Official Title: A RANDOMIZED, OPEN-LABEL, TWO-TREATMENT, TWO-PERIOD, TWO-WAY CROSSOVER STUDY TO INVESTIGATE THE RELATIVE BIOAVAILABILITY OF ENTRECTINIB CAPSULE FORMULATIONS F1 AND F06 UNDER FED CONDITIONS IN HEALTHY SUBJECTS

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Protocol GP41048

Covance Study 8397009

IND 120500

for

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by

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STUDY IDENTIFICATION

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent systemic clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CPET	Clinical Pharmacology Protocol Execution Team
CRF	Case Report Form
CSR	Clinical Study Report
C_t	last measurable concentration
CV	coefficient of variation
CYP	cytochrome P450
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HDYF?	How do you feel?
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation/International Council for Harmonisation
IMP	investigational medicinal product

IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
λ_z	apparent terminal elimination rate constant
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
QT	time from the start of the Q wave to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected through use of Fridericia's formula
R	Reference
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
T	Test
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time to maximum observed concentration
UA	urinalysis
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution during the terminal elimination phase
WBC	white blood cell

1 SYNOPSIS

Title of Study:	A Randomized, Open-label, Two-Treatment, Two-Period, Two-Way Crossover Study to Investigate the Relative Bioavailability of Entrectinib Capsule Formulations F1 and F06 Under Fed Conditions in Healthy Subjects
Objectives:	The primary objective of this study is: • To investigate the relative bioavailability of entrectinib F1 and F06 capsule formulations under fed conditions in healthy adult male and female subjects. The secondary objective of this study is: • To explore the safety and tolerability of a single 600-mg oral dose of entrectinib F1 and F06 capsule formulations in healthy adult male and female subjects.
Methodology/Study Design:	This is a randomized, open-label, 2-treatment, 2-period, 2-way crossover study to investigate the relative bioavailability of entrectinib F1 and F06 capsule formulations under fed conditions in healthy male and female subjects. Potential subjects will be screened to assess their eligibility to enter the study within 27 days (Days -28 to -2) prior to study entry. Dosing will be on Day 1 of each period. Replacement subjects may be enrolled, only if deemed necessary by the Sponsor. Samples will be collected for analysis at specified timepoints.
Number and General Description of Subjects:	A total of 14 subjects will be enrolled in the study at a single clinical site to complete a minimum of 12 subjects.
Diagnosis and Main Criteria for Inclusion:	Healthy males and females, between 18 and 60 years of age, inclusive, within body mass index range of 18.0 to 32.0 kg/m^2, inclusive, weighing at least 50 kg at Screening who are in good health, as determined by no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), clinical laboratory evaluations, and vital signs.
Test Product(s), Dose, and Mode of Administration:	Subjects will receive the following 2 treatments in a randomized sequence. Each treatment will be dosed as 3 × 200-mg capsules provided with 240 mL of water following a standardized "pediatric" meal that will be entirely consumed within 30 minutes: • Single 600-mg oral dose of Entrectinib F1 capsule formulation (Test). • Single 600-mg oral dose of Entrectinib F06 capsule formulation (Reference).
Duration of Treatment:	Planned Enrollment/Screening Duration: approximately 4 weeks. Length of Each Confinement: Subjects will be confined at the study site from the time of Check-in (Day -1) of each period until Clinic Discharge on Day 5. There will be at least a 14-day washout between doses in Periods 1 and 2. There will be a follow-up telephone call 12 to 14 days after the last dose of study drug (Period 2). Planned Study Conduct Duration: approximately 8 weeks.
Criteria for Evaluation: Safety	Safety and tolerability assessments will include recording of adverse events, clinical laboratory evaluations, vital sign measurements, physical examinations, and ECGs.
Criteria for Evaluation: Pharmacokinetics	The following pharmacokinetic (PK) parameters will be derived from the plasma concentrations of entrectinib and M5 using the model independent approach: maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (entrectinib only, CL/F), and apparent volume of distribution during the terminal elimination phase (entrectinib only, V_z/F).
Statistical Methods:	Descriptive statistics (mean, median, minimum, maximum, standard deviation, geometric mean, and geometric coefficient of variation) will be calculated for all PK parameters and PK concentration data. The primary parameters for analysis will be C_{max} and $AUC_{0-\infty}$ of entrectinib and M5. A

	linear mixed model will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effects for treatment, period, and sequence, and a random effect for subject within sequence. Estimates of geometric mean ratios on the original scale, together with the corresponding 90% confidence intervals (CIs), will be derived for the comparisons between Test and Reference treatments. Descriptive statistics will be calculated on the safety parameters. No formal statistical analyses are planned.

2 INTRODUCTION

2.1 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.[1,2] Therefore, these kinases represent attractive targets for anticancer therapy.

Refer to the Investigator's Brochure (IB)[3] for detailed background information on entrectinib and for details on nonclinical and clinical studies.

2.1.1 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.

2.1.2 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 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.

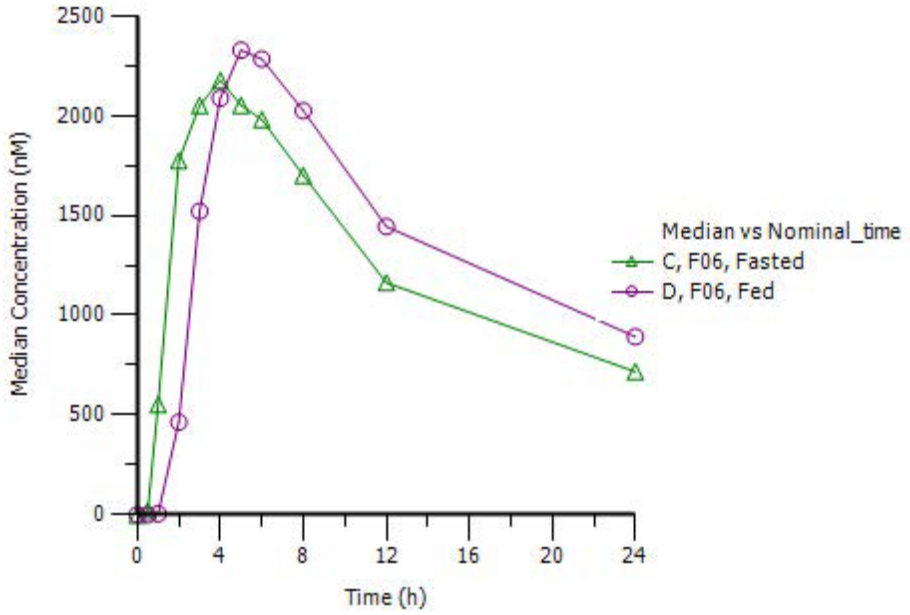
Entrectinib is not phototoxic based on results from an in vivo rat study. However, microscopic findings in rats of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at high doses were considered entrectinib-related.

