is considered appropriate to explore the effect of hepatic impairment because entrectinib pharmacokinetics are not time dependent and single dose pharmacokinetics are predictive of steady state pharmacokinetics. This study is not blinded because it is not believed that knowledge of the treatment administered will introduce bias into the assessment of entrectinib pharmacokinetics.

### 3.3.4 Rationale for Assessments

The pharmacokinetic sampling schedule has been selected on the basis of data from previous studies in which single doses of entrectinib have been administered to healthy volunteers and patients. Specifically, the entrectinib and M5 pharmacokinetic profiles observed when entrectinib was co-administered with itraconazole (Study RXDX-101-12) were used to inform the pharmacokinetic sampling schedules. The frequency and duration of plasma sampling is considered to be sufficient to accurately estimate relevant pharmacokinetic parameters in all hepatic function groups; it is considered that sampling out to 144 hr after dosing will allow adequate characterization of the terminal phase of entrectinib even in individuals with severe hepatic impairment. The pharmacokinetic parameters to be derived and subject to statistical analysis are consistent with the relevant regulatory guidelines [3, 4]. Samples will also be taken from all participants to allow estimation of protein binding and thereby permit comparisons of unbound pharmacokinetic parameters.

Although it is potentially of interest to explore whether the contribution of renal clearance to total clearance is affected by hepatic dysfunction, data from healthy subjects indicate that very little entrectinib or M5 is excreted unchanged into the urine. It is therefore unlikely that measurement of entrectinib concentrations in urine would allow any meaningful conclusions to be drawn. For this reason, there will be no urine collection during the study.

# 4. MATERIALS AND METHODS

## 4.1 POPULATION

The study will enroll male and female volunteers with mild, moderate or severe hepatic impairment and control volunteers with normal hepatic function.

### 4.1.1 Inclusion Criteria

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

**All volunteers**

1. Male or female
2. Aged 18 to 75 years of age, inclusive, at screening.
3. A body mass index (BMI) between 18.0 and 38.0 kg/$m^2$, and weighing at least 50 kg, at screening.
4. Agreement to comply with measures to prevent pregnancy and restrictions on sperm donation.
5. Able and willing to give written informed consent and to comply with study protocol and study restrictions.

**Additional criteria for volunteers with normal hepatic function**

6. Normal hepatic function and no history of clinically significant hepatic dysfunction.
7. Healthy for age-group in the opinion of the Investigator. Assessment of health status is based on a detailed medical history, physical examination, vital signs and 12-lead ECG assessment, and laboratory safety test results. Concurrent chronic disorders such as hypertension and diabetes are permissible providing they are stable and adequately controlled.

**Additional criteria for Volunteers with hepatic impairment**

8. Mild, moderate or severe hepatic dysfunction (i.e. Child-Pugh A, B or C, NCI-ODWG Mild, Moderate or Severe) arising from cirrhosis of the liver as the result of parenchymal liver disease. Cirrhosis should be documented by relevant laboratory test results and medical history, including confirmation of the diagnosis by liver biopsy, hepatic ultrasound, computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan.
9. Stable hepatic function. Stable hepatic function is defined as no recent (i.e. within the preceding 14 days) clinically significant change in disease status according to the Investigator's clinical judgment (e.g., no worsening of clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin by more than 50%).

### 4.1.2 Exclusion Criteria

Volunteers are not eligible for the study if any of the following criteria are met:

**All volunteers**

1. Transjugular intrahepatic portosystemic shunt or other porta-caval shunt.

2. A history of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers within the three months preceding screening.

3. Recent history (i.e. within the last 6 months prior to screening) or signs of severe hepatic encephalopathy (e.g., a portal systemic encephalopathy score >2).

4. Advanced ascites or ascites which require emptying and albumin supplementation, as judged by the Investigator.

5. Hepatocellular carcinoma, acute liver disease (e.g., caused by an infection or drug toxicity) or serum ALT or AST at screening not consistent with stable disease in the opinion of the Investigator.

6. Recipient of a liver transplant.

7. Uncontrolled hypertension, defined as SBP $>$ 160 mmHg and/or DBP $\geq$ 105 mmHg, considered clinically significant by the Investigator.

8. Clinically significant impairment of renal function, defined as a creatinine clearance of <60 mL/min estimated from serum creatinine concentrations using *Cockcroft-Gault equation*.

