Official Title: A Randomized, Open-Label, Two Part Study to Explore the Performance of Entrectinib Prototype Mini-Tablet Formulations and the Effect of Drug Substance Particle Size on Entrectinib Bioavailability in Healthy Volunteers

NCT Number: NCT03961100

Document Date: Protocol Version 1: 04-April-2019
Protocol Non-substantial Amendment Version 1.0: 11-July-2019

PROTOCOL

TITLE:	**A RANDOMIZED, OPEN-LABEL, TWO PART STUDY TO EXPLORE THE PERFORMANCE OF ENTRECTINIB PROTOTYPE MINI-TABLET FORMULATIONS AND THE EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON ENTRECTINIB BIOAVAILABILITY IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	GP41341
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-000783-15
IND NUMBER:	IND 120500
TEST PRODUCT:	Entrectinib (RXDX-101) (RO7102122)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1.0 02 APR 2019

TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM 7

PROTOCOL ACCEPTANCE FORM 8

PROTOCOL SYNOPSIS 9

1. BACKGROUND 16
   - 1.1 Background on Entrectinib 16
   - 1.1.1 Toxicology and Safety Pharmacology 16
   - 1.1.2 Clinical Summary 17
   - 1.1.2.1 Safety 17
   - 1.1.2.2 Pharmacokinetics 17
   - 1.2 Study Rationale and Benefit-Risk Assessment 19
   - 1.2.1 Study Rationale 19
   - 1.2.2 Risk-Benefit Assessment 19

2. OBJECTIVES AND ENDPOINTS 20
   - 2.1 Pharmacokinetic Objectives (Primary Study Objective) 20
   - 2.2 Safety Objective (Secondary Study Objective) 20
   - 2.3 Additional Objective 20

3. STUDY DESIGN 20
   - 3.1 Description of the Study 20
   - 3.2 End of Study and Length of Study 23
   - 3.3 Rationale for Study Design 24
   - 3.3.1 Rationale for Subject Population 24
   - 3.3.2 Rationale for Entrectinib Dose and Schedule 24
   - 3.3.3 Rationale for Pharmacokinetic Sampling Schedule 24

4. MATERIALS AND METHODS 25
   - 4.1 Subjects 25
   - 4.1.1 Inclusion Criteria 25
   - 4.1.2 Exclusion Criteria 26
   - 4.2 Method of Treatment Assignment and Blinding 28

4.2.1 Part 1 28
4.2.2 Part 2 28
4.3 Study Treatment and Other Treatments Relevant to the Study Design 29
4.3.1 Study Treatment Formulation, Packaging, and Handling 29
4.3.2 Study Treatment Dosage, Administration, and Compliance 30
4.3.2.1 Entrectinib 30
4.3.3 Investigational Medicinal Product Accountability 30
4.4 Concomitant Therapy, Prohibited Food, and Additional Restrictions 31
4.4.1 Permitted Therapy 31
4.4.2 Prohibited Therapy 32
4.4.3 Prohibited Food 32
4.4.4 Additional Restrictions 32
4.5 Study Assessments 33
4.5.1 Informed Consent Forms and Screening Log 33
4.5.2 Medical History, Concomitant Medication, and Demographic Data 34
4.5.3 Physical Examinations 34
4.5.4 Vital Signs 35
4.5.5 Laboratory, Biomarker, and Other Biological Samples 35
4.5.6 Electrocardiograms 36
4.5.7 Palatability Questionnaire 37
4.6 Treatment, Subject, Study, and Site Discontinuation 37
4.6.1 Stopping Criteria 37
4.6.2 Subject Discontinuation from the Study 38
4.6.3 Study Discontinuation 39
4.6.4 Site Discontinuation 40
5. ASSESSMENT OF SAFETY 40
5.1 Safety Plan 40
5.2 Safety Parameters and Definitions 40

5.2.1 Adverse Events 41
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 41
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 42
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 42
5.3.1 Adverse Event Reporting Period 43
5.3.2 Eliciting Adverse Event Information 43
5.3.3 Assessment of Severity of Adverse Events 43
5.3.4 Assessment of Causality of Adverse Events 44
5.3.5 Procedures for Recording Adverse Events 45
5.3.5.1 Diagnosis versus Signs and Symptoms 45
5.3.5.2 Adverse Events That Are Secondary to Other Events 45
5.3.5.3 Persistent or Recurrent Adverse Events 46
5.3.5.4 Abnormal Laboratory Values 46
5.3.5.5 Abnormal Vital Sign Values 47
5.3.5.6 Abnormal Liver Function Tests 47
5.3.5.7 Deaths 48
5.3.5.8 Preexisting Medical Conditions 48
5.3.5.9 Hospitalization or Prolonged Hospitalization 48
5.3.5.10 Cases of Accidental Overdose or Medication Error 49
5.4 Immediate Reporting Requirements from Investigator to Sponsor 50
5.4.1 Emergency Medical Contacts 51
5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest 51
5.4.2.1 Events that Occur Prior to Study Drug Initiation 51
5.4.2.2 Events That Occur after Study Drug Initiation 51
5.4.3 Reporting Requirements for Pregnancies 52
5.4.3.1 Pregnancies in Female Subjects 52
5.4.3.2 Pregnancies in Female Partners of Male Subjects 52

5.4.3.3 Abortions 52
5.4.3.4 Congenital Anomalies/Birth Defects 53
5.5 Follow-Up of Subjects after Adverse Events 53
5.5.1 Investigator Follow-Up 53
5.5.2 Sponsor Follow-Up 53
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 53
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 54
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 55
6.1 Determination of Sample Size 56
6.2 Summaries of Conduct of Study 56
6.3 Summaries of Demographic and Baseline Characteristics 56
6.4 Safety Analyses 56
6.5 Pharmacokinetic Analyses 57
6.6 Other Analyses 57
6.7 Interim Analyses 57
7. DATA COLLECTION AND MANAGEMENT 58
7.1 Data Quality Assurance 58
7.2 Electronic Case Report Forms 58
7.3 Source Data Documentation 58
7.4 Use of Computerized Systems 59
7.5 Retention of Records 59
8. ETHICAL CONSIDERATIONS 60
8.1 Compliance with Laws and Regulations 60
8.2 Informed Consent 60
8.3 Institutional Review Board or Ethics Committee 61
8.4 Confidentiality 61
8.5 Financial Disclosure 62
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 62

9.1 Study Documentation 62
9.2 Protocol Deviations 62
9.3 Site Inspections 63
9.4 Administrative Structure 63
9.5 Dissemination of Data and Protection of Trade Secrets 63
9.6 Protocol Amendments 64
10. REFERENCES 65

LIST OF TABLES

Table 1 Part 1 Treatment Sequences 28
Table 2 Part 2 Treatment Sequences 29
Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE 44
Table 4 Causal Attribution Guidance 45

LIST OF FIGURES

Figure 1 Median entrectinib plasma concentration versus time profile following a single 600 mg dose to healthy volunteers under fed or fasted conditions 18
Figure 2 Overview of Part 1 Design 22
Figure 3 Overview of Part 2 Design 23

LIST OF APPENDICES

Appendix 1 Schedule of Activities 66
Appendix 2 Schedule of Pharmacokinetic Samples 69
Appendix 3 Palatability Questionnaire 70

PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, OPEN-LABEL, TWO PART STUDY TO EXPLORE THE PERFORMANCE OF ENTRECTINIB PROTOTYPE MINI-TABLET FORMULATIONS AND THE EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON ENTRECTINIB BIOAVAILABILITY IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	GP41341
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-000783-15
IND NUMBER:	IND 120500
TEST PRODUCT:	Entrectinib (RXDX-101) (RO7102122)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Genentech, Inc.

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

[redacted]
Principal Investigator's Name (print)

[redacted]
Principal Investigator's Signature

04 APR 2019
Date

Please retain the signed original of this form for your study files.

PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, OPEN-LABEL, TWO PART STUDY TO EXPLORE THE PERFORMANCE OF ENTRECTINIB PROTOTYPE MINI-TABLET FORMULATIONS AND THE EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON ENTRECTINIB BIOAVAILABILITY IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	GP41341
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-000783-15
IND NUMBER:	IND 120500
TEST PRODUCT:	Entrectinib (RXDX-101) (RO7102122)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Genentech, Inc.

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

[redacted] PhD
Clinical Pharmacologist

[redacted] 3rd April 2019
Date

[redacted] this form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, OPEN-LABEL, TWO PART STUDY TO EXPLORE THE PERFORMANCE OF ENTRECTINIB PROTOTYPE MINI-TABLET FORMULATIONS AND THE EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON ENTRECTINIB BIOAVAILABILITY IN HEALTHY VOLUNTEERS**
PROTOCOL NUMBER:	GP41341
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-000783-15
IND NUMBER:	IND 120500
TEST PRODUCT:	Entrectinib (RXDX-101) (RO7102122)
MEDICAL MONITOR	[redacted]
PHASE:	I
INDICATION:	Oncology
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the bioavailability, palatability, safety and tolerability of entrectinib in healthy volunteers. Specific objectives and corresponding endpoints for the study are outlined below.