2.1.3 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 (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 significant effect on oral bioavailability from clinical capsule formulations containing acidulant (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-101-15[4] 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 drug-drug interaction studies entrectinib exhibited potential to inhibit and induce the activities of CYP3A. A study on the interaction with transporters in vitro revealed that entrectinib is a poor P-glycoprotein (P-gp) substrate and has the potential to inhibit the transporters P-gp (MDR1), breast cancer resistance protein, and MATE1.

2.1.4 CLINICAL PROGRAM

The clinical program to date includes 10 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.

In the four main entrectinib studies in oncology patients, the most common treatment-related adverse events (AEs) were dysgeusia (39%), fatigue (31%), dizziness (23%), constipation (22%), diarrhea (19%), nausea (19%), paresthesia (17%), weight increased (17%), blood creatinine increased (14%), myalgia (14%), vomiting (12%), peripheral edema (12%), anemia (11%), and arthralgia (10%). 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 safety findings.

2.2 STUDY RATIONALE

Different entrectinib capsule formulations have been used in pivotal and supportive clinical studies in adults (F2A) and children (F1). Furthermore, a different capsule formulation (F06) is intended for commercial use in both populations, [redacted] While the F2A and F06 capsule formulations are bioequivalent, it has been demonstrated that the F1 capsule formulation has a distinctly different in vivo pharmacokinetic (PK) performance compared with the F2A formulation in certain circumstances. [redacted] The principal aim of this study is, therefore, to compare the in vivo PK profiles of the F1 and F06 capsule formulations under typical clinical dosing conditions, with the intention of quantifying the relative bioavailability of these two capsule formulations in order to support dosing recommendations for the use of F06 capsules in pediatric populations.

2.3 DOSE RATIONALE

The recommended dose of entrectinib for cancer patients is 600 mg once daily and 600 mg is therefore the dose chosen for the current study. 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.

Entrectinib will be given with food in order to match dosing instructions for patients in pivotal and supportive clinical trials, which recommend administering entrectinib within 30 minutes following a meal. [redacted]

2.4 BENEFIT:RISK ASSESSMENT

There will be no therapeutic benefit for the healthy subjects 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 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 entrectinib in healthy volunteers. Of the potential 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 effective contraception throughout the study.

Overall, no significant safety concerns have been identified about the use of 600 mg entrectinib in healthy subjects. All subjects will be resident in the study center and remain under medical supervision following each study drug administration and will undergo a standard battery of safety assessments. Hence, the risks to participants in this study are considered acceptable.

3 STUDY OBJECTIVES AND CORRESPONDING ENDPOINTS

3.1 PRIMARY OBJECTIVE

The primary objective of this study is:

- To investigate the relative bioavailability of entrectinib F1 and F06 capsule formulations under fed conditions in healthy adult male and female subjects.

3.2 SECONDARY OBJECTIVE

The secondary objective of this study is:

- To explore the safety and tolerability of a single 600-mg oral dose of entrectinib F1 and F06 capsule formulations in healthy adult male and female subjects.

3.3 PRIMARY ENDPOINTS

The primary endpoints are:

- The geometric mean ratios and associated 90% confidence intervals (CIs) of entrectinib and M5 metabolite PK parameters area under the concentration-time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$) and maximum observed concentration (C_{max}).

3.4 SECONDARY ENDPOINTS

The secondary endpoints are:

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

4 STUDY DESIGN

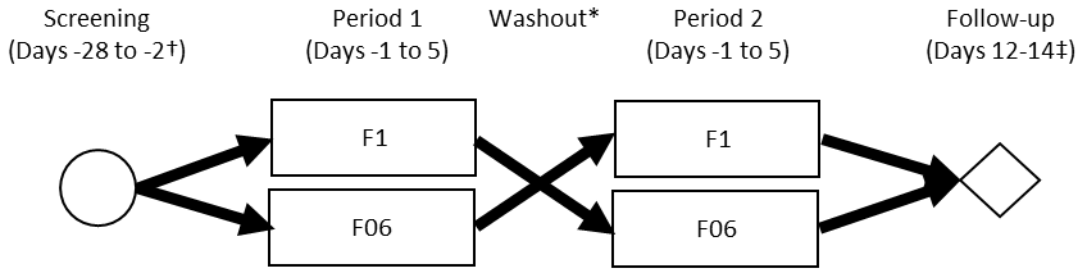
4.1 DESCRIPTION OF THE STUDY

This is a randomized, open-label, 2-treatment, 2-period, 2-way crossover study to investigate the relative bioavailability of entrectinib F1 and F06 capsule formulations under fed conditions in healthy male and female subjects. In each treatment period, subjects will receive a single 600-mg oral dose of entrectinib, provided as 3 × 200-mg capsules, after a standardized light meal (see Section 7.2.2). It is planned that a total of 14 subjects will receive the following 2 treatments in a randomized sequence:

- Entrectinib F1 capsule formulation (Test), fed
- Entrectinib F06 capsule formulation (Reference), fed

An overview of the study design is provided in Figure 2.

Figure 2 Overview of Study Design



* Minimum 14 days between study drug adminstrations in Periods 1 and 2
† Relative to study drug administration in Period 1
‡ Relative to study drug administration in Period 2

Potential subjects will be screened to assess their eligibility to enter the study within 27 days (Days -28 to -2) prior to study entry. Replacement subjects may be enrolled, only if deemed necessary by the Sponsor, to ensure that 12 subjects complete the study (have evaluable PK data from both Periods 1 and 2).

Eligible subjects will be admitted to the study site on the day prior to the first entrectinib dosing (Check-in [Day -1] of Period 1) to collect baseline data and to familiarize the subjects with study procedures that will be used during the rest of the study. On Day 1 of Period 1, subjects will be randomly assigned to 1 of 2 treatment sequences (i.e., TR or RT) according to a pre-specified randomization scheme based on the order of study enrollment. The assigned treatments will be administered under fed conditions on Day 1 of each period. Doses of entrectinib will be separated by a washout period of at least 14 days. Pharmacokinetic blood samples for analysis of entrectinib and its active metabolite M5 concentrations will be collected according to Table 7-2.

Subjects will be confined at the study site from the time of Check-in (Day -1) of each period until Clinic Discharge on Day 5 in each period. The site will attempt to contact all subjects who received at least 1 dose of entrectinib (including subjects who terminate the study early) approximately 12 to 14 days after the last study drug administration. A detailed list of assessments to be conducted in this study is included in Table 7-1.

In this study, physical examinations, 12-lead ECGs, vital signs, How do you feel? (HDYF?) inquiries, and clinical laboratory evaluations (Appendix A) will be performed at specified times during the study (for specific timepoints and details on each study variable, refer to Section 7). After informed consent has been obtained but prior to initiation of study drug administration, only serious adverse events (SAEs) caused by protocol-mandated interventions will be reported.

After study drug administration on Day 1 of Period 1, all AEs, whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (i.e., from Day 1 of Period 1 until Early Termination [ET] or until the Follow-up telephone call). A schedule of activities is presented in Table 7-1.

The end of study is defined as the date of the last scheduled study procedure for the last participating subject.