9. A history of gastrointestinal surgery (e.g. gastric bypass) or other gastrointestinal disorder (e.g. malabsorption syndrome) that might affect absorption of medicines from the gastrointestinal tract. Cholecystectomy is permissible.

10. Clinically significant change in health status, as judged by the Investigator, or any major illness within the four weeks before screening, or clinically significant acute infection or febrile illness within the 14 days before screening.

11. Apart from hepatic dysfunction, any other ongoing condition or disease, or laboratory test result, that the Investigator considers would render the participant unsuitable for the study, place the volunteer at undue risk, interfere with the ability of the volunteer to complete the study (e.g. short life expectancy), or confound interpretation of study data. Concurrent chronic disorders such as hypertension and diabetes are permissible providing they are stable and adequately controlled.

12. Women who are pregnant or lactating.

13. QTcF interval >480 msec or the presence of any other abnormal ECG finding, which, in the Investigator's opinion, is clinically significant.

14. Use of moderate or potent inhibitors or inducers of cytochrome P450 3A4 enzyme within the 28 days before screening.

15. Participation in any other clinical study involving administration of an investigational medicinal product or use of an unapproved device within 28 days before screening.

16. A positive test result for human immunodeficiency virus (HIV).

17. Recent history (i.e. within the last 6 months prior to screening) of alcoholism, drug abuse, or drug addiction, or a positive test for alcohol or drugs of abuse. Alcohol consumption not exceeding 21 units for men and 14 units for women per week (1 unit equals 250 mL of beer, 75 mL of wine, or 25 mL of spirits) is permitted, although volunteers should not consume alcohol in the 48 hrs preceding study center visits or during the period of in-patient confinement.

18. Known history of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds or other excipients in the entrectinib formulation.

19. Donation or loss of over 500 mL of blood within the three months before screening.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a non-randomized, open label study. All volunteers will receive the same study drug treatment (i.e. a single 100 mg dose of entrectinib).

Volunteers with reduced hepatic function will be assigned to a functional category based on assessments at the Screening visit. Each individual will be categorized according to the Child Pugh system for classifying hepatic impairment (Table 3) and also according to the National Cancer Institute (NCI) organ dysfunction working group (NCI-ODWG) system (Table 4).

**Table 3: Child-Pugh scoring system for assessment of hepatic dysfunction**

| | Score | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Encephalopathy grade | 0 | 1 or 2 | 3 or 4 |
| Ascites | Absent | Slight | Moderate |
| Serum bilirubin (mg/dL)* | <2 | 2 to 3 | >3 |
| Serum albumin (g/dL)† | >3.5 | 2.8 to 3.5 | <2.8 |
| Prothrombin time (seconds prolonged) | <4 | 4 to 6 | >6 |
| Individuals are assigned a score for each parameter, and the sum of these scores is used as the basis for classification of clinical severity:<br>• 5 to 6 points – mild hepatic impairment (Child-Pugh A)<br>• 7 to 9 points – moderate (Child-Pugh B)<br>• >9 points – severe (Child-Pugh C). | | | |

Source: [1]

* Corresponding bilirubin values in SI units: <34.2, 34.2 to 51.3, >51.3 µmol/L

† Corresponding albumin values in SI units: >35, 28 to 35, <28 g/L

**Table 4: NCI ODWG definitions of hepatic impairment**

| | **Mild** | **Moderate** | **Severe** |
|---|---|---|---|
| Total bilirubin | B1: ≤ULN<br>B2: >1–1.5× ULN | >1.5–3× ULN | >3× ULN |
| AST | B1: >ULN<br>B2: Any | Any | Any |

AST, aspartate aminotransferase; ULN, upper limit of normal.

Source: [2]

Assessment of encephalopathy will primarily be based on clinical signs and symptoms as detailed below; an encephalogram is not obligatory for grading of encephalopathy:

- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Subjects with severe hepatic encephalopathy (Grade >2) are to be excluded from the study (see Section 4.1.2).

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is entrectinib.

### 4.3.1 Study Treatment Formulation, Packaging, and Handling

Entrectinib will be supplied by the Sponsor as 100 mg capsules (F06 formulation) as finished kits / as capsules in bottles. Further information on the formulation and handling of entrectinib is provided in the pharmacy manual.

The lot numbers for the study drugs will be printed on the IMP drug labels.