	Objectives	Endpoints
Primary	Part 1: To explore the relative bioavailability of entrectinib from two multi-particulate formulations and the reference F06 capsule formulation under fed conditions Part 2: To explore the relative bioavailability of two entrectinib F06 capsule formulations under fasted conditions	The geometric mean ratio and associated 90% confidence intervals of entrectinib and M5 $AUC_{0\text{-}inf}$ and C_{max} parameters
Secondary	To explore the safety and tolerability of a single oral dose of entrectinib in healthy volunteers	Incidence and severity of adverse events, incidence of abnormalities in laboratory safety tests, physical examinations, 12-lead ECGs and vital sign measurements
Additional	To explore the palatability (taste and acceptability) of coated and uncoated multi-particulate formulations	Completion of palatability questionnaire

Study Design

Description of Study

This is a randomized, open-label, single-center, two-part study in healthy volunteers to explore the performance of entrectinib multi-particulate formulations (Part 1) and the effect of drug substance particle size on entrectinib bioavailability (Part 2).

Part 1

Part 1 is a randomized, open-label, three-treatment, three-period, three-sequence, three-way crossover design. In each treatment period, subjects will receive a single 600 mg oral dose of entrectinib under fed conditions. Entrectinib will be administered as one of three possible formulations:

- Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710 2122/F15) (test formulation 1; T1)
- Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710 2122/F16) (test formulation 2; T2)
- F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 3 × 200 mg (Ro 710 2122/F04) (reference formulation; R)

Study treatments will be administered orally within 30 mins of consumption of a standardized light “pediatric” breakfast. The test formulation, provided in a bottle, will be mixed with approximately one tablespoon (~15 mL) of yogurt, which will be swallowed without chewing with approximately 240 mL of water. In each period, palatability (taste and acceptability) of the test formulations will be assessed by completion of a questionnaire shortly after drug administration.

The reference formulation will be dosed as 3 x 200 mg capsules, swallowed whole with approximately 240 mL of water.

A total of 15 subjects will be enrolled. Subjects will be randomly assigned to one of three treatment sequences (i.e., T1T2R, T2RT1, RT1T2) according to a pre-specified randomization scheme based on the order of study enrollment.

Blood samples for measurement of plasma concentrations of entrectinib and its active metabolite M5 will be collected before and at intervals up to 96 hours after study drug dosing in each period.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

Part 2

Part 2 is a randomized, open-label, two-treatment, two-period, two-sequence, two-way crossover design. In each treatment period, subjects will receive a single 200 mg oral dose of entrectinib under fasted conditions. Entrectinib will be administered as one of two possible formulations:

- Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules (coarse active pharmaceutical ingredient [API]), 200 mg (test formulation; T)
- Entrectinib (RXDX-101) F06 hard capsules (fine API), 200 mg (Ro 710 2122/F04) (reference formulation; R)

The formulations will be dosed as 1 × 200 mg capsules, swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours).

A total of 16 subjects will be enrolled. Subjects will be randomly assigned to one of two treatment sequences (i.e., TR or RT) according to a pre-specified randomization scheme based on the order of study enrollment.

Blood samples for measurement of plasma concentrations of entrectinib and its active metabolite M5 will be collected before and at intervals up to 96 hours after study drug dosing in each period.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

Number of Subjects

It is planned that total of 15 subjects will be enrolled in Part 1 and 16 subjects will be enrolled in Part 2 of the study to achieve 12 evaluable subjects in each part. Subjects who withdraw from the study may be replaced at the discretion of the Sponsor and investigator to ensure that in each part 12 subjects complete the study and have evaluable pharmacokinetic data from all treatment periods.

Target Population

Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Able and willing to comply with the study restrictions and to give written informed consent before any study procedure.
- Healthy male or female subjects of non-childbearing potential aged 18 to 60 years, inclusive, at time of signing Informed Consent Form (ICF)
- A body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive, and weighing $\geqslant$50 kg, at screening.
- 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 and 12-lead ECG assessment, and laboratory safety test results.
- Agreement to comply with measures to prevent pregnancy and restrictions on egg and sperm donation.

  Female subjects of non-childbearing potential do not need to use any methods of contraception. Non-childbearing potential is defined as either post menopausal (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 [e.g., 40 IU/L]), or surgically sterile (e.g., bilateral oophorectomy, bilateral salpingectomy, hysterectomy; note: tubal ligation is not considered an appropriate method of surgical sterilization) for at least 90 days.

  For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an approved method of effective contraception, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential, men must remain abstinent or use a condom plus an approved method of effective contraception (partner's use of combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal]; partner's use of progestogen only hormonal contraception [oral, injectable/implantable, intrauterine hormone]; partner's use of implantable intrauterine device; partner's use of female cap or diaphragm (double barrier); surgical sterilization [e.g., vasectomy or partner's bilateral tubal occlusion]) during the treatment period and for 104 days after the final dose of entrectinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local ICF.

Exclusion Criteria

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

- Women of childbearing potential, women or are pregnant or breastfeeding, or intending to become pregnant during the study or within 14 days after the final dose of entrectinib or have a pregnant partner.
    - All women must have a negative serum pregnancy test at screening and a negative urine test at every admission.
- A clinical significant medical 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.
- 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.
- A clinically significant abnormality in laboratory test results. In case of borderline or questionable results, tests may be repeated to confirm eligibility. Red blood cell count must not be lower than the lower limit of normal (RBC<LLN).
- A clinically significant abnormal physical examination finding.
- QTcF interval >450 msec or the presence of any other abnormal ECG finding, which, in the investigator's opinion, is clinically significant.
- Confirmed by repeat (e.g., 2 consecutive measurements) systolic blood pressure greater than 140 or less than 90 mmHg, or diastolic blood pressure greater than 90 or less than 50 mmHg, or resting pulse rate greater than 90 or less than 40 beats per minute.
- Clinically significant change in health status, as judged by the investigator, or any major illness within the four weeks before screening, or clinically significant acute infection or febrile illness within the 14 days before screening.
- Any other ongoing condition or disease, or laboratory test result, that the investigator considers would render the participant unsuitable for the study, place the subject at undue risk, interfere with the ability of the subject to complete the study, or confound interpretation of study data.
- Use of moderate or potent inhibitors or inducers of CYP P450 3A4 enzyme or P gp transporter within the 28 days before screening, or use of other prohibited medications within the 7 days before screening.
- Participation in any other clinical study involving an investigational medicinal product (IMP) or device within 3 months prior to planned dosing day (Day 1).
- A positive test result for hepatitis B, hepatitis C (HCV), or human immunodeficiency virus (HIV).

- Recent history of alcoholism, drug abuse, or addiction within the last year prior to screening, or a positive test for alcohol or drugs of abuse at screening or admission for each period.
- Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
- Current smokers and those who have smoked within the last 12 months. A confirmed (by repeat) breath carbon monoxide reading of greater than 10 ppm at screening or admission for each period.
- Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
- Known history of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds.
- Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active.
- Donation or loss of over 400 mL of blood within the three months before screening.
- Subjects who are study site employees, or immediate family members of a study site or Sponsor employee.
- Subjects who have previously been enrolled in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2.
- Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening.
- Failure to satisfy the investigator of fitness to participate for any other reason.

End of Study

The end of this study is defined as the date when the last subject, last visit occurs or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur up to 10 weeks after the last subject is enrolled.

Length of Study

The total duration of the study for each enrolled subject (screening through to end of study) will be up to 10 weeks for subjects in Part 1 and up to 8 weeks for subjects in Part 2.

Investigational Medicinal Products

The IMP for this study is entrectinib; all treatments will be administered orally.

Test Product (Investigational Drug)

Part 1

Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710 2122/F15)

Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710 2122/F16)

Part 2

Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules (coarse active pharmaceutical ingredient [API]), 200 mg

Comparator

The reference treatment in Part 1 and Part 2 is entrectinib (RXDX-101) F06 hard capsules (fine API), 200 mg (Ro 710-2122/F04)

Statistical Methods

Primary Analysis

The plasma pharmacokinetics of entrectinib and M5 will be summarized by estimating the following PK parameters (as appropriate for data collected):

- t_{max}: the time to maximum plasma concentration
- C_{max}: the maximum observed plasma concentration

- AUC_{0-t}: the 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-inf}: area under the concentration-time curve extrapolated to infinity
- AUC%extrap: the percentage of AUC_{0-inf} accounted for by extrapolation of the apparent elimination slope from Ct to infinity
- λ_z: apparent terminal elimination rate constant
- $t_{1/2}$: apparent terminal elimination half-life (whenever possible)
- V_z/F: apparent volume of distribution base on area for oral dose
- CL/F: apparent clearance following oral dosing
- MPR: metabolite to parent ratio of AUC_{0-inf}, where appropriate
- Frel: relative bioavailability for AUC_{0-inf}, where appropriate

The primary parameters for analysis will be C_{max} and AUC_{0-inf} of entrectinib and M5. A linear mixed model will be applied to analyze the log-transformed primary pharmacokinetic parameters. The model assumes fixed effects for treatment, period, and sequence, and a random effect for subject nested 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.

Determination of Sample Size

It is planned that total of 15 subjects will be enrolled in Part 1 and 16 subjects will be enrolled in Part 2 of the study to achieve 12 evaluable subjects in each part. Subjects who withdraw from the study may be replaced at the discretion of the Sponsor and investigator to ensure that in each part 12 subjects complete the study and have evaluable pharmacokinetic data from all treatment periods.