4.2 RATIONALE FOR STUDY DESIGN

A crossover design will be used to reduce the residual variability as every subject acts as their own control. A single-dose crossover design is the standard design to compare PK. Subjects will be randomized to 1 of 2 treatment sequences to minimize assignment bias.

This study is an open-label investigation because the PK parameters are believed not to be subject to bias. The crossover design further minimizes the effect of inter-subject variability. Blood sampling of up to 96 hours postdose will allow the PK parameters of entrectinib and metabolite M5 to be adequately characterized based on prior data. The 14-day washout between entrectinib doses is considered sufficient to prevent carryover effects of the treatments based on the entrectinib apparent terminal elimination half-life ($t_{1/2}$) of approximately 20 to 30 hours and M5 $t_{1/2}$ of approximately 40 hours.

4.3 RATIONALE FOR SUBJECT POPULATION

Healthy adult male and female subjects were chosen for inclusion in this study because they are free of health problems that could otherwise make them more susceptible to drug toxicity or confound the interpretation of the study results, are not routinely using concomitant medications that could interact with the study drug and provide a standard basis for comparison (i.e., control) with less variability.

4.4 RATIONALE FOR EXPLORATORY ASSESSMENTS

Not applicable.

4.5 RATIONALE FOR PHARMACOKINETIC SAMPLING SCHEDULE

The PK sampling schedule has been selected on the basis of data from previous studies in which a single dose of entrectinib was administered to healthy volunteers. The frequent sampling schedule is designed to capture data at a sufficient number of timepoints to provide a detailed

profile of the concentration-time curve, including C_{max}, time to maximum observed concentration (t_{max}), and $t_{1/2}$.

5 SUBJECT SELECTION

A total of 14 healthy volunteer male and female subjects who meet all the protocol inclusion criteria and none of the exclusion criteria will be enrolled into the study.

5.1 SCREENING PROCEDURES

Refer to Table 7-1 for procedures performed for all potential subjects at the Screening visit.

5.2 CHECK-IN PROCEDURES

Refer to Table 7-1 for procedures performed at Check-in (Day -1), when subjects will report to the study site.

For subjects to continue their participation in the study, the drug and alcohol (as applicable) screen (and for females of childbearing potential, the pregnancy test) must be negative and the clinical laboratory evaluations must be within the normal laboratory range (unless deemed not clinically significant by the Investigator). In addition, continued compliance with concomitant medication and other restrictions will be verified.

5.3 INCLUSION CRITERIA

Subjects who meet the following criteria may be included in the study:

1. Males or females, between 18 and 60 years of age, inclusive, at Screening;
2. Within body mass index (BMI) range 18.0 to 32.0 kg/m^2, inclusive, and weighing at least 50 kg, at Screening;
3. Healthy in the opinion of the Investigator. Healthy is defined by the absence of evidence of any active disease or clinically significant medical condition based on a detailed medical history, physical examination, vital signs, 12-lead ECG, and laboratory safety test results;
4. Clinical laboratory evaluations (including chemistry panel [fasted at least 8 hours], complete blood count [CBC], and urinalysis [UA]) within the reference range for the test laboratory, unless deemed not clinically significant by the Investigator. Congenital nonhemolytic hyperbilirubinemia (eg, suspicion of Gilbert's syndrome based on total and direct bilirubin) is acceptable. In case of borderline or questionable results, tests may be repeated to confirm eligibility;

5. Negative test for selected drugs of abuse at Screening (does not include alcohol) and at Check-in (Day -1) of Period 1 (does include alcohol; Appendix A);
6. Negative hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and negative HIV antibody screens (Appendix A);
7. Females will not be pregnant or breastfeeding, and females of childbearing potential will agree to use highly-effective contraception as detailed in Section 7.4;
8. Females of childbearing potential (Section 7.4) must agree to refrain from donating eggs during the treatment period and for 6 weeks after the final dose of study drug;
9. Males will agree to use contraception as detailed in Section 7.4 and will refrain from sperm donation from Check-in (Day -1) of Period 1 and for 90 days after the final dose of study drug;
10. Able to comprehend and willing to sign an Informed Consent Form (ICF) and to comply with the study protocol and study restrictions.

5.4 EXCLUSION CRITERIA

The following will exclude potential subjects from the study:

1. 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 will be allowed);
2. Presence of a clinically significant disease, illness, medical condition or disorder, or any other medical history determined by the Investigator to be clinically significant and relevant. Ongoing chronic disorders which are not considered clinically significant are permissible providing they are stable;
3. Have a QT interval corrected through use of Fridericia's formula (QTcF) >450 msec, or concurrent use of medications that may prolong the QT interval. If the QTcF measurement is >450 msec, the ECG will be repeated 2 additional times and a triplicate average will be used to determine eligibility;
4. Confirmed (e.g., 2 consecutive measurements) systolic blood pressure >140 or <90 mmHg, diastolic blood pressure >90 or <50 mmHg, or pulse rate >100 or <40 beats per minute;
5. Clinically significant change in health status, as judged by the Investigator, or any major illness within the 4 weeks before Screening, or clinically significant acute infection or febrile illness within the 14 days before Screening;
6. Any other ongoing condition, disease, or laboratory test result, that the Investigator considers would render the subject unsuitable for the study, place the subject at undue risk, interfere with the ability of the subject to participate in or complete the study, or confound interpretation of study data;

7. Use of moderate or potent inhibitors or inducers of CYP3A enzyme or the transporter P-gp within the 28 days prior to Screening and during the study duration, or use of other prohibited medications within the 14 days before Screening and during the study duration (see Section 7.6);
8. Participation in any other clinical study involving an investigational medicinal product (IMP) or device within 30 days or 5 half-lives (if known), whichever is longer, before Screening;
9. History of alcoholism, drug abuse, or addiction within 1 year prior to Screening;
10. History of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds;
11. Poor peripheral venous access;
12. Donation or loss of over 500 mL of blood or donation of plasma from 3 months prior to Screening through Follow-up;
13. Receipt of blood products within 2 months prior to Check-in (Day -1) of Period 1.

5.5 REMOVAL OF SUBJECTS FROM STUDY PARTICIPATION

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may remove a subject from the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of discontinuation will immediately be made to the Sponsor's Study Monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final study day assessments (see Section 7.15). The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's electronic Case Report Form (eCRF). All dropouts will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator to have stabilized or returned to baseline, as applicable.

For subjects who are discontinued by the Investigator or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. Except for replacements, the subjects will be assigned a number by study site staff. Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. Replacement subjects will be assigned a subject number by adding 100 or 1000 to the number of the subject they are replacing (e.g., Subject No. 105 replaces Subject No. 005).

The entire study may be discontinued at the discretion of the Investigator, Sponsor, or Sponsor's Medical Monitor based on the occurrence of the following:

- AEs unknown to date with respect to their nature, severity, and duration;
- Increased frequency, and/or severity, and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

6 ASSESSMENT OF SAFETY

Subjects will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs throughout the study, and clinical laboratory safety testing and measurement of ECGs and vital signs at intervals.