Study drugs will be stored at controlled room temperature (store below 25°C) under secure conditions. The study drugs will be transferred into the volunteer's dose container by qualified study site employees. Each unit dose container will be appropriately labeled.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

Each volunteer will receive a single 100 mg dose of entrectinib with food. The study treatment will be administered orally as 1 x 100 mg F06 capsule, and given with approximately 240 mL of water within 30 minutes of consumption of a standardized meal.

Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Section 5.4.4. This is a single dose study and dose modification or treatment interruption is not possible. Guidelines for clinical management of individuals who experience AEs are provided in Section 5.1.

### 4.3.3 Investigational Medicinal Product Accountability

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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 Continued Access to Entrectinib

Currently, the Sponsor does not have any plans to provide entrectinib to volunteers who have completed the study.

## 4.4 CONCOMITANT THERAPY, PROHIBITED FOOD AND ADDITIONAL RESTRICTIONS

### 4.4.1 Concomitant Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by an individual in addition to protocol-mandated treatment from 7 days prior to study drug treatment to the end of the study. All such medications should be reported to the Investigator and recorded on the eCRF.

Concurrent administration of drugs used to manage hepatic dysfunction and related disorders are permitted providing there has been no alteration to the treatment regimen within one week preceding screening and the dosing regimen is not anticipated to change during the study. Similarly, other medications for chronic conditions (e.g. diabetes, hypertension) are permitted providing the volunteer has been on a stable dose and dosing regimen for at least one month preceding screening. However, use of the following categories of medication are specifically prohibited (see Appendix 2 for examples):

- Moderate or potent inhibitors or inducers of CYP3A enzymes.

### 4.4.2 Contraception

Women of childbearing potential must agree to remain abstinent (i.e. refrain from heterosexual intercourse) or use a highly-effective method of contraception (failure rate of <1% per year) throughout the study *and for 5 weeks after the last study treatment.* Women must refrain from donating eggs during this same period. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

A woman is considered to be of childbearing potential if she is postmenarcheal but has not reached a postmenopausal state, and has not undergone surgical sterilization. Postmenopausal is defined as at least 12 months without a period (i.e., amenorrhea) in a female at least 45 years of age and accompanied by a serum follicle-stimulating hormone [FSH] level judged by the Investigator to be consistent with postmenopausal status in the absence of a reversible medical iatrogenic cause. Surgically sterile is defined as permanently sterile via hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy by reported medical history and/or medical records.

*Men* with female partners of child-bearing potential must agree to remain abstinent (i.e. refrain from heterosexual intercourse) or use *barrier* contraception throughout the study *and for 3 months after the last study treatment. Men* whose female partners are pregnant must also use barrier contraception throughout the study *and for 3 months after the last study treatment* to avoid potential exposure of the fetus to the study drug. All *men* must also refrain from donating sperm during the study *and for 3 months after the last study treatment*.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

For volunteers who are exclusively in same-sex relationships or are abstinent (when this is in line with the preferred and usual lifestyle of the volunteer), contraceptive requirements do not apply. If a volunteer who is in a same-sex relationship or abstinent at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception, as described previously.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the volunteer. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

### 4.4.3 Food

Volunteers should not consume grapefruit or Seville oranges during the study. During periods of in-patient residency, volunteers will also be required to refrain from using tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, and nicotine gum), abstain from consumption of alcohol, and follow restrictions on consumption of food and beverages containing caffeine/xanthines, according to standard practices for the study center.

While resident in the study center, volunteers will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

### 4.4.4 Additional Restrictions

Volunteers should refrain from strenuous exercise from 48 hours prior to admission to the study center and during the period of confinement and will otherwise maintain their normal level of physical activity throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

## 4.5 STUDY ASSESSMENTS

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

Assessments will be made at specified times relative to study drug dosing, though in each case the actual times of assessment will also be recorded in the eCRF.

At time points when assessments coincide; procedures will be performed in the following order: AE and concomitant medication monitoring, 12-lead ECG and vital signs, pharmacokinetic blood sampling.

### 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 (ICFs) for enrolled volunteers and for volunteers who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that volunteers meet all eligibility criteria before enrollment. The Investigator will maintain a screening log to record details of all volunteers screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and use of alcohol and drugs of abuse, will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the volunteer within seven days prior to study drug treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

### 4.5.3 Physical Examinations

A complete physical examination performed at screening should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the eCRF.