The sample size has been chosen to ensure that the ratios of the geometric means for the pharmacokinetic 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-inf} and C_{max} following administration of a single dose of entrectinib were estimated to be 20% and 16%, respectively. Based on a coefficient of variation 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 two entrectinib pharmacokinetic parameters (AUC_{0-inf} and C_{max}).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
API	active pharmaceutical ingredient
BMI	body mass index
CNS	central nervous system
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
HCV	hepatitis C
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
NTRK	neurotrophic tyrosine receptor kinase
P-gp	p-glycoprotein
PK	pharmacokinetic
QTc	QT interval corrected for heart rate
QTcF	corrected QT interval by Fridericia's formula
SUSAR	suspected unexpected serious adverse reaction
TRK	tyrosine receptor kinase
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON ENTRECTINIB

Entrectinib (RXDX-101) is a potent inhibitor of the tyrosine receptor kinases (TRK)A (encoded by the gene neurotrophic tyrosine receptor kinase [NTRK]1), TRKB (encoded by the gene NTRK2), TRKC (encoded by the gene NTRK3), ROS1 (encoded by the gene ROS1), and anaplastic lymphoma kinase (ALK; encoded by the gene ALK), with median inhibitory concentrations for kinase inhibition in the low nanomolar range (1.7, 0.1, 0.1, 0.2, and 1.6 nM, respectively). Gene rearrangements in each of these genes have been observed in a variety of tumor types, including non-small cell lung cancer, colorectal carcinoma, salivary gland cancers, papillary thyroid cancer, melanoma, and sarcomas; overexpression of NTRK2 and ALK and point mutations of ALK have also been observed in neuroblastoma. Thus, a pan-TRK, ROS1, and ALK inhibitor such as entrectinib may have broad potential therapeutic utility. Approval is being sought for use of entrectinib in adults and children for oncology indications.

1.1.1 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.

1.1.2 Clinical Summary

The pharmacokinetics (PK) of entrectinib and its active metabolite (M5) and safety have been evaluated in healthy subjects following single doses of entrectinib in multiple clinical pharmacology studies.

1.1.2.1 Safety

Safety data are available from 323 healthy subjects from 10 dedicated single dose clinical pharmacology studies. Single doses of between 100 mg and 800 mg entrectinib were generally well tolerated when administered to healthy subjects. No serious adverse events (SAEs) were reported. The most commonly reported adverse events were gastrointestinal disorders or nervous system disorders including oral paresthesia, oral hypoesthesia, dysgeusia, constipation, diarrhea, and headache.

As of 8 March 2018, 394 patients have received entrectinib in the four ongoing clinical studies of entrectinib: 57 in study ALKA-372-001 (ALKA), 78 in study RXDX-101-01 (STARTRK-1), 239 in study RXDX-101-02 (STARTRK-2), and 20 in study RXDX-101-03 (STARTRK-NG). Entrectinib has been well tolerated. Across the 4 main entrectinib clinical studies in patients, the most common (⩾10% incidence) treatment-related adverse events 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 adverse events were reversible with dose modifications, and importantly, there was no evidence of cumulative toxicity, clinically significant hepatic toxicity, or QTc prolongation.

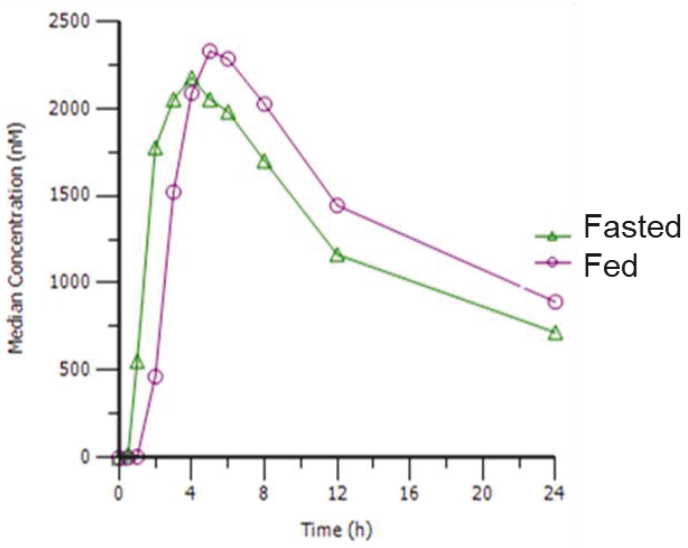
Across the four main clinical studies, 141 (36%) patients experienced a serious adverse event, regardless of causality. Thirty-one (8%) patients experienced a treatment-related serious adverse event. One fatal treatment-related serious adverse event has been reported (sudden death not otherwise specified). Most treatment-related serious adverse events resolved with dose interruption or permanent discontinuation of study drug.

1.1.2.2 Pharmacokinetics

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

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

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



Source: Study RXDX-101-154 Clinical Study Report Figure 14.3.

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

Entrectinib is primarily cleared by metabolism, with the majority of a dose being recovered as metabolites in feces and very little elimination of parent drug or metabolites via the kidney. Based on in vitro incubations, cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for the biotransformation of entrectinib, with lesser contributions from other CYPs and Phase II enzymes. The M5 metabolite (formed by demethylation) is a major circulating metabolite and is also pharmacologically active.

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

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

1.2 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.2.1 Study Rationale

An entrectinib capsule formulation is proposed for clinical use by adults and children who are able to swallow capsules. However, an age-appropriate formulation for younger children and adult patients with difficulty swallowing is also required. Two multi-particulate formulations (entrectinib film-coated mini-tablets [Ro 710-2122/F15 and Ro 710-2122/F16]) have been developed for administration with soft food, one with a functional coating for taste masking and one with a simple aesthetic coating. The principal aim of the first part of this study is to explore the in vivo pharmacokinetic performance of the two multi-particulate formulations in comparison with the F06 capsule formulation (entrectinib [RXDX-101] F06 hard capsule [Ro 710-2122/F04]) under typical clinical dosing conditions. These data will be used in order to support introduction of the multi-particulate formulation into an ongoing pediatric study (Study CO40778 [RXDX-101-03]).

Physiologically-based pharmacokinetic modelling indicates that particle size of the drug substance is not an important factor influencing entrectinib bioavailability, but there are limited observed data from clinical dosing to validate this conclusion. The principal aim of the second part of this study is therefore to explore the effect of drug substance particle size on entrectinib bioavailability by comparing entrectinib exposures from two F06 capsule formulations containing coarsely- and finely-milled drug substance with different particle size distributions.

1.2.2 Risk-Benefit Assessment

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

The risks of participation are primarily those associated with adverse reactions to the study drug, although there may also be some discomfort from collection of blood samples and other study procedures. The tolerability profile of entrectinib from administration of single doses up to 800 mg to healthy subjects has been characterized from previous clinical studies. There have been few adverse events following entrectinib dosing in previous clinical studies in healthy volunteers and no specific safety concerns have been identified about the use of 600 mg entrectinib in healthy volunteers in this study. 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 volunteers. All volunteers will be resident in the clinic and remain under medical supervision following study drug administration and will undergo a

standard battery of safety assessments. Hence, the risks to participants in this study are considered acceptable.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the bioavailability, palatability, safety and tolerability of entrectinib in healthy volunteers. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PHARMACOKINETIC OBJECTIVES (PRIMARY STUDY OBJECTIVE)

The primary objectives for this study are to explore the relative bioavailability of entrectinib from two multi-particulate formulations and the reference F06 capsule formulation under fed conditions (Part 1) and to explore the relative bioavailability of two entrectinib F06 capsule formulations under fasted conditions (Part 2) on the basis of the following endpoints:

- The geometric mean ratio and associated 90% confidence intervals (CI) of entrectinib and M5 area under the concentration–time curve from Time 0 to infinity ($AUC_{0\text{-}inf}$) and maximum concentration observed (C_{max}) parameters

2.2 SAFETY OBJECTIVE (SECONDARY STUDY OBJECTIVE)

The safety (secondary) objective for this study is to explore the safety and tolerability of a single oral dose of entrectinib in healthy volunteers on the basis of the following endpoints:

- Incidence and severity of adverse events,
- Incidence of abnormalities in laboratory safety tests, physical examinations, 12-lead ECGs and vital sign measurements

2.3 ADDITIONAL OBJECTIVE

An additional objective for this study is to explore the palatability (taste and acceptability) of coated and uncoated multi-particulate formulations on the basis of the following endpoint:

- Completion of palatability questionnaire

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a randomized, open-label, single-center, two part study in healthy volunteers to explore the performance of entrectinib multi-particulate formulations (Part 1) and the effect of drug substance particle size on entrectinib bioavailability (Part 2).

Part 1

Part 1 is a randomized, open-label, three-treatment, three-period, three-sequence, three-way crossover design. In each treatment period, subjects will receive a single 600 mg oral dose of entrectinib under fed conditions. Entrectinib will be administered as one of three possible formulations:

- Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F15) (test formulation 1; T1)
- Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F16) (test formulation 2; T2)
- F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 3 × 200 mg (Ro 710-2122/F04) (reference formulation; R)

Study treatments will be administered orally within 30 mins of consumption of a standardized light “pediatric” breakfast. The composition of the “pediatric” breakfast is as follows:

- 1 hard-boiled egg
- 2 slices of wholemeal bread
- Fruit (e.g., strawberry) jam

The test formulation, provided in a bottle, will be mixed with approximately one tablespoon (~15 mL) of yogurt, which will be swallowed without chewing with approximately 240 mL of water. In each period, palatability (taste and acceptability) of the test formulations will be assessed by completion of a questionnaire shortly after drug administration.