7 STUDY PROCEDURES

7.1 SCHEDULE OF STUDY ACTIVITIES

The Schedule of Activities is presented in Table 7-1. The PK sampling scheme is presented in Table 7-2. The clinical laboratory and safety assessment windows are presented in Table 7-3.

Table 7-1 Schedule of Activities

	Screening	Periods 1 and 2																Follow-Up[a]
Days:	-28 to -2	-1	1											2		3	4	5	12 to 14 days after last dose
Time (hours) relative to dosing: / Study procedures		Check-In	Predose	0	0.5 (30 min)	1	2	3	4	5	6	8	12	24	36	48	72	96/ Discharge /ET	
Confined to the Study Site		<———>																	
Ambulatory (outpatient) Study Site Visits	X																		
Informed Consent	X																		
Demographics	X																		
Previous Medication and Compliance with Inclusion/Exclusion Criteria	X	X																	
Medical History	X	X[b]																	
Physical Examination[c]		X																	
Height, Weight, and BMI	X																		
Single 12-Lead Safety ECG	X		X				X				X							X	
Vital Signs[d]	X		X				X				X							X	
Chemistry Panel, CBC, and UA[e]	X	X																X	
Drug and Alcohol Screen[e]	X	X																	
Hepatitis B, C, and HIV screen[e]	X																		
FSH[e]	X																		
Pregnancy test[f]	X	X																X	
AE Monitoring (HDYF? inquiry)[g]				<———>															
Concomitant Medication Monitoring			<———>																
Randomization (Period 1)			X																
Study Drug Administration[h]				X															
Blood Sampling for Entrectinib and M5 PK[i]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Standardized Meal			X																

AE = adverse event; BMI = body mass index; CBC = complete blood count (hematology); ECG = electrocardiogram; ET = Early Termination; FSH = follicle-stimulating hormone; HDYF? = how do you feel?; HIV = human immunodeficiency virus; min = minutes; PK = pharmacokinetic; UA = urinalysis.

[a] Telephone call.

[b] Interim medical history, only includes any medical history that occurred between the end of the Screening visit and the Check-in visit.

[c] A routine physical examination on Day -1 of Period 1 and an abbreviated physical examination on Day -1 of Period 2 (Section 7.13). Symptom-driven physical examinations may be performed at other times at the Investigator's discretion.

[d] Vital signs include: oral temperature, respiratory rate, and supine blood pressure and pulse.
[e] Refer to Appendix A for details and a list of evaluations. Includes alcohol testing at Check-in (Day -1) only. The FSH test is for postmenopausal females only.
[f] Females of childbearing potential only.
[g] Adverse event checks with interspersed HDYF? inquiries. Adverse events are collected after the first administration of drug.
[h] There will be at least a 14-day washout between doses in Periods 1 and 2.
[i] For PK blood samples collected during the study, also refer to Table 7-2.

Table 7-2 Pharmacokinetic Sampling Scheme (Periods 1 and 2)

Study Day	Pharmacokinetic Sampling Timepoints (Hours)	Window (+/-)	Analytes (Matrix)
Day 1	Predose	Any convenient time prior to dosing	Entrectinib and M5 (plasma)
	0.5	3 minutes	Entrectinib and M5 (plasma)
	1	5 minutes	Entrectinib and M5 (plasma)
	2	10 minutes	Entrectinib and M5 (plasma)
	3	10 minutes	Entrectinib and M5 (plasma)
	4	10 minutes	Entrectinib and M5 (plasma)
	5	10 minutes	Entrectinib and M5 (plasma)
	6	10 minutes	Entrectinib and M5 (plasma)
	8	10 minutes	Entrectinib and M5 (plasma)
	12	10 minutes	Entrectinib and M5 (plasma)
Day 2	24	10 minutes	Entrectinib and M5 (plasma)
	36	30 minutes	Entrectinib and M5 (plasma)
Day 3	48	30 minutes	Entrectinib and M5 (plasma)
Day 4	72	30 minutes	Entrectinib and M5 (plasma)
Day 5	96	30 minutes	Entrectinib and M5 (plasma)

Table 7-3 Clinical Laboratory and Safety Assessment Windows

Safety Assessment Timepoints	Window (+/-)
Predose	-45 minutes
0 to 8 hours postdose	15 minutes
12 to 36 hours postdose	1 hour
Day 3 to Day 5	4 hours

[a] Safety assessments may include vital signs, electrocardiograms, physical examinations, and clinical laboratory assessments. Not all safety assessments will be performed at each timepoint specified.

7.2 STUDY TREATMENT

The IMP for this study is entrectinib.

7.2.1 DRUG SUPPLIES AND ACCOUNTABILITY

The Sponsor or designee will provide the Investigator with adequate quantities of the study drugs (see Table 7-4).

Table 7-4 Study Drugs

Study Drug	Entrectinib	Entrectinib
Formulation[a]	Capsule (F1; Test)	Capsule (F06; Reference)
Strength	200 mg (Dosed as 3 × 200-mg capsules)	200 mg (Dosed as 3 × 200-mg capsules)
Supplier	Genentech	Genentech
Manufacturer	Genentech	Genentech

[a] Specific ingredients/purity will be identified on the Certificate of Analysis (or equivalent) that is supplied with the study drugs.

The lot numbers for the study drugs will be provided to the study site by the supplier/manufacturer as soon as available.

Study drugs will be stored at controlled room temperature (not above 25°C) under secure conditions. The study drugs will be transferred from the bulk supplies into the subject's dose container by qualified study site employees. Each unit dose container will be appropriately labeled.

The Investigator or designee will maintain an accurate record of the receipt of the test materials as shipped by the Sponsor or designee, including the date received. One copy of this receipt will be returned to the Sponsor when the contents of the test material shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

If deemed appropriate by the Sponsor, sufficient samples will be randomly selected from the supply provided by the Sponsor or designee and retained by the study site to meet the retention requirements described in US Title 21 Code of Federal Regulations (CFR) 320.38 and 320.63.

At the completion of the study, all unused drug supplies (except for retention supplies, if appropriate) will be returned to the Sponsor or designee or disposed of by the study site, per the Sponsor's or designee's written instructions.

7.2.2 DOSE PREPARATION AND ADMINISTRATION AND STANDARDIZED MEAL

Each unit dose will be prepared by qualified clinical staff based on the study randomization that will be provided by a Covance Biostatistician.

In Periods 1 and 2, subjects will be required to fast overnight for at least 10 hours until 30 minutes prior to their scheduled entrectinib dose on Day 1, when they will be given a light

meal in the form of a standardized "pediatric" breakfast which will be entirely consumed within 30 minutes. Details regarding the standardized breakfast are as follows:

Standardized "Pediatric" Breakfast
1 hard-boiled egg
2 slices of wheat bread
1 strawberry jam
8 fluid ounces of water with no ice

After completion of the standardized meal, one of the following assigned treatments will be administered on Day 1 of each period (Hour 0):

- Single 600 mg oral dose of Entrectinib F1 capsule formulation (Test), fed
- Single 600 mg oral dose of Entrectinib F06 capsule formulation (Reference), fed

Each dose will be administered orally with approximately 240 mL of room temperature water. A hand and mouth check will be performed to verify that the dose administered was swallowed. Subjects will be instructed not to crush, split or chew the entrectinib capsules. Subjects will fast for at least 4 hours following entrectinib dosing.