A brief physical examination on admission to the study centre on Day -1 and at follow-up. Symptom-driven physical examinations may be performed at other times at the Investigator's discretion. Changes from baseline abnormalities should be recorded. New or worsened clinically significant abnormalities should be recorded as AEs on the eCRF.

### 4.5.4 Vital Signs

Vital signs will be measured at specified time-points as outlined in the schedule of activities (see Appendix 1 ). Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the volunteer is in a supine position (see Section 4.5.6), and temperature.

### 4.5.5 Laboratory Samples

For sampling and processing procedures, storage conditions, and shipment instructions, see the laboratory manual. All biological samples will be destroyed when the final Clinical Study Report has been completed.

When a volunteer withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the volunteer specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

*Screening blood samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.*

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

#### 4.5.5.1 Pharmacokinetics

Blood samples for measurement of plasma concentrations of entrectinib and M5 levels will be collected via an indwelling catheter and/or via direct venipuncture using Vacutainer or equivalent evacuated collection tubes. Blood samples will be collected at the time-points detailed in the schedule of activities (see Appendix 1 ). In addition, a blood sample will also be collected for estimation of entrectinib and M5 plasma protein binding using an ex vivo protein binding assay (see Appendix 1 ).

Plasma concentrations of entrectinib and M5 will be determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) bioanalytical procedure at a bioanalytical laboratory designated by the Sponsor. Plasma unbound fractions of entrectinib and M5 will be determined by appropriate assays.

#### 4.5.5.2 Laboratory Safety Tests

Blood samples for the following laboratory safety tests will be collected at the time-points detailed outlined in the schedule of activities (see Appendix 1 ).

- Hematology: erythrocytes, leukocyte count with differential (neutrophils, eosinophils, lymphocytes, monocytes and basophils), hemoglobin, hematocrit, platelet count

- Coagulation: prothrombin time and international normalized ratio, and activated partial thromboplastin time

- Serum biochemistry: sodium, potassium, chloride, glucose (fasting), urea, albumin, calcium, magnesium, inorganic phosphorus, ALP, AST, ALT, creatine phosphokinase, lactate dehydrogenase, serum creatinine, gamma glutamyl transferase, total and direct bilirubin, total protein, total cholesterol, HDL-C, LDL-C, triglycerides and uric acid

Blood samples should be obtained following a fast of at least 4 hours.

In addition, urine samples will be collected for measurement of urinary protein, blood, glucose, leukocytes, pH and sediment. Urine samples that are positive may be sent for further follow-up microscopic examination (i.e. RBCs, WBCs, casts, crystals, epithelial cells, bacteria) as deemed appropriate by the Investigator.

#### 4.5.5.3 Other

A blood sample for screening for HIV, hepatitis B (HBV) and hepatitis C (HCV) infection will be collected at the screening visit.

A urine screen for selected drugs of abuse will be performed at screening visit and repeated along with an alcohol breath test on admission to the study center (Day -1).

All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed on admission to the study center (Day -1) and at the follow-up visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Post-menopausal status should be confirmed by a FSH test at the screening visit as appropriate.

### 4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified time-points, as outlined in the schedule of activities (see Appendix 1 ), and may be obtained at unscheduled time-points as indicated.

All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the volunteer has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio,

conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the volunteer's permanent study file at the site.

If at a particular post-dose time-point the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the Investigator. The Investigator should also evaluate the volunteer for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Patient Discontinuation from Study

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 volunteer 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
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor
- Study termination or site closure

Every effort should be made to obtain information on volunteers who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the eCRF. If a volunteer requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator. Patients who withdraw from the study may be replaced.

### 4.6.2 Study 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 AEs in this or other studies indicates a potential health hazard to volunteers
- Patient enrollment is unsatisfactory

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

A decision to not enroll volunteers with severely impaired hepatic function because the key pharmacokinetic objectives of the study have already been met will not be considered early termination of the study.

### 4.6.3 Site Discontinuation

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:

- Excessively slow recruitment
- 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 volunteers have completed the study and all obligations have been fulfilled)

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

Entrectinib is not approved in any European country at the time of writing, and clinical development is ongoing. The safety plan for volunteers in this study is based on clinical experience with entrectinib in completed and ongoing studies. The anticipated important safety risks for entrectinib are described in the entrectinib Investigator's Brochure.