The reference formulation will be dosed as 3 x 200 mg capsules, swallowed whole with approximately 240 mL of water.

A total of 15 subjects will be enrolled. Subjects will be randomly assigned to one of three treatment sequences (i.e., T1T2R, T2RT1, RT1T2, [Table 1]) according to a pre-specified randomization scheme based on the order of study enrollment.

Blood samples for measurement of plasma concentrations of entrectinib and its active metabolite M5 will be collected before and at intervals up to 96 hours after study drug dosing in each period.

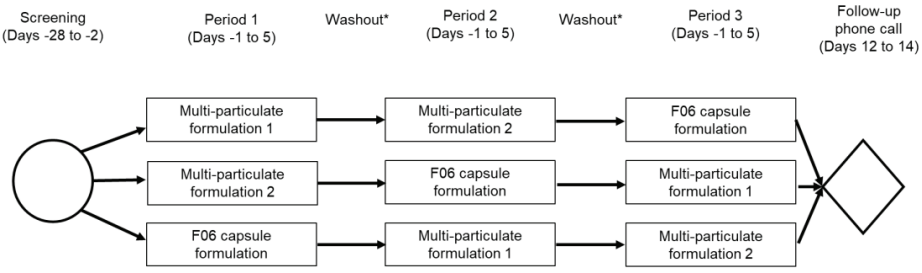
Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

The total duration of the study for each enrolled subject (screening through to end of study) will be up to 10 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug.
- Three treatment periods, separated by a treatment-free washout so that there are at least 14 days between each of the three study drug administrations.
- Safety follow-up phone call: 12 to 14 days after the last dose of study drug.

Subjects will be resident in the clinic from the morning of Day -1 until at least Day 3 in each treatment period. Subjects will also have ambulatory clinic visits at screening, and Days 4 and 5 in each treatment period.

Figure 2 Overview of Part 1 Design



*≥14 days
Multi-particulate formulation 1: Entrectinib film-coated tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F15) (test formulation 1; T1)
Multi-particulate formulation 2: Entrectinib film-coated tablets, 600 mg (240 × 2.5mg) (Ro 710-2122/F16) (test formulation 2; T2)
F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 200 mg (Ro 710-2122/F04) (reference formulation; R)

Part 2

Part 2 is a randomized, open-label, two-treatment, two-period, two-sequence, two-way crossover design. In each treatment period, subjects will receive a single 200 mg oral dose of entrectinib under fasted conditions. Entrectinib will be administered as one of two possible formulations:

- Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules (coarse active pharmaceutical ingredient [API]), 200 mg (test formulation; T)
- Entrectinib (RXDX-101) F06 hard capsules (fine API), 200 mg (Ro 710-2122/F04) (reference formulation; R)

The formulations will be dosed as 1 × 200 mg capsules, swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours).

A total of 16 subjects will be enrolled. Subjects will be randomly assigned to one of two treatment sequences (i.e., TR or RT) according to a pre-specified randomization scheme based on the order of study enrollment.

Blood samples for measurement of plasma concentrations of entrectinib and its active metabolite M5 will be collected before and at intervals up to 96 hours after study drug dosing in each period. Samples will be analyzed using a validated liquid chromatography

tandem mass spectrometry (LC-MS/MS) method, which will be described in the bioanalytical report.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

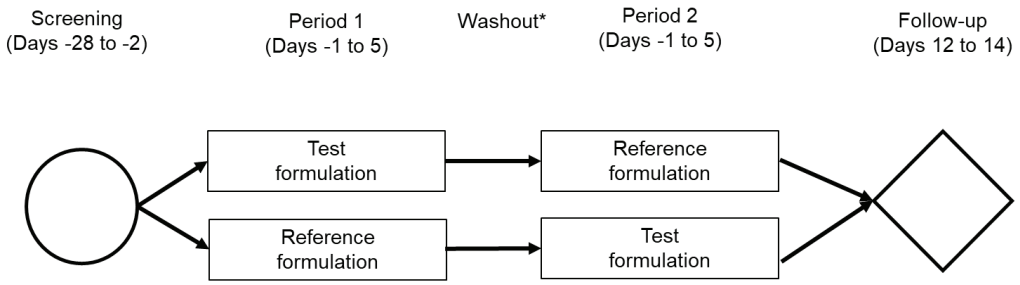
The total duration of the study for each enrolled subject (screening through to end of study) will be up to 8 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug.
- Two treatment periods, separated by a treatment-free washout so that there are at least 14 days between the two study drug administrations.
- Safety follow-up phone call: 12 to 14 days after the last dose of study drug.

Subjects will be resident in the clinic from the morning of Day -1 until at least Day 3 in each treatment period. Subjects will also have ambulatory clinic visits at screening, and Days 4 and 5 in each treatment period.

Figure 3 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 3 Overview of Part 2 Design



*≥14 days
Test formulation: Entrectinib F06 HPMC Capsules (unmilled/coarse active pharmaceutical ingredient), 200 mg
Reference formulation: Entrectinib (RXDX-101) F06 hard capsules, 200 mg (Ro 710-2122/F04)

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last subject, last visit occurs or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur up to 10 weeks after the last subject is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Subject Population

Healthy volunteers, instead of a patient population, have been chosen for this study as the US Food and Drug Administration (FDA, 2002) and European Medicines Agency (EMA, 2010) guidelines recommend that healthy subjects be included in trials assessing bioavailability and bioequivalence.

Based on the above considerations and target population, healthy female subjects of non-childbearing potential and healthy male subjects, aged ≥18 and ≤60 years are considered suitable for this study.

3.3.2 Rationale for Entrectinib Dose and Schedule

Part 1

The recommended dose of entrectinib for cancer patients is 600 mg once daily and 600 mg is therefore the dose chosen for Part 1. 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. Following advice from the US FDA on pharmacokinetic bridging between F1 and F06 formulations, the meal composition (i.e., size and fat content) has been selected in order to be representative of a typical breakfast for a pediatric population.

Part 2

The recommended dose of entrectinib for cancer patients is 600 mg once daily administered as 3 × 200-mg capsules, and so a single dose of the highest available capsule strength (200 mg) will be used in Part 2. 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.

3.3.3 Rationale for Pharmacokinetic Sampling Schedule

The pharmacokinetic sampling schedule has been selected on the basis of data from previous studies in which single doses of entrectinib have been administered to healthy volunteers and patients. The frequent sampling schedule that follows the single dose of entrectinib is designed to capture data at a sufficient number of time points to provide a detailed profile of the absorption, distribution, and elimination of this drug, including time to maximum observed concentration (t_{max}) and terminal half-life ($t_{1/2}$).

4. MATERIALS AND METHODS

4.1 SUBJECTS

Approximately 31 (15 in Part 1 and 16 in Part 2) healthy male and female volunteers will be enrolled at one investigative site located in the UK.

Up to 4 replacement subjects per study part are permitted in this study to ensure sufficient evaluable subjects; a maximum of 19 subjects in Part 1 and 20 subjects in Part 2 may be dosed in each study part.

Quotient Sciences (the Clinical Research Unit) must have a full medical history from each subject's general practitioner within the last 12 months, prior to enrollment in the study.

Before subjects are admitted to the clinic, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 3 months of the dosing date.

4.1.1 Inclusion Criteria

Subjects must meet the following criteria for study entry:

1. Able and willing to comply with the study restrictions and to give written informed consent before any study procedure.
2. Healthy male or female subjects of non-childbearing potential aged 18 to 60 years, inclusive, at time of signing Informed Consent Form (ICF)
3. A body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive, and weighing ≥50 kg, at screening.
4. 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 and 12-lead ECG assessment, and laboratory safety test results.
5. Agreement to comply with measures to prevent pregnancy and restrictions on egg and sperm donation.

- Female subjects of non-childbearing potential do not need to use any methods of contraception. Non-childbearing potential is defined as either post-menopausal (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 [e.g., 40 IU/L]), or surgically sterile (e.g., bilateral oophorectomy, bilateral salpingectomy, hysterectomy; note: tubal ligation is not considered an appropriate method of surgical sterilization) for at least 90 days.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom plus an approved method of effective contraception, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential, men must remain abstinent or use a condom plus an approved method of effective contraception (partner's use of combined [estrogen and progestogen-containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal]; partner's use of progestogen-only hormonal contraception [oral, injectable/implantable, intrauterine hormone]; partner's use of implantable intrauterine device; partner's use of female cap or diaphragm (double barrier); surgical sterilization [e.g., vasectomy or partner's bilateral tubal occlusion]) during the treatment period and for 104 days after the final dose of entrectinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local ICF.

Inclusion criterion 4 from the list above will be reassessed at admission/pre-dose in Period 1.

4.1.2 Exclusion Criteria

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

1. Women of childbearing potential, women who are pregnant or breastfeeding, or intending to become pregnant during the study or within 14 days after the final dose of entrectinib or have a pregnant partner.

   All women must have a negative serum pregnancy test at screening and a negative urine test at every admission.