Water (except water provided with the standardized meal and entrectinib dosing) will be restricted for 1 hour prior to and 1 hour after each entrectinib administration, but will be allowed ad libitum at all other times.

Doses of entrectinib will be separated by a washout period of at least 14 days.

Appropriate unit doses, as described above, will be administered to consecutively numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual time will be recorded in the source documents and transcribed into the eCRFs.

7.3 REMOVAL OF STUDY BLIND

Not applicable; this is an open-label study and will not be blinded.

7.4 CONTRACEPTION

Postmenopausal is defined as at least 12 months without a period (i.e., amenorrhea) in a woman at least 45 years of age and documented by a serum follicle-stimulating hormone [FSH] level consistent with postmenopausal status (i.e., ≥40 IU/L) 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 for at least 90 days prior to Screening.

Females who are not postmenopausal or surgically sterile are of childbearing potential and must agree to use 1 of the following examples of highly-effective contraception (failure rate of <1% per year) from the time of signing the informed consent or 10 days prior to Check-in (Day -1) of Period 1 and for 6 weeks after the final dose of study drug:

- Bilateral tubal ligation;
- Bilateral tubal occlusion (Essure);
- Vasectomized male partner;
- Hormonal contraceptives that inhibit ovulation;
- Hormone-releasing intrauterine device (IUD);
- Copper IUD.

Male subjects will either be surgically sterile with documented azoospermia (confirmed by reported medical history and/or medical records) for at least 90 days prior to Screening, or will be required to use 1 of the following approved methods of contraception from Check-in (Day -1) of Period 1 and for 90 days after the final dose of study drug:

- Male condom with spermicide.

For subjects who are exclusively in same-sex relationships or are abstinent (when this is in line with the preferred and usual lifestyle of the subject), contraceptive requirements do not apply. If a subject 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.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. If a male subject cannot provide proof of sterilization by medical records, the subject must agree to either true abstinence or a method of birth control as outlined above.

Male subjects (including men who have had vasectomies) whose partners are currently pregnant should use a barrier method with spermicide for the duration of the study through Follow-up. This is to ensure that the fetus is not exposed to the drug in the ejaculate.

7.5 DIET, FLUID, AND ACTIVITY CONTROL

Subjects will refrain from use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, and nicotine gum) within 6 months prior to Check-in (Day -1) of Period 1 and during the entire study.

Subjects will abstain from consuming alcohol- or caffeine-containing foods and beverages for 72 hours prior to Check-in (Day -1) of Period 1 and during the entire study, unless deemed acceptable by the Investigator.

Subjects will abstain from consuming grapefruit- or Seville orange-containing foods and beverages for 7 days prior to Check-in (Day -1) of Period 1 and during the entire study, unless deemed acceptable by the Investigator.

Subjects will refrain from strenuous exercise from 48 hours prior to Check-in (Day -1) of Period 1 and during the period of confinement at the study site 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).

With the exception of dosing, as applicable, while confined at the study site, subjects will receive a normal clinic diet at scheduled times that do not conflict with other study-related activities.

See Section 7.2.2 for diet and fluid restrictions in regards to dose administration.

Subjects will remain ambulatory or seated upright for 4 hours following entrectinib administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

7.6 CONCOMITANT MEDICATIONS

Subjects should not take any prescription or over-the-counter medication, vitamins, or minerals from 14 days prior to Screening and during the study, unless the Investigator has given prior consent. The following categories of medication are specifically prohibited from 28 days prior to Screening and during the study:

- Moderate or potent inhibitors or inducers of CYP3A enzyme or P-gp transporter;

- Gastric pH-modifying agents such as proton pump inhibitors, H_2-receptor antagonists, and antacids;
- Psychoactive drugs or other drugs used for mental disorders. Examples include antidepressants, anti-psychotics, sedatives, and stimulants.

Acetaminophen (paracetamol) up to 2 g per day, medications to treat AEs, hormonal contraceptives and hormone replacement therapy are allowed throughout the study. Ondansetron is permitted as a treatment for nausea for individual subjects at the discretion of the Investigator. Other medications for chronic, non-clinically significant, conditions (e.g., thyroid hormone replacement medication) may be permitted providing the subject has been on a stable dose and dosing regimen for at least 3 months preceding Screening.

The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator, unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study, including the name, strength, frequency of dosing, and the reason for its use, will be documented in the source documents and the eCRF.

7.7 PHARMACOKINETIC BLOOD SAMPLE COLLECTION AND PROCESSING

Blood samples for PK analysis 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 timepoints listed in Table 7-2.

Processing, storage, and shipping instructions for these PK blood samples are presented in a separate laboratory manual.

After the plasma samples collected in the study are analyzed for entrectinib and M5 concentrations, any residual samples may be used for analysis such as metabolite profiling and identification, interacting drug concentration measurements, ex vivo protein binding, or development of PK or pharmacodynamic assays. Residual PK samples will be destroyed no later than 5 years after the final Clinical Study Report (CSR) has been completed. When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests in writing 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. Sample retention may be detailed in the Laboratory Manual.

7.8 ANALYTICAL METHODOLOGY

Plasma concentrations of entrectinib and M5 will be determined using a validated liquid chromatography tandem mass spectrometry bioanalytical procedure by an external vendor.

7.9 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations (including chemistry panel [fasted at least 8 hours], CBC, and UA) will be collected at the timepoints listed in Table 7-1.

Screens for a hepatitis panel and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse (not including alcohol) will be performed at Screening and repeated (but including an alcohol breath test) at Check-in (Day -1). A serum qualitative pregnancy test (females of childbearing potential only) and FSH test (postmenopausal females only) will be performed at the timepoints specified in Table 7-1.

7.10 12-LEAD ELECTROCARDIOGRAMS

A single 12-lead ECG will be obtained at the timepoints specified in Table 7-1.

To minimize variability in autonomic tone and heart rate, subjects will rest quietly and in a supine position for at least 5 minutes prior to recording the ECG. Blood draws, other procedures, activity, and environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and between ECG recordings, to minimize variability due to the effects of activity and stress on cardiac electrophysiology. Whenever possible, ECG tracings for each subject should be obtained from the same type of machine throughout the study.

When 12-lead ECGs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs will be obtained as close as possible to the scheduled blood draw, but prior to the blood draw.

7.11 VITAL SIGNS

Vital signs (including oral temperature, respiratory rate, and supine blood pressure and pulse rate) will be obtained at the timepoints specified in Table 7-1.