Several measures will be taken to ensure the safety of volunteers participating in this study. Eligibility criteria have been designed to exclude volunteers at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs.

### 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including serious AEs and AEs of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests 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.

The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with the International Conference on Harmonisation/International Council for Harmonisation (ICH) guidelines, Food and Drug Administration (FDA) regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- 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 (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious AE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the Investigator, places the volunteer at immediate risk of death)

  This does not include any AE 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 AE results in substantial disruption of the volunteer'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 volunteer 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 AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; 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 AE recorded on the eCRF.

Serious AEs 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.
- All grades syncope events
- Grade ≥2 congestive cardiac failure
- Grade ≥2 QT prolongation
- Grade ≥3 cognitive disturbances (including confusion, mental status changes, hallucinations, or memory loss)

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each AE recorded on the 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 AEs at each volunteer contact. All AEs, whether reported by the volunteer or noted by study personnel, will be recorded in the volunteer's medical record and on the eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious AEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious AEs).

After initiation of study drug, all AEs will be reported until 28 days after the final dose of study drug.

Instructions for reporting AEs that occur after the AE 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 AE information at all volunteer 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 AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. Table 5 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

**Table 5 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 AE [d] |

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

Note: Based on the most recent version of NCI CTCAE (v5.0), 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 AE (see Section 5.4.2 for reporting instructions), per the definition of serious AE in Section 5.2.2.

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

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the volunteer, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE 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 AEs on the eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the eCRF.

#### 5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the 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 eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE 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, AEs 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 AE that is separated in time from the initiating event should be recorded as an independent event on the 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 gastrointestinal 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 AEs should be recorded separately on the eCRF if it is unclear as to whether the events are associated.

#### 5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between volunteer evaluation time-points. Such events should only be recorded once on the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the eCRF. Details regarding any increases in severity will be captured on the 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 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 AEs.

A recurrent AE is one that resolves between volunteer evaluation time-points and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the eCRF.

#### 5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE 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 AEs.

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 AE.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the 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 AE. 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 eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

#### 5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE 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 AE.

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 eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

#### 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 AE 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 eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious AE or an AE of special interest (see Section 5.4.2).

#### 5.3.5.7 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of hepatic disease.

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 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 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").

If the death is attributed to progression of liver disease, "hepatic disease progression" should be recorded on the eCRF.

Deaths that occur after the AE reporting period should be reported as described in Section 5.6.

#### 5.3.5.8 Pre-existing Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the 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 Worsening of Liver Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of liver disease should be recorded as an AE if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of hepatic function on the eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of hepatic function").

#### 5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious AE (per the definition of serious AE 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 AE or a serious AE:

- Hospitalization for respite care

- 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 AE

An event that leads to hospitalization under the following circumstances is not considered to be a serious AE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

## 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 AEs (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)
- Accidental overdoses or medication errors (see Section 5.4.4 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 AEs to the local health authority and IRB/EC.

### 5.4.1 Emergency Medical Contacts

Medical Monitor: Harald Zeuner
F. Hoffmann-La Roche AG
+ 41 61 68 80 861 (Office Telephone No.)
+ 41 79 46 03 417 (Mobile Telephone No.)

### 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 drug, only serious AEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor 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.

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious AEs and AEs of special interest will be reported until 28 days after the 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 eCRF and submit the report via the electronic data capture (EDC) system. An electronic report will be generated and sent to Roche Safety Risk Management.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor 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 serious AEs that occur $>$28 days after the dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female volunteers of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted 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. Pregnancy should not be recorded on the eCRF. The Investigator should counsel the volunteer, discussing the

risks of the pregnancy and the possible effects on the fetus. Monitoring of the volunteer should continue until conclusion of the pregnancy. Any serious AEs 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 eCRF. In addition, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Volunteers

Male volunteers will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 28 days after the dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted 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 volunteer exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An Investigator who is contacted by the male volunteer 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 AE (as the Sponsor considers abortions to be medically significant), recorded on the 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 volunteer exposed to study drug or the female partner of a male volunteer exposed to study drug should be classified as a serious AE, recorded on the eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### 5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the eCRF. If the associated AE 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). For entrectinib, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with entrectinib, regardless of whether they result in an AE, should be recorded on the eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two eCRF pages, one to report the accidental overdose and one to report the headache.