2. A clinical significant medical 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.
3. 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.
4. A clinically significant abnormality in laboratory test results. In case of borderline or questionable results, tests may be repeated to confirm eligibility. Red blood cell count be lower than the lower limit of normal (RBC<LLN).
5. A clinically significant abnormal physical examination finding.
6. QTcF interval >450 msec or the presence of any other abnormal ECG finding, which, in the investigator's opinion, is clinically significant.
7. Confirmed by repeat (e.g., 2 consecutive measurements) systolic blood pressure greater than 140 or less than 90 mmHg, or diastolic blood pressure greater than

90 or less than 50 mmHg, or resting pulse rate greater than 90 or less than 40 beats per minute.

8. Clinically significant change in health status, as judged by the investigator, or any major illness within the four weeks before screening, or clinically significant acute infection or febrile illness within the 14 days before screening.
9. Any other ongoing condition or disease, or laboratory test result, that the investigator considers would render the participant unsuitable for the study, place the subject at undue risk, interfere with the ability of the subject to complete the study, or confound interpretation of study data.
10. Use of moderate or potent inhibitors or inducers of CYP P450 3A4 enzyme or P-gp transporter within the 28 days before screening, or use of other prohibited medications within the 7 days before screening.
11. Participation in any other clinical study involving an investigational medicinal product (IMP) or device within 3 months prior to planned dosing day (Day 1).
12. A positive test result for hepatitis B, hepatitis C (HCV), or human immunodeficiency virus (HIV).
13. Recent history of alcoholism, drug abuse, or addiction within the last year prior to screening, or a positive test for alcohol or drugs of abuse at screening or admission for each period.
14. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
15. Current smokers and those who have smoked within the last 12 months. A confirmed (by repeat) breath carbon monoxide reading of greater than 10 ppm at screening or admission for each period.
16. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
17. Known history of clinically significant hypersensitivity, or severe allergic reaction, to entrectinib or related compounds.
18. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active.
19. Donation or loss of over 400 mL of blood within the three months before screening.
20. Subjects who are study site employees, or immediate family members of a study site or Sponsor employee.
21. Subjects who have previously been enrolled in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2.
22. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening.
23. Failure to satisfy the investigator of fitness to participate for any other reason.

Exclusion criteria 1, 4, 6, 7, 9, 10, 15, 23 from the list above will be re-assessed at admission in Period 1.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study is open-label; no blinding is required.

4.2.1 Part 1

Using a computer-generated randomization schedule, subject numbers will be allocated to one of three treatment sequences (Table 1) in Part 1. The allocation will be balanced with 5 subjects assigned to each of the treatment sequences.

Table 1 Part 1 Treatment Sequences

Treatment Sequence	Period 1	Period 2	Period 3
T1T2R	Test formulation 1	Test formulation 2	Reference formulation
T2RT1	Test formulation 2	Reference formulation	Test formulation 1
RT1T2	Reference formulation	Test formulation 1	Test formulation 2

T1; Test formulation 1 = Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F15)
T2; Test formulation 2 = Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F16)
R; reference formulation = F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 600 mg (3 × 200 mg) (Ro 710-2122/F04)

Eligible subjects will be assigned a unique identification number on the morning of dosing in Period 1 according to the code [redacted] to [redacted] for Part 1, using the lowest number available. Replacement subjects will be allocated subject numbers [redacted] to [redacted], where the last 2 digits are the same as those of the original subject (e.g., if Subject [redacted] withdraws the replacement will have Subject Number [redacted]). Replacement subjects will be assigned to the same treatment sequence as the subject they replaced.

A treatment allocation list will be produced prior to dosing using the randomization schedule and will be retained in the Investigator Site File (ISF).

The original randomization schedule and proof of quality control procedures will be held by the Data Sciences department at Quotient Sciences until the study is archived, at which time the randomization materials will be retained in the ISF.

4.2.2 Part 2

Using a computer-generated randomization schedule, subject numbers will be allocated to a treatment sequence (Table 2) in a 1:1 ratio in Part 2. The allocation will be balanced with 8 subjects assigned to each treatment sequence.

Table 2 Part 2 Treatment Sequences

Treatment Sequence	Period 1	Period 2
TR	Test formulation	Reference formulation
RT	Reference formulation	Test formulation

T = Test formulation; Entrectinib F06 HPMC Capsules (coarse API), 200 mg

R = Reference formulation; Entrectinib (RXDX-101) F06 hard capsules, 200 mg (fine API) (Ro 710-2122/F04)

A treatment allocation list will be produced prior to dosing using the randomization schedule and will be retained in the ISF.

The original randomization schedule and proof of quality control procedures will be held by the Data Sciences department at Quotient Sciences until the study is archived, at which time the randomization materials will be retained in the ISF.

Eligible subjects will be assigned a unique identification number on the morning of dosing in Period 1 according to the code [redacted] to [redacted], using the lowest number available. Replacement subjects will be allocated subject numbers [redacted] to [redacted], where the last 2 digits are the same as those of the original subject (e.g., if Subject [redacted] withdraws the replacement will have Subject Number [redacted]).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is entrectinib.

4.3.1 Study Treatment Formulation, Packaging, and Handling

The reference treatment in Part 1 and Part 2, Entrectinib (RXDX-101) F06 hard capsules, 200 mg (fine API) (Ro 710-2122/F04) will be provided by the Sponsor as capsules for oral administration.

In Part 1, two multi-particulate formulations will be investigated. The formulations will be manufactured, packaged, and provided by the Sponsor as 2.5 mg film-coated mini-tablets for oral administration. The formulation will be supplied as a 600-mg dose in a bottle.

In Part 2, the test formulation, Entrectinib F06 HPMC Capsules 200 mg (coarse API) for oral administration will be manufactured by Quotient Sciences.

For information on the formulation and handling of entrectinib, see the Investigational Medicinal Product Dossier (IMPD).

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the dosing instructions for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.

Guidelines for treatment interruption or discontinuation for subjects who experience adverse events are provided in Section 4.6.

4.3.2.1 Entrectinib

In Part 1, each subject will be randomized to receive a single oral dose of 600 mg entrectinib in each of three treatment periods; the following formulations will be administered:

- Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F15) (test formulation 1; T1)
- Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 × 2.5 mg) (Ro 710-2122/F16) (test formulation 2; T2)
- F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 600 mg (3 × 200 mg) (Ro 710-2122/F04) (reference formulation; R)

The test formulation will be mixed with approximately one tablespoon (~15 mL) of yoghurt which will be swallowed without chewing with approximately 240 mL of water. The reference formulation will be dosed as 3 × 200 mg capsules, swallowed whole with approximately 240 mL of water. Additional water may be given with the IMP if required.

In Part 2, each subject will be randomized to receive a single oral dose of 200 mg entrectinib under fasted conditions in each of two treatment periods; the following formulations will be administered:

- Entrectinib F06 HPMC capsules (coarse API), 200 mg (test formulation; T)
- Entrectinib (RXDX-101) F06 hard capsules, 200 mg (Ro 710-2122/F04) (fine API) (reference formulation; R)

The formulations will be dosed as 1 × 200 mg capsules, swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours).

4.3.3 Investigational Medicinal Product Accountability

Quotient Sciences will manufacture the Entrectinib F06 HPMC capsules (coarse API). The Entrectinib (RXDX-101) F06 hard capsules (fine API) (Ro 710-2122/F04) and the

multi-particulate formulations (Entrectinib film-coated mini-tablets), will be provided by the Sponsor.

The study site will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from screening until the Follow-up phone call (12 to 14 days after the last dose of study drug). All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Paracetamol up to 4 g per day, medications to treat adverse events, vitamins and minerals, hormonal contraceptives and hormone replacement therapy are allowed throughout the study. 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.

If any medication is required, the name, strength, frequency of dosing and reason for its use will be documented in the subject's source data.

4.4.2 Prohibited Therapy

Subjects should not take any prescription or over-the-counter medication from 14 days prior to dosing until after the Follow-up phone call (12 to 14 days after the last dose of study drug) unless the investigator has given prior consent. The following categories of medication are specifically prohibited:

- Moderate or potent inhibitors or inducers of CYP3A enzymes or P-gp transporter.
- Gastric pH-modifying agents such as proton pump inhibitors, H2 receptor antagonists, and antacids.
- Psychoactive drugs or other drugs used for mental disorders. Examples include antidepressants, anti-psychotics, sedatives, and stimulants.

4.4.3 Prohibited Food

Subjects should refrain from eating food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to admission until 96 hours post-dose in each period.

Subjects should not consume grapefruit, Seville oranges or food and beverages containing caffeine/xanthines during the study (from 24 hours prior to admission in Period 1 until 96 hours post-dose in each period).

Subjects will be required to refrain from smoking from 12 months prior to screening until 96 hours after the final dose of IMP, and abstain from consumption of alcohol during the 24 hours prior to screening and from admission to the clinic in Period 1 until 96 hours post-dose in each period.

4.4.4 Additional Restrictions

No food or fluids other than water will be allowed for 8 hours prior to each study visit until after study laboratory samples are obtained (see Appendix 1).

In Part 1, subjects will be provided with a light snack on the evening of Day -1 and will fast from all food and drink (except water) until the following morning, when they will be provided with a pediatric breakfast. The breakfast should be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes after the start of breakfast. Subjects should be encouraged to eat their meal evenly over the 25-minute period. It is acknowledged that some subjects will take less time to eat, but dosing should still occur 30 minutes after the start of breakfast.