Supine blood pressure and pulse rate will be obtained after the subject has been supine for at least 5 minutes. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint and the vitals will be obtained as close as possible to the scheduled blood draw, but prior to the blood draw.

7.12 HOW DO YOU FEEL? INQUIRY

Subjects will be asked a non-leading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Table 7-1. Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study. See Section 8.3 and Section 8.4 for reporting requirements for AEs and SAEs, respectively.

7.13 PHYSICAL EXAMINATIONS

A routine or abbreviated physical examination will be performed at the timepoints specified in Table 7-1. Symptom-driven physical examinations may be performed at other times at the Investigator's discretion.

A routine physical examination will consist of an assessment of general appearance, skin, thorax/lungs, abdomen, lymph nodes, head, ears, eyes, nose, throat, and neck (including thyroid); and cardiovascular, musculoskeletal, and neurological systems. An abbreviated physical examination will consist of an assessment of general appearance, skin, thorax/lungs, cardiovascular system, and abdomen.

7.14 CLINIC DISCHARGE PROCEDURES

Refer to Table 7-1 for procedures performed on the day of discharge.

7.15 STUDY COMPLETION/EARLY TERMINATION PROCEDURES

Refer to Table 7-1 for procedures performed at follow-up or at ET.

8 ADVERSE EXPERIENCES

8.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest (AESIs), 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. 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, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 8.4.

8.1.1 ADVERSE EVENTS

According to the ICH Guideline for Good Clinical Practice (GCP), 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);
- 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).

8.1.2 SERIOUS ADVERSE EVENTS (IMMEDIATELY REPORTABLE TO THE SPONSOR)

An SAE 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 subject 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;
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject'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 subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as non-SAEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache) without any further findings. An event should be considered "serious" only if it meets the regulatory criteria outlined in the above-mentioned paragraph outlining seriousness criteria.

Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity, seriousness, and causality need to be independently assessed for each AEs recorded on the eCRF.

Serious AEs are required to be reported by the Investigator to the Sponsor via the Covance Project Manager immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2 for reporting instructions).

8.1.3 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 via the Covance Project Manager immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 8.3.1.6);
- 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 subject exposed to a medicinal product. The 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).

8.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (as defined in Section 8.1) are recorded on the AE eCRF and reported to the Sponsor via the Covance Project Manager in accordance with protocol instructions (see Section 8.4.2).

For each AE recorded on the AE eCRF, the Investigator will make an assessment of seriousness (see Section 8.1.2 for seriousness criteria), severity, and causality (see Sections 8.2.3 and 8.2.4).

8.2.1 ADVERSE EVENT REPORTING PERIOD

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

After informed consent has been obtained but prior to initiation of study drug administration, only SAEs caused by a protocol-mandated intervention (e.g., discontinuation of medications) will be reported (see Section 8.4.2 for instructions for reporting SAEs). After initiation of study drug administration, all AEs will be reported until 28 days after the last dose.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 8.5.

The Investigator is not required to actively monitor subjects after the study has ended or for AEs after the end of the AE reporting period (defined as 28 days after the last dose of study drug). However, the Sponsor should be notified if the Investigator becomes aware of any death, other SAEs, or AESIs occurring after the end of the AE reporting period that are believed to be related to prior study drug treatment. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female subject exposed to study drug (or the female partner of a male subject exposed to study drug).

8.2.2 ELICITING ADVERSE EVENT INFORMATION

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation timepoints. 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?"

8.2.3 ASSESSMENT OF SEVERITY OF ADVERSE EVENTS

The AE severity grading scale for the NCI CTCAE (version 5.0) will be used for assessing AE severity. Table 8-1 will be used for assessing AE severity for AEs that are not specifically listed in the NCI CTCAE.

Table 8-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the 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 subjects who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 8.4.2 for reporting instructions), per the definition of SAE in Section 8.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 8.4 for reporting instructions), per the definition of SAE in Section 8.1.2.

8.2.4 ASSESSMENT OF CAUSALITY OF ADVERSE EVENTS

Investigators should use their knowledge of the subject, 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 (see also Table 8-2):

- 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 subject 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.

Table 8-2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug based on facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. **Investigators should apply facts, evidence, or rationales based on scientific principles and clinical judgment to support a causal/contributory association with a study drug.**
NO	**Adverse events will be considered related, unless they fulfill the criteria as specified below.** Evidence exists that the adverse event has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). Note: The Investigator's assessment of causality for individual adverse event reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual adverse event reports, the Sponsor will promptly evaluate all reported serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities. **Attribution of serious adverse events will be reviewed on an ongoing basis, and may be changed as additional clinical data emerges (e.g., reversibility of adverse event, new clinical findings in subject with adverse event, effects of re-treatment, and adverse events in other subjects)**.

8.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

8.3.1 RECORDING ADVERSE EVENTS ON THE CASE REPORT FORM

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF. Colloquialisms and abbreviations should be avoided.

All AEs should be recorded on the AE eCRF page. If the AE qualifies as an SAE or non-serious AESI, the Investigator should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on a paper Clinical Trial SAE/AESI Reporting Form. The completed paper Clinical Trial SAE/AESI Reporting Form and safety fax coversheet should be emailed to Roche Safety Risk Management via the Covance Project Manager within 24 hours of learning of the event (see Section 8.4.2). The AE and SAE eCRF should also be completed within this timeframe. It is important that the information on the SAE Reporting Form and AE and SAE eCRF is consistent and identical.

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

8.3.1.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

If known, a diagnosis should be recorded on the AE 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 AE 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.

8.3.1.2 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 AE 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 subsequent fracture, all 3 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 AE eCRF if it is unclear as to whether the events are associated.

8.3.1.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution between subject evaluation timepoints. Such events should only be recorded once in the AE 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 AE 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 8.4.2 for reporting instructions). The AE eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and by completing all data fields related to SAEs.

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

8.3.1.4 ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should 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.

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 times the upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE 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 AE eCRF (see Section 8.3.1.3 for details on recording persistent AEs).

8.3.1.5 ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should 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 AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF (see Section 8.3.1.3 for details on recording persistent AEs).

8.3.1.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST (>3 × ULN) in combination with either an elevated total bilirubin (>2 × 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 the occurrence of either of the following as an AE:

- Treatment-emergent ALT or AST >3 × ULN in combination with total bilirubin >2 × ULN;
- Treatment-emergent ALT or AST >3 × ULN 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 AE eCRF (see Section 8.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AESI (see Section 8.4.2).

8.3.1.7 DEATHS

All deaths that occur during the protocol-specified AE reporting period (see Section 8.2.1), regardless of relationship to study drug, will be recorded on the AE eCRF as well as on the paper Clinical Trial SAE Reporting Form and immediately reported to the Sponsor via the Covance Project Manager (see Section 8.4.2 for reporting instructions).

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 AE eCRF. Generally, only 1 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 AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the AE reporting period should be reported as described in Section 8.5.

8.3.1.8 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF page.

A pre-existing 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 an AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "accelerated worsening of headaches").