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the volunteer is lost to follow-up, or the volunteer withdraws consent. Every effort should be made to follow all serious AEs

considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study should be followed until pregnancy outcome.

### 5.5.2 Sponsor Follow-Up

For serious AEs, AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 AE that occurs after the end of the AE reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the eCRF. However, if the EDC system is not available, 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 AEs and AEs 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 AE cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Entrectinib Investigator's Brochure

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

## 6.1 DETERMINATION OF SAMPLE SIZE

It is planned that approximately 24 volunteers will be enrolled, with a target of six in each hepatic function group. The actual number enrolled will be determined by the Sponsor during the study from review of emerging data to ensure that at least six individuals are recruited in each hepatic function group for both classification systems, i.e. additional volunteers will be recruited if differences between the two categorization systems mean that there are fewer than six evaluable individuals in any hepatic function analysis group. Volunteers who withdraw from the study before Day 7 may also be replaced to ensure that at least six volunteers in each group have evaluable pharmacokinetic data.

No formal sample size calculations were performed. Six volunteers per group is consistent with recommendations in US and European regulatory guidelines [3, 4]. Based on the observed variability in entrectinib exposure parameters in previous clinical studies (e.g. $AUC_{inf}$ CV% 9-34% from F06 capsules in healthy volunteers under fed conditions) six volunteers per group is considered appropriate to estimate the magnitude of the effect of hepatic impairment on entrectinib pharmacokinetic parameters.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The number of volunteers who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age and sex) 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 hepatic function group.

## 6.4 SAFETY ANALYSES

The safety analysis population will consist of all volunteers who received one dose of study drug, with volunteers grouped according to hepatic function category.

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to NCI CTCAE v5.0.

Safety will be assessed by a review of AEs, vital signs, clinical laboratory assessments, and ECGs. Adverse events will be summarized by hepatic function group. Duplicate summaries will be presented for the Child Pugh and NCI-ODWG systems for classifying hepatic function. Clinical laboratory assessments, vital signs (including oral temperature,

respiratory rate, and supine blood pressure and pulse rate), and ECGs will be listed by volunteer and scheduled time. Changes from baseline and the incidence of out-of-reference range values will be derived as appropriate.

## 6.5 PHARMACOKINETIC ANALYSES

Plasma concentrations of entrectinib and its active metabolite M5, and derived plasma pharmacokinetic parameters, will be listed and summarized by group using descriptive statistics. Individual and mean concentration versus time profiles will be plotted. Duplicate summaries will be presented for groups categorized according to the Child Pugh and NCI-ODWG system for classifying hepatic function. In effect there may be eight analysis groups (i.e. Normal Child-Pugh, Normal NCI-ODWG, Mild Child-Pugh, Mild NCI-ODWG, Moderate Child-Pugh, Moderate NCI-ODWG, Severe Child-Pugh, and Severe NCI-ODWG).

The following pharmacokinetic parameters will be derived for entrectinib and M5 using standard non-compartmental methods:

- $C_{max}$: Maximum observed plasma concentration
- $AUC_{last}$: Area under the plasma concentration-time curve from time 0 to the last measurable concentration.
- $AUC_{inf}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinity.
- $T_{max}$: Time of Maximum observed plasma concentration
- $\lambda_z$: Apparent terminal elimination rate constant
- $t_{1/2}$: Apparent terminal elimination half-life
- M:P ratio: Molecular weight-adjusted metabolite to parent ratio based on $AUC_{inf}$
- CL/F: Apparent oral clearance (entrectinib only)
- V/F: Apparent volume of distribution (entrectinib only)
- $f_u$: Fraction of drug unbound in plasma

The fractions of entrectinib and M5 unbound in plasma ($f_u$) will be determined by ex vivo protein binding assay and used to calculate exposure parameters adjusted for protein binding (i.e., unbound $C_{max}$, unbound $AUC_{inf}$).

An analysis of variance (ANOVA) will be used to estimate the effect of hepatic impairment on log-transformed total and unbound entrectinib and M5 exposure parameters and will include the factor hepatic impairment (i.e. mild, moderate and severe, and none). Estimates of geometric mean ratios on the original scale, together with the corresponding 90% confidence intervals (CIs), will be derived for the comparisons between each hepatic impairment group and the control group with normal hepatic function. Duplicate analyses will be performed for groups based on Child-Pugh and NCI-ODWG classifications.