In Part 2, subjects will be provided with a light snack on the evening of Day -1 and no food will be allowed until 4 hours after dosing and water will be permitted freely until 1 hour prior to and after 1 hour following dosing of entrectinib.

Lunch will be provided at approximately 4 h post-dose, an evening meal at approximately 10 h post-dose and an evening snack at approximately 14 h post-dose.

On subsequent days, meals will be provided at appropriate times. Meals will be similar among cohorts.

Subjects will be allowed water up to 1 hour before the scheduled dosing time and will be provided with 240 mL of water at 1 hour post dose. Water will be allowed ad libitum after 1 h post-dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

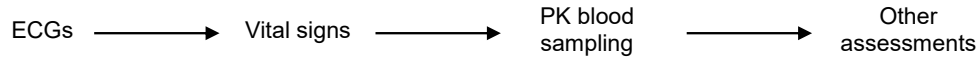
Subjects should refrain from strenuous exercise from 48 hours prior to admission to the clinic and during the period of confinement and will otherwise maintain their normal level of physical activity throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually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

4.5 STUDY ASSESSMENTS

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

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

Pharmaockinetic samples should take priority over other procedures scheduled at the same time point.



Electrocardiograms should be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, e.g., physical examinations etc., will be performed within the required time windows.

All safety assessments will be timed and performed relative to the start of dosing.

4.5.1 Informed Consent Forms and Screening Log

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

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask

questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an ICF. Until written consent has been obtained from the subject, no study specific procedure or investigation will be performed. If an amendment is made to the participant information sheet, participants will be re consented to the most current version of the ICF(s) where appropriate.

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

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the investigator.

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized/has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline (screening). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject since screening will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Height and weight will be recorded at screening.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline (Period 1 admission) should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed on Day -1, and as clinically indicated throughout the study. Changes from baseline abnormalities should be recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, and systolic and diastolic blood pressure while the subject is in a supine position for 5 minutes, and oral temperature.

The acceptable deviations from the nominal vital signs measurement time points are:

- The pre-dose vital signs measurements will be taken $\leqslant$ 2 hours before dosing.
- Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points.
- Discharge vital signs measurements will be taken ± 1 hour from the nominal time point.
- For return visits vital signs measurements will be taken ± 4 hours from the nominal return visit time point.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. The Day 1, pre-dose assessment in each period will be used as baseline.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to The Doctors Laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum): sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, and LDH
- Coagulation: INR, aPTT, and PT
- Virology: HIV, hepatitis B surface antigen (HBsAg), Anti-HCV at screening
- Follicle Stimulating Hormone (FSH; post-menopausal female subjects only)
- Pregnancy test

  All women will have a serum pregnancy test at screening and a urine pregnancy test on Day -1 of each period.
- Urinalysis (pH, specific gravity, glucose, protein, ketones, blood) and urine drug screen samples will be analyzed by dipstick at the clinic. The urine drug screen will test for the following: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic anti-depressants. Microscopic urinalysis examination, if required (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

Scheduled blood samples for safety laboratory tests will be taken following an 8-hour fast. The acceptable deviation from the nominal post-dose time point (96 hours) is ±2 hours.

Alcohol breath tests and carbon monoxide breath tests will be performed at the clinic. A positive alcohol breath test will exclude that subject from dosing during that admission. A carbon monoxide result of greater than 10 ppm will exclude the subject from the study.

Samples for the following laboratory tests will be sent to [redacted] for analysis:

- Plasma samples for pharmacokinetic analysis

For sampling procedures, storage conditions, and shipment instructions, see the Clinical Sample Processing Manual.

The total blood volume for each subject will not exceed 550 mL in a 4-week period. The first 0.5 mL of blood withdrawn via cannula will be discarded.

Residual pharmacokinetic samples will be destroyed no later than 5 years after the final Clinical Study Report 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 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.

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

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified time points, as outlined in the schedule of activities (see Appendix 1). The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken $\leqslant$ 2 hours before dosing
- Post-dose ECG measurements will be taken ± 15 minutes from the nominal post-dose time point
- Discharge ECG measurements will be taken ± 1 hour from the nominal time point.
- For return visits ECG measurements will be taken ± 4 hours from the nominal return visit time point.

ECGs acquired on different days should be as closely time-matched as feasible. ECG recordings may be obtained at unscheduled time points as indicated. The Day 1, pre-dose assessment in each period will be used as baseline.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal, whenever feasible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post dose time point the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a pharmacokinetic sample is not scheduled for that time point, an unscheduled pharmacokinetic sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the subject for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.7 Palatability Questionnaire

Subjects will be asked to complete the palatability questionnaire presented in Appendix 3 at the times indicated in the schedule of activities (Appendix 1).

4.6 TREATMENT, SUBJECT, STUDY, AND SITE DISCONTINUATION

4.6.1 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (i.e., a serious adverse event considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (i.e., severe non-serious adverse events considered at least possibly related to the IMP administration) in two subjects in the

same cohort of the study, independent of within or not within the same system organ class.

Relatedness will be determined by the investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

In addition, subjects must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the subject's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the subject
- Pregnancy
- Concurrent illness or requirement for prohibited medication
- Experiencing a serious or severe adverse event including but not limited to:
    - corrected QT interval by Fridericia's formula (QTcF) interval of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)
    - ALT concentration >3 × the upper limit of the reference range

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

For a subject who withdraws because of an IMP-related adverse event, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the study prematurely because of an IMP-related adverse event or termination of the study will be considered to have completed the study, and will not be replaced. Subjects who discontinue study treatment may be replaced at the discretion of the Sponsor and the investigator to ensure a minimum of 12 evaluable subjects in each study part.

A subject is considered evaluable if they have sufficient data to ensure the primary objective of the relevant study part is met.

4.6.2 Subject Discontinuation from the Study

Subjects have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a subject from the study at any time.

Reasons for subject discontinuation from the study may include, but are not limited to, the following:

- Subject withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Subject non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for subject discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a subject requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

For a subject who withdraws because of an IMP-related adverse event, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the study prematurely because of an IMP-related adverse event or termination of the study will be considered to have completed the study, and will not be replaced. Subjects who discontinue study treatment may be replaced at the discretion of the Sponsor and the investigator to ensure a minimum of 12 evaluable subjects in each study part.

A subject is considered evaluable if they have sufficient data to ensure the primary objective of the relevant study part is met.

4.6.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

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

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the Principal Investigator or Sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and Sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Entrectinib is not approved, and clinical development is ongoing. The safety plan for volunteers in this study is based on clinical experience with entrectinib in completed and ongoing studies. The anticipated important safety risks for entrectinib are described in the entrectinib IB.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.8 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs subject hospitalization (see Section 5.3.5.9)
- Results in persistent or significant disability/incapacity (i.e., the adverse event 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)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see

Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

- All grades of syncope
- Congestive heart failure ⩾Grade 2
- QT prolongation ⩾Grade 2
- Cognitive disturbances ⩾Grade 3
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until the Follow-up phone call (12 to 14 days after the final dose of study drug).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 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]

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 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 adverse event 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 4):

- 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 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of 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.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting 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).

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between subject evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with

cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

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

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ 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 Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

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

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.9 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The subject has not experienced an adverse event

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

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

5.3.5.10 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 adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For entrectinib, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with entrectinib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF 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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor contact information:

Medical Monitors:	[redacted] (Primary)
	[redacted] (Secondary)
Telephone Nos.:	[redacted] (Western Europe)
	[redacted] (Western Europe)
	[redacted] (Western Europe)

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

5.4.2.1 Events that Occur Prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the Follow-up phone call (12 to 14 days after the final dose of study drug). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur >14 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Subjects

Female subjects will be instructed to immediately inform the investigator if they become pregnant during the study or within 44 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event 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 serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Subjects

Male subjects will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 104 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male 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.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Sections 5.4.2 and 5.6).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 and 5.6). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female subject exposed to study drug or the female partner of a male subject exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 and 5.6).

5.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 to 14 days after the final dose of study drug [the Follow-up phone call]), if the event is believed to be related to prior study drug treatment. These events should be reported

through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

Suspected unexpected serious adverse reactions (SUSARs) are adverse events that are believed to be related to an IMP and are both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and serious. SUSARs are subject to expedited reporting to the MHRA, EMA, and EC.

It is the responsibility of the Sponsor to determine whether a reported serious adverse event fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

To determine reporting requirements for single adverse event 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.

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

<u>Fatal or life-threatening SUSARs</u>

It is the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. This responsibility may be delegated to the pharmacovigilance provider.

The Sponsor is required to notify the EC of other SUSARs as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the Sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- Serious adverse events that occur after the subject has completed the clinical study where the Sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects, such as:
    - a serious adverse event which could be associated with the study procedures and which could modify the conduct of the study
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
    - any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objective of this study is to explore the relative bioavailability of entrectinib from two multi-particulate formulations (film-coated mini-tablets), and from two entrectinib capsule formulations. A linear mixed model will be applied to analyze the log-transformed primary pharmacokinetic parameters, $AUC_{0\text{-}inf}$ and C_{max} and descriptive statistical summaries will be provided (e.g., mean, median, standard deviation, minimum, maximum and n). Additional statistics will be provided for PK-related data including coefficient of variation, geometric mean, geometric coefficient of variation (CV%), and geometric n (i.e., the number of subjects with an observation that were included in the natural logarithmic transformation). Subjects will be grouped according to treatment actually received and subjects with sufficient data to enable estimation of key parameters will be included in the analysis.

6.1 DETERMINATION OF SAMPLE SIZE

It is planned that total of 15 subjects will be enrolled in Part 1 and 16 subjects will be enrolled in Part 2 of the study to achieve 12 evaluable subjects in each part. Subjects who withdraw from the study may be replaced at the discretion of the Sponsor and investigator to ensure that in each part 12 subjects complete the study and have evaluable pharmacokinetic data from all treatment periods.

The sample size has been chosen to ensure that the ratios of the geometric means for the pharmacokinetic parameters of entrectinib can be estimated with sufficient precision. In a previous study (Study RXDX-101-15) the within-subject coefficients of variation for $AUC_{0\text{-}inf}$ and C_{max} following administration of a single dose of entrectinib were estimated to be 20% and 16%, respectively. Based on a coefficient of variation 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 two entrectinib pharmacokinetic parameters ($AUC_{0\text{-}inf}$ and C_{max}).

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, height, weight, and BMI) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment for each study part separately.

Demographic and baseline characteristics will be recorded at screening.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all subjects who received at least one dose of study drug, with subjects grouped according to treatment received.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded as mild, moderate, or severe (Section 5.3.3).

Summary tables will be presented by treatment. If a subject has more than one episode of a particular event, only one episode (the most severe or the strongest causal relationship to study drug) will be counted. A subject with more than one different adverse event within a particular body system will only be counted once in the total number of subjects experiencing adverse events for the body system. Similarly, a

subject who experiences an adverse event in more than one body system will only be counted once in the total number of subjects experiencing adverse events in all body systems.

6.5 PHARMACOKINETIC ANALYSES

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

The plasma pharmacokinetics of entrectinib and M5 will be summarized by estimating the following parameters (as appropriate for data collected):

- t_{max}: the time to maximum plasma concentration
- C_{max}: the maximum observed plasma concentration
- AUC_{0-t}: the 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-inf}: area under the concentration-time curve extrapolated to infinity
- AUC%extrap: the percentage of AUC_{0-inf} accounted for by extrapolation of the apparent elimination slope from Ct to infinity
- λ_Z: apparent terminal elimination rate constant
- $t_{1/2}$: apparent terminal elimination half-life (whenever possible)
- V_z/F: apparent volume of distribution base on area for oral dose
- CL/F: apparent clearance following oral dosing
- MPR: metabolite to parent ratio of AUC_{0-inf}, where appropriate
- Frel: relative bioavailability for AUC_{0-inf}, where appropriate

The primary parameters for analysis will be C_{max} and AUC_{0-inf} of entrectinib and M5. A linear mixed model will be applied to analyze the log-transformed primary pharmacokinetic parameters. The model assumes fixed effects for treatment, period, and sequence, and a random effect for subject nested 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.

6.6 OTHER ANALYSES

Palatability questionnaire data will be listed and summarized using descriptive statistics.

6.7 INTERIM ANALYSES

No interim analyses are planned; Part 1 and Part 2 will be analyzed separately.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. The sites will be responsible for data capture into the EDC system. In the event of discrepant data, the CRO will request data clarification from the site, which the site will resolve electronically in the EDC system.

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

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of an EDC system. The site will receive training for appropriate eCRF completion. eCRFs will be submitted electronically and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated

instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

Subjects must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the informed

consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the subject, and relevant supporting information must be submitted to the EC by the Principal Investigator and reviewed and approved by the EC before the study is initiated. In addition, any subject recruitment materials must be approved by the EC.

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

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

8.4 CONFIDENTIALITY

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

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject, 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 exploratory biomarker analyses, data derived from these analyses 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 (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech.

The study will be conducted at a single-center: Quotient Sciences, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK.

Central facilities will be used for certain study assessments throughout the study (e.g., clinical laboratory tests and pharmacokinetic analyses) as specified in Section 4.5.

Monitoring will be performed by [redacted], United Kingdom.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Quotient Sciences. Substantial protocol amendments will be submitted to the EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

EMA – Guidance on the investigation of bioequivalence. 20 January 2010.

Entrectinib Investigator Brochure Version 8 April 2018; Addendum 2, November 2018.

FDA Guidance: Food effect, bioavailability and fed bioequivalence studies. 2002.

Appendix 1
Schedule of Activities

Appendix 1: Schedule of Activities

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Informed consent	x																		
Inclusion/exclusion criteria	x	x																	
Medical history	x																		
Physical examination[d]	x	x																	
Height and weight	x																		
12-lead safety ECG	x		x				x				x					x		x	
Vital signs[g]	x		x				x				x					x		x	
Laboratory safety tests[b]	x	x																x	
Urine drug screen	x	x																	
Alcohol breath test	x	x																	
Carbon monoxide breath test	x	x																	
HIV/hepatitis screen	x																		
Pregnancy test[c]	x	x																x	
AE monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x																

Appendix 1: Schedule of Activities

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Study drug administration				x															
Blood sampling for entrectinib and M5 pharmacokinetics[e]			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Palatability questionnaire					x[f]														
Confinement in the clinic		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Ambulatory clinic visits	x																x	x	

a: Telephone call

b: Hematology, serum biochemistry, coagulation, and urinalysis; FSH at screening. Samples should be obtained following a fast of at least 8 hours.

c: Serum pregnancy test for all women at screening; urine test on Day -1 of each period.

d: A complete physical examination at screening, a limited, symptom-directed physical examination on Day -1 of each treatment period. Symptom-driven physical examinations may be performed at other times at the investigator's discretion.

e: Permissible time windows for pharmacokinetic sampling and other assessments are: pre-dose, any convenient time prior to dosing; 0.5 to 1 hour, ±0.1 hour; 2 to 8 hours, ±0.25 hour, 12 to 36 hours, ±1 hour, 48 to 96 hours, ±4 hour

f: Multi-particulate formulation treatment periods in Part 1 only

g: Pulse rate, systolic and diastolic blood pressure and oral temperature.

Appendix 2
Schedule of Pharmacokinetic Samples

Visit[a]	Time point[a]	Sample Type
Day 1	Predose -0.5 h	Entrectinib and M5 PK (plasma)
	0.5 h post-dose	Entrectinib and M5 PK (plasma)
	1.0	Entrectinib and M5 PK (plasma)
	2.0	Entrectinib and M5 PK (plasma)
	3.0	Entrectinib and M5 PK (plasma)
	4.0	Entrectinib and M5 PK (plasma)
	5.0	Entrectinib and M5 PK (plasma)
	6.0	Entrectinib and M5 PK (plasma)
	8.0	Entrectinib and M5 PK (plasma)
	12.0	Entrectinib and M5 PK (plasma)
Day 2	24.0	Entrectinib and M5 PK (plasma)
	36.0	Entrectinib and M5 PK (plasma)
Day 3	48.0	Entrectinib and M5 PK (plasma)
Day 4	72.0	Entrectinib and M5 PK (plasma)
Day 5	96.0	Entrectinib and M5 PK (plasma)

PK = pharmacokinetic.

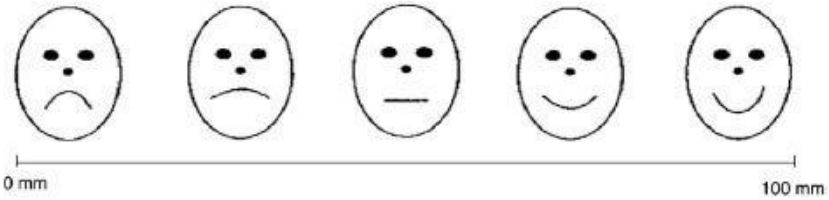
[a] Visit and time points are applicable to all periods in both study parts.

Permissible time windows are: -0.5 hour, any convenient time prior to dosing; 0.5 to 1 hours, ±0.1 hours; 2 to 8 hours, ±0.25 hour; 12 to 36 hours, ±1 hours; 48 to 96 hours, ±4 hours

Appendix 3
Palatability Questionnaire

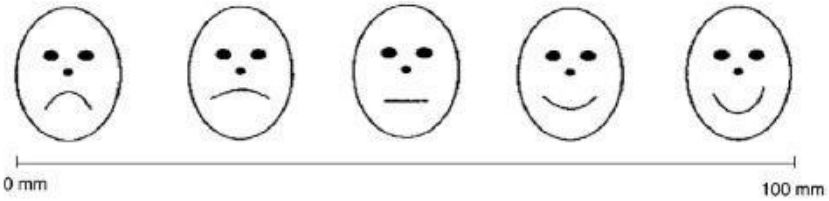
To be completed immediately after taking the multi-particulate with yoghurt. Please indicate your answer to the following questions by making a **mark on the line**.

Overall, how did you like taking the multi-particulate in yoghurt?



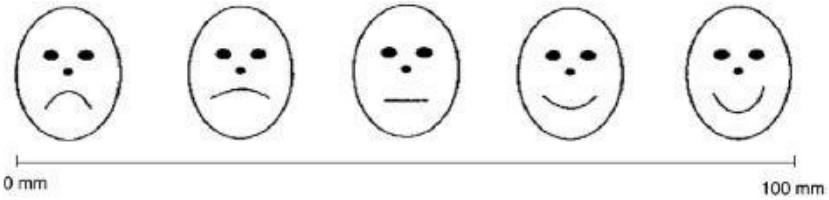
I did not like it I liked it very much

How gritty/lumpy did the multi-particulate in yoghurt feel in your mouth (gritty/lumpy means you can feel “bits” in the sample)?



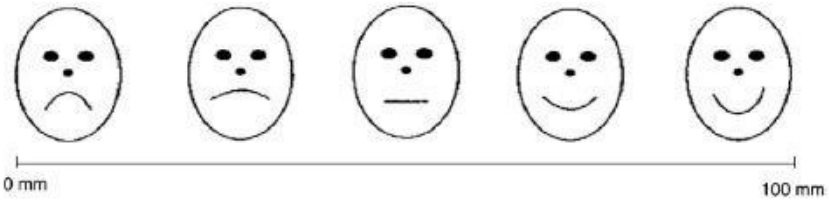
Very gritty/lumpy Very smooth

How did you like the feeling of the multi-particulate in yoghurt in your mouth?



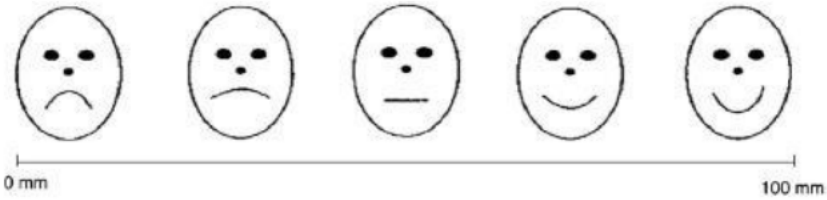
I did not like it I liked it very much

How did you like the taste/flavour of the multi-particulate in yoghurt?



I did not like it I liked it very much

How did you like the feeling when swallowing the multi-particulate in yoghurt?



I did not like it I liked it very much

How easy was it to swallow the multi-particulate in yoghurt?

Very difficult Very easy

Initial taste or flavour

Please describe the intensity of any initial taste or flavour of the multi-particulate in yoghurt

No taste | Slight taste | Moderate taste | Intense taste | Very intense taste

If there was an initial taste, how would you describe it?

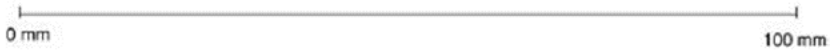
	Not at all	Mildly	Extremely
Bitter	0 mm		100 mm
Salty	0 mm		100 mm
Sweet	0 mm		100 mm
Sour	0 mm		100 mm
Metallic	0 mm		100 mm

If you experienced another taste or flavour, please describe

.....

Aftertaste

Please describe the intensity of any taste or flavour after swallowing the multi-particulate in yoghurt



No taste | Slight taste | Moderate taste | Intense taste | Very intense taste

If there was an aftertaste or flavour, how would you describe it?

	Not at all	Mildly	Extremely
Bitter	0 mm		100 mm
Salty	0 mm		100 mm
Sweet	0 mm		100 mm
Sour	0 mm		100 mm
Metallic	0 mm		100 mm

If you experienced another taste or flavour, please describe

.....

Could you still feel any of the bits/lumps in your mouth after swallowing

Yes ☐ No ☐

Would you take this medicine again?

Yes ☐ No ☐

Other comments

Do you have any other comments about the multi-particulate in yoghurt? If so, please describe in your own words

.....

.....

AMENDMENT SUMMARY DOCUMENT
PROTOCOL NON-SUBSTANTIAL AMENDMENT

EudraCT Number:	2019-000783-15
Sponsor Study No.	GP41341
Quotient Sciences Study No.:	QSC201525
Protocol Title:	A RANDOMIZED, OPEN-LABEL, TWO PART STUDY TO EXPLORE THE PERFORMANCE OF ENTRECTINIB PROTOTYPE MINI-TABLET FORMULATIONS AND THE EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON ENTRECTINIB BIOAVAILABILITY IN HEALTHY VOLUNTEERS
Document Version Amended	Version 1.0, 02 APR 2019
Included in Non-Substantial Amendment	NSA02, 04 JUL 2019

Reviewed and Approved by:

[redacted] 09 JUL 2019 Date

Principal Investigator [redacted] 11 Jul 2019 Date

[redacted] 10 July 2019 Date

On behalf of [redacted] **ech, Inc.** 05-Jul-2019 Date

Information related to the amendment:

MHRA	☐	Approval required
	☑	Approval not required
Ethics Committee	☐	Approval required
	☑	Approval not required
Informed Consent	☐	Modified
	☑	Unchanged
Master Source	☑	Modified
	☐	Unchanged
Risk Management Plan	☐	Modified
	☑	Unchanged
Other Study Documents	☐	Modified (specify)
	☑	Unchanged

Reason for Change:

The purpose of this protocol amendment is to clarify a typographical error in the current version of the Clinical Study Protocol (Version 1.0, dated 02 Apr 2019). The Schedule of Activities indicates that a pregnancy test should be performed at the Day 5 return visit; however, the footnote and text in Section 4.5.5 of the protocol do not reference a pregnancy test on Day 5.

Genentech have confirmed that this is a typographical error and that pregnancy tests are not required on Day 5. The Schedule of Activities will be updated to remove the pregnancy test on Day 5.

A minor formatting update will also be made to the footnotes of the Schedule of Activities.

As these changes do not significantly affect the scientific value of the trial, or the safety or physical or mental integrity of the subjects of the trial, this amendment is considered to be non-substantial.

Section to be Changed:

Appendix 1: Schedule of Activities

Revised Schedule of Activities:

From: Appendix 1: Schedule of Activities

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Informed consent	x																		
Inclusion/exclusion criteria	x	x																	
Medical history	x																		
Physical examination[d]	x	x																	
Height and weight	x																		
12-lead safety ECG	x		x				x				x					x		x	
Vital signs[g]	x		x				x				x					x		x	
Laboratory safety tests[b]	x	x																x	
Urine drug screen	x	x																	
Alcohol breath test	x	x																	
Carbon monoxide breath test	x	x																	
HIV/hepatitis screen	x																		
Pregnancy test[c]	x	x																x	
AE monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x																

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Study drug administration				x															
Blood sampling for entrectinib and M5 pharmacokinetics[e]			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Palatability questionnaire					x[f]														
Confinement in the clinic		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Ambulatory clinic visits	x																x	x	

a: Telephone call

b: Hematology, serum biochemistry, coagulation, and urinalysis; FSH at screening. Samples should be obtained following a fast of at least 8 hours.

c: Serum pregnancy test for all women at screening; urine test on Day -1 of each period.

d: A complete physical examination at screening, a limited, symptom-directed physical examination on Day -1 of each treatment period. Symptom-driven physical examinations may be performed at other times at the investigator's discretion.

e: Permissible time windows for pharmacokinetic sampling and other assessments are: pre-dose, any convenient time prior to dosing; 0.5 to 1 hour, ±0.1 hour; 2 to 8 hours, ±0.25 hour, 12 to 36 hours, ±1 hour, 48 to 96 hours, ±4 hour

f: Multi-particulate formulation treatment periods in Part 1 only

g: Pulse rate, systolic and diastolic blood pressure and oral temperature.

To: Appendix 1: Schedule of Activities

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Informed consent	x																		
Inclusion/exclusion criteria	x	x																	
Medical history	x																		
Physical examination[d]	x	x																	
Height and weight	x																		
12-lead safety ECG	x		x				x				x					x		x	
Vital signs[g]	x		x				x				x					x		x	
Laboratory safety tests[b]	x	x																x	
Urine drug screen	x	x																	
Alcohol breath test	x	x																	
Carbon monoxide breath test	x	x																	
HIV/hepatitis screen	x																		
Pregnancy test[c]	x	x																*	
AE monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization			x																

Study Procedures	Screen.	Study days in each period																	Follow -up[a]
Days	-28 to -2	-1	1											2		3	4	5	13 to 15
Time relative to study drug dosing			Pre-dose	0	0.5	1	2	3	4	5	6	8	12	24	36	48	72	96	
Study drug administration				x															
Blood sampling for entrectinib and M5 pharmacokinetics[e]			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Palatability questionnaire					x[f]														
Confinement in the clinic		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Ambulatory clinic visits	x																x	x	

a: Telephone call

b: Hematology, serum biochemistry, coagulation, and urinalysis; FSH at screening. Samples should be obtained following a fast of at least 8 hours.

c: Serum pregnancy test for all women at screening; urine test on Day -1 of each period.

d: A complete physical examination at screening, a limited, symptom-directed physical examination on Day -1 of each treatment period. Symptom-driven physical examinations may be performed at other times at the investigator's discretion.

e: Permissible time windows for pharmacokinetic sampling and other assessments are: pre-dose, any convenient time prior to dosing; 0.5 to 1 hour, ±0.1 hour; 2 to 8 hours, ±0.25 hour, 12 to 36 hours, ±1 hour, 48 to 96 hours, ±4 hour

f: Multi-particulate formulation treatment periods in Part 1 only

g: Pulse rate, systolic and diastolic blood pressure and oral temperature.