8.3.1.9 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 an SAE (per the definition of SAE in Section 8.1.2) except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or SAE:

- Hospitalization for respite care;
- Hospitalization for a pre-existing 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 subject has not experienced an AE.

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

- Hospitalization that was necessary because of the subject's requirement for outpatient care outside of normal outpatient clinic operation hours.

8.4 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 via the Covance Project Manager; 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 (see Section 8.4.2) after learning of the event, regardless of relationship to study drug:

- SAEs (see Section 8.4.2 for further details);
- AESIs (see Section 8.1.3 for further details);
- Pregnancies (see Section 8.4.2.3 for further details);
- Accidental overdoses or medication errors (see Section 8.4.3 for details on reporting requirements).

The Investigator must report new significant follow-up information for these events to the Sponsor immediately via the Covance Project Manager (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 SAEs to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

8.4.1 REPORTING REQUIREMENTS FOR FATAL OR LIFE-THREATENING SERIOUS ADVERSE EVENTS

Any life-threatening (e.g., imminent risk of death) or fatal AE that is attributed to study drug by the Investigator will be telephoned to the Medical Monitor immediately, followed by completion of the paper Clinical Trial SAE Reporting Form within 24 hours of learning of the event as described in Section 8.4.2.

Medical Monitor: [redacted]
F. Hoffman-La Roche AG
[redacted] (Office Telephone No.)
[redacted] (Mobile Telephone No.)

8.4.2 REPORTING REQUIREMENTS FOR ALL SERIOUS ADVERSE EVENTS

8.4.2.1 EVENTS THAT OCCUR PRIOR TO STUDY DRUG INITIATION

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by protocol-mandated intervention should be reported. The paper Clinical Trial SAE/AESI Reporting Form provided to the Investigator should be completed and submitted to the Sponsor via the Covance Project Manager 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 below.

The Covance Project Manager to receive the Investigator-generated SAE reports:

Name: [redacted], RN, BSN, CCRC
Email Address: [redacted]
[redacted] (Office Telephone No.)
[redacted] (Mobile Telephone No.)

8.4.2.2 EVENTS THAT OCCUR AFTER STUDY DRUG INITIATION

After initiation of study drug, SAEs and AESIs will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately on a paper Clinical Trial SAE/AESI Reporting Form. The paper Clinical Trial SAE/AESI Reporting Form should be completed and submitted to the Sponsor (via the Covance Project Manager) 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 in Section 8.4.2.1. All information will also need to be entered into the AE eCRF.

Relevant follow-up information should be submitted to Roche Safety Risk Management via the Covance Project Manager on an updated paper Clinical Trial SAE/AESI Reporting Form as soon as it becomes available and/or upon request. Any updates to the paper Clinical Trial SAE/AESI Reporting Form must also be updated in electronic data capture (EDC) on the AE eCRF.

8.4.2.3 REPORTING REQUIREMENTS FOR PREGNANCIES

8.4.2.3.1 PREGNANCIES IN FEMALE SUBJECTS

Female subjects of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed by the Investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and emailed to Roche Safety Risk Management via the Covance Project Manager (see Section 8.4.2 for reporting instructions). Pregnancy should not be recorded on the AE eCRF. The Investigator should discontinue study drug and counsel the subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Any SAEs 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 AE eCRF. In addition, the Investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

8.4.2.3.2 PREGNANCIES IN FEMALE PARTNERS OF MALE SUBJECTS

Male subjects will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed by the Investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and emailed to Roche Safety Risk Management via the Covance Project Manager (see Section 8.4.2 for reporting instructions). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject 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 subject 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.

8.4.2.3.3 CONGENITAL ANOMALIES/BIRTH DEFECTS AND ABORTIONS

Any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug or the female partner of a male subject exposed to the study drug should be classified as an SAE, recorded on the AE eCRF, and reported to the Sponsor immediately via the Covance Project Manager (see Section 8.4.2 for reporting instructions) (i.e., no more than 24 hours after learning of the event; see Section 8.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant events).

8.4.3 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 AE 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 8.4.2). 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 AE 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 AE eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

8.4.4 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

8.4.4.1 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 subject is lost to follow-up, or the subject

withdraws consent. Every effort should be made to follow all SAEs 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 AE eCRF and in the subject's medical record to facilitate source data verification.

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

8.4.4.2 SPONSOR FOLLOW-UP

For SAEs, AESIs, 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.

8.5 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

At the Follow-up/ET visit or, the Investigator should instruct each subject to report to the Investigator any subsequent AEs that the subject's personal physician believes could be related to prior study drug treatment or study procedures. The Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined as 28 days after the last dose of study drug) if the event is believed to be related to prior study drug treatment.

These events should be reported through the use of the AE eCRF. However, if the EDC system is not available, the Investigator should report these events directly to the Sponsor or its designee, by faxing or by scanning and emailing the paper Clinical Trial SAE/AESI Reporting Form using the below fax number or email address provided to Investigators.

Genentech US Drug Safety
Email Address: us_drug.safety@gene.com
Fax No.: (650) 225-4682

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

The Sponsor will promptly evaluate all SAEs and AESIs 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 IB

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.

The IRB will be notified by the investigative site in writing (e.g., email) within the timeframe required per local IRB regulations for when a reportable AE is first recognized or reported. In addition, a copy of the written confirmation or summary of the AE, as submitted to the Sponsor, will also be submitted to the IRB within that same timeframe from when the AE is first recognized or reported. The IRB Serious and Unexpected AE Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

9 STATISTICAL ANALYSES

The Safety Population will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

The PK Population will consist of all subjects who received at least 1 dose of study drug and have at least 1 evaluable postdose PK sample.

Baseline is defined as the last result prior to the first dose of study drug on Day 1 of Period 1. As necessary, baseline will be further defined in the Statistical Analysis Plan (SAP).

9.1 SAFETY AND TOLERABILITY ANALYSIS

Safety will be assessed by a review of AEs, vital signs, clinical laboratory assessments, and ECGs. Clinical laboratory assessments, vital signs (including oral temperature, respiratory rate, and supine blood pressure and pulse rate), and ECGs will be listed by subject number and scheduled time. Changes from baseline will be summarized, as appropriate.

Verbatim descriptions of AEs will be coded according to current Medical Dictionary for Regulatory Activities version 21.1 (or higher) guidelines. Adverse events will be summarized.

Enrollment and discontinuations from the study will be summarized overall. Demographics and baseline characteristics such as age, sex, and BMI will be summarized overall.

9.2 PHARMACOKINETIC ANALYSIS

The following PK parameters will be derived from the plasma concentrations of entrectinib and M5 using the model independent approach:[5]

C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2} = (\ln 2)/\lambda_z$
CL/F	apparent systemic clearance, calculated as dose/$AUC_{0-\infty}$ (entrectinib only)
V_z/F	apparent volume of distribution during the terminal elimination phase, calculated as (CL/F)/λ_z (entrectinib only)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix WinNonlin (Certara Inc., version 6.4 or higher).

Other parameters may be added, as appropriate. Final PK parameters reported will be detailed in the SAP.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the SAP.

9.3 INTERIM ANALYSIS

There will not be any interim analysis for this study.

9.4 STATISTICAL ANALYSIS OF PHARMACOKINETIC DATA

Descriptive statistics (mean, median, minimum, maximum, standard deviation, geometric mean, and geometric coefficient of variation [CV]) will be calculated for all PK parameters and PK concentration data.

Plasma concentrations of entrectinib and its active metabolite M5, and derived plasma PK parameters, will be listed and summarized by treatment using descriptive statistics. Individual and mean concentration versus time profiles will be plotted.

The primary parameters for analysis will be C_{max} and $AUC_{0-\infty}$ of entrectinib and M5. A linear mixed model will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effects for treatment, period, and sequence, and a random effect for subject within sequence. Estimates of geometric mean ratios on the original scale, together with the corresponding 90% CIs, will be derived for the comparisons between Test and Reference treatments.

All calculations will be performed using SAS® version 9.4 or greater.

Specification of PK parameters for analysis; criteria for study termination; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of subjects to be included in the analyses population(s) will be presented in the CSR and/or SAP, as appropriate.

9.5 STATISTICAL ANALYSES OF SAFETY DATA

Descriptive statistics will be calculated for the safety parameters. No formal statistical analyses are planned.

9.6 SAMPLE SIZE

A total of 14 subjects will be enrolled to ensure that 12 subjects complete the study and have evaluable PK data from both treatment periods.

The sample size has been chosen to ensure that the ratios of the geometric means for the PK parameters of entrectinib can be estimated with sufficient precision. In a previous study

(Study RXDX-101-15), the within-subject coefficients of variation for $AUC_{0-\infty}$ and C_{max} following administration of a single dose of entrectinib were estimated to be 20% and 16%, respectively. Based on a CV of 20%, with 12 evaluable subjects it is estimated that the lower and upper bounds of the 90% CIs of the ratio will be within 1.25x of the corresponding point estimates for each of the 2 entrectinib PK parameters ($AUC_{0-\infty}$ and C_{max}).

9.7 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance will be performed according to Covance Standard Operating Procedures or per client request and as applicable according to the contract between Covance and the Sponsor.

10 ADMINISTRATIVE ASPECTS

10.1 CHANGE IN PROTOCOL

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the IRB (see Form FDA 1572).

10.2 INVESTIGATOR MEETING; SITE INITIATION

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator and clinical staff with the materials necessary for conducting the clinical study.

10.3 DISCLOSURE

All information provided regarding the study, as well as all information collected and documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable timeframe, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

10.4 MONITORING (CLINICAL RESEARCH ASSOCIATE)

The Sponsor will designate a Sponsor's Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor have access to all documents, including study data, subject medical records, and eCRFs, at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

10.5 INSTITUTIONAL REVIEW BOARD

In accordance with 21 CFR 56, the protocol, advertisement, and ICF will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator.

The IRB will be informed by the Investigator of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator. If requested, the Investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data and documents.

The Investigator will provide the IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

10.6 INFORMED CONSENT

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The Investigator or designee will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be

documented by the use of a written ICF approved by the IRB and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign 2 copies of the ICF. One copy will be given to the subject, and the other will be maintained with the subject's records.

10.7 RECORDS

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor or designee. Copies of each eCRF will be retained by the Investigator. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (e.g., laboratory records, Case Report Forms (CRFs), data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

10.7.1 ELECTRONIC CASE REPORT FORMS

Electronic CRFs are to be completed using the Medidata RAVE EDC system. The site will receive training and have access to a manual for appropriate eCRF completion. Electronic CRFs will be submitted electronically to Covance and should be handled in accordance with instructions from Genentech/Covance. All eCRFs should be completed by designated, trained examining personnel as appropriate.

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRF by providing an electronic signature. The completed eCRFs will be transferred to the Sponsor or designee.

In addition, at the end of the study, the Investigator will receive subject data for the site in a readable format (e.g., a compact disc) that must be kept with the study records.

10.7.2 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 subject 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, subject diaries or 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, subject files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial. Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed. To facilitate source data verification and review, the Investigator and institution(s) 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.

10.7.3 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 FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the Study Monitor, Genentech's or Covance's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at study sites can serve as source documents for the purposes of this protocol. If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

10.7.4 STUDY MEDICATION ACCOUNTABILITY

The recipient of study medication will acknowledge receipt by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the Sponsor. If the study site is able to destroy study drug, the method of destruction must be documented. Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

10.7.5 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law. Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study Investigators or subjects 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.

Data generated by this study must be available for inspection upon request by representatives of the US FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for the study site, if 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 CSRs and other summary reports will be provided upon request.

10.7.6 RETENTION OF RECORDS

The US FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the study drug. All state and local laws for retention of records also apply. No records should 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. For studies conducted outside the U.S. under a U.S. Investigational New Drug Application (IND), the Investigator must comply with the record retention requirements set forth in the US FDA IND regulations and the relevant national and local health authorities, whichever is longer.

All primary data, or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the study site archives.

10.8 REFERENCE TO DECLARATION OF HELSINKI/BASIC PRINCIPLES

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable ICH Guidelines, are commonly known as GCP, which are consistent with the Declaration of Helsinki.

PRINCIPAL INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

[redacted] DO
Principal Investigator
Covance Clinical Research Unit

06 NOV 2018
Date

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to the conduct of the study as described herein.

[redacted]

6-NOV-2018

[redacted], PhD

Date

Clinical Pharmacologist
Roche Products Ltd.

REFERENCES

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2. Weinstein IB and Joe AK. Oncogene addiction. Cancer Res 2008;68:3077-80.
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APPENDIX A – CLINICAL LABORATORY EVALUATIONS

Chemistry Panel (Fasted at least 8 hours):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Creatine kinase (CK)/Creatine phosphokinase (CPK)
Glucose
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Uric acid

Complete Blood Count:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (absolute):
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Drug Screen:
Including but not limited to the following:
Alcohol (ethanol) [b]
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids (THC)
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine [a]

Other Tests:
Hepatitis B virus core antibody [a]
Hepatitis B surface antigen [a]
Hepatitis C virus antibody [a]
Human Immunodeficiency Virus antibody [a]
Pregnancy test (females only; serum qualitative)
Follicle-stimulating hormone (FSH; postmenopausal females only) [a]

[a] Measured at the Screening visit only.
[b] Alcohol breath testing will be performed at Check-in (Day -1) only.

APPENDIX B – APPROXIMATE MAXIMUM BLOOD VOLUME COLLECTED

Note: Additional samples may be drawn for safety purposes.

	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Serology	7.0	1	7.0
Chemistry Laboratory Panel (includes serum pregnancy and FSH)	8.5	5	42.5
CBC (hematology)	4.0	5	20.0
PK Samples	4.0	30	120.0
		Total	**189.5**

CBC = complete blood count; FSH = follicle-stimulating hormone; PK = pharmacokinetic.