The relationship between entrectinib pharmacokinetic parameters (e.g. $C_{max}$ and $AUC_{inf}$) and measures of hepatic function (e.g., Child-Pugh scores, albumin, bilirubin, or AST concentrations, prothrombin time etc.) will be explored using linear or non-linear models or regression analyses, as appropriate.

### 6.6 INTERIM ANALYSIS

Pharmacokinetic and safety data from at least three volunteers with mild hepatic impairment and three volunteers with moderate hepatic impairment (Child-Pugh categorization system) will be reviewed before volunteers with severely impaired hepatic function are enrolled. Data will be listed and summarized as appropriate but there will be no formal statistical analysis. Recruitment of volunteers with severely impaired hepatic function will only proceed if there is agreement between the Sponsor and the Investigator that data from this group are necessary to fulfill the objectives of the study and that dosing is not anticipated to present an unacceptable risk to those individuals.

## 7. DATA COLLECTION AND MANAGEMENT

### 7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the CRO, using the standard procedures to handle and process transfer of these data.

The Sponsor will perform oversight of the data management of this study. Data will be periodically transferred from the CRO to the Sponsor using pre-agreed procedures to handle and process the transfer of these data.

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

### 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of an EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the CRO and should be handled in accordance with the CRO's standard procedures.

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 volunteer data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data 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 volunteer 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 IMP, including eCRFs, electronic or paper PRO data (if applicable), 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.

# 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 (IND) 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 volunteer 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 volunteer'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 volunteer or the volunteer's legally authorized representative before his or her participation in the study. The case history or clinical records for each volunteer 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 volunteer 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 volunteer 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 volunteer or the volunteer's legally authorized representative. All signed and dated Consent Forms must remain in each volunteer'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 volunteer authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for volunteer 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 volunteer, 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 volunteer 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 AEs to the Sponsor, Investigators must comply with requirements for reporting serious AEs to the local health authority and

IRB/EC. Investigators may receive written IND safety reports or other safetyrelated- 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 volunteer enrolled in the study through assignment of a unique volunteer identification number. This means that volunteer 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 volunteer, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study Investigators or volunteers unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor 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.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

## 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 volunteer 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 volunteer 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, volunteers' 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 by F. Hoffmann-La Roche Ltd and managed by a CRO. The Sponsor will provide medical monitoring and will be responsible for expedited reporting of new safety findings but other activities will be delegated to the CRO.

Central facilities will be used for certain study assessments throughout the study (e.g., bioanalysis). Accredited local laboratories may be used for routine safety monitoring; local laboratory ranges will be collected.

## 9.5 DISSEMINATION 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, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the

European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

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 volunteers or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

## 10. REFERENCES

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2. National Cancer Institute Organ Dysfunction Working Group (NCI ODWG). Protocol Template for Organ Dysfunction Studies (MS Word) — updated February 26, 2018. Available from: https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm.

3. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

4. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. European Medicines Agency, Committee for Medicinal Products for Human Use. CPMP/EWP/2339/02

5. Weinstein, I.B. and Joe, A., Oncogene addiction. Cancer Res, 2008. 68(9):3077-80

6. Weinstein, I.B. and Joe, A.K., Mechanisms of disease: Oncogene addiction - a rationale for molecular targeting in cancer therapy. Nat Clin Pract Oncol, 2006. 3(8):448-57.

