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

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REPORTING AND ANALYSIS PLAN

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

Quotient Sciences Study Number: QSC201525
Sponsor Study Number: GP41341

Sponsor:

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Principal Investiga[redacted]iences) [redacted] 01 Jul 2019 09:31:022-0700 — Date

[redacted] (Genentech, Inc)

1 Table of Contents

2 List of Abbreviations

ADaM	analysis data model
AE	adverse event
API	active pharmaceutical ingredient
ATC	anatomical therapeutic chemical
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
CV%	coefficient of variation
D	'substantial' decrease from baseline for vital signs parameters
DP	decimal place
ECG	electrocardiogram
FreI	relative bioavailability
FSH	follicle stimulating hormone
GMR	geometric mean ratio
h	hour
H	flag used for value that is above normal reference range
HPMC	hydroxypropyl methylcellulose
HR	heart rate
I	'substantial' increase from baseline for vital signs parameters increase in QTcF interval from baseline
ICF	informed consent form

ICH	International Conference on Harmonisation
IMP	investigational