# Appendix 1 Schedule of Activities

| Study Procedures | Screen. | Study day | | | | | | | | | | | | | | | | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | -28 to -2 | -1 | 1 | | | | | | | | | | | 2 | | 3 | 4 | 5 | 7 | 12 to 14 |
| Time relative to study drug dosing | | | pre | 0 | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 12 | 24 | 36 | 48 | 72 | 96 | 144 | |
| **Administrative procedures** | | | | | | | | | | | | | | | | | | | | |
| Informed consent | x | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | x | x | | | | | | | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | | | | | | | | |
| **Safety evaluations** | | | | | | | | | | | | | | | | | | | | |
| Physical examination[d] | x | x | | | | | | | | | | | | | | | | | | x |
| Height and weight | x | | | | | | | | | | | | | | | | | | | |
| 12-lead safety ECG | x | | x | | | | x | | | | x | | | | | x[a] | | | | x |
| Vital signs | x | | x | | | | x | | | | x | | | | | x[a] | | | | x |
| Laboratory safety tests[b] | x | x | | | | | | | | | | | | | | x[a] | | | | x |
| Urine drug and alcohol screen | x | x | | | | | | | | | | | | | | | | | | |
| Serology screen | x | | | | | | | | | | | | | | | | | | | |
| Pregnancy test[c] | x | x | | | | | | | | | | | | | | | | | | x |
| AE monitoring | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medication monitoring | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Study drug administration | | | | x | | | | | | | | | | | | | | | | |
| **Pharmacokinetic evaluations** | | | | | | | | | | | | | | | | | | | | |
| Blood sampling for entrectinib and M5 pharmacokinetics[e] | | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Blood sampling for ex vivo protein binding assay | | | | | | | | | x | | | | | | | | | | | |
| **Other procedures** | | | | | | | | | | | | | | | | | | | | |
| Standardized meal | | | x | | | | | | | | | | | | | | | | | |
| Confinement in the study center[a] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | (x) | (x) | (x) | |
| Ambulatory study center visits[a] | x | | | | | | | | | | | | | | | | x | x | x | x |

## Appendix 1 Schedule of Activities (cont.)

[a]: Study participants will be resident in the study centre from Day -1 until at least Day 3. Discharge is at the discretion of the Investigator and individuals may remain resident until Day 7. ECGs, vital signs and lab safety tests should be performed on the day of discharge.

[b]: Hematology (erythrocytes, leukocyte count with differential [neutrophils, eosinophils, lymphocytes, monocytes and basophils], hemoglobin, hematocrit, platelet count), coagulation (prothrombin time and international normalized ratio, and activated partial thromboplastin time), serum biochemistry (sodium, potassium, chloride, glucose [fasting], urea, albumin, calcium, magnesium, inorganic phosphorus, ALP, AST, ALT , creatine phosphokinase, lactate dehydrogenase, serum creatinine, gamma glutamyl transferase, total and direct bilirubin, total protein, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides and uric acid) and urinalysis (protein, blood, glucose, leukocytes and pH), plus FSH for women to confirm post-menopausal status at screening as appropriate. Samples should be obtained following a fast of at least 4 hours.

[c]: Women of child-bearing potential only. Serum test at screening, urine tests on subsequent occasions. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[d]: A full physical examination at screening, a brief physical examination on Day -1 and at follow-up. Symptom-driven physical examinations may be performed at other times at the Investigator's discretion.

[e]: Permissible time windows for pharmacokinetic sampling and other assessments are: pre, any convenient time prior to dosing; 0.5-1 hr, ±0.1 hr (i.e. ±6 mins); 2-8 hr, ±0.25 hr (i.e. ±15 mins), 12-36 hr, ±1 hr, 48-144 hr, ±4 hr

# Appendix 2 Examples of Prohibited Concomitant Medications

**Moderate or potent inhibitors or inducers of CYP3A enzymes**

*CYP3A inhibitors*

amprenavir, aprepitant, atazanavir, atazanavir / ritonavir, boceprevir, casopitant, ceritinib, ciprofloxacin, clarithromycin, cobicistat, conivaptan, crizotinib, cyclosporine, danoprevir / ritonavir, darunavir, darunavir / ritonavir, diltiazem, dronedarone, duvelisib, elvitegravir / ritonavir, erythromycin, faldaprevir, fluconazole, grapefruit juice, idelalisib, imatinib, indinavir, indinavir /ritonavir, isavuconazole, itraconazole, ketoconazole, letermovir, lopinavir / ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, netupitant, nilotinib, posaconazole, ravuconazole, ribociclib, ritonavir, saquinavir, saquinavir / ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, tofisopam, troleandomycin, verapamil, voriconazole

*CYP3A inducers*

apalutamide, avasimibe, bosentan, carbamazepine, dabrafenib, daclatasvir / asunaprevir / beclabuvir, efavirenz, elagolix, enzalutamide, etravirine, genistein, ivosidenib, lersivirine, lesinurad, lopinavir, lorlatinib, lumacaftor, mitotane, modafinil, nafcillin, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, ritonavir, semagacestat, St John's Wort, talviraline, telotristat ethyl, thioridazine, tipranavir / ritonavir.

Source: University of Washington Drug-Drug Interaction Database (https://didb.druginteractioninfo.org, accessed 29 May 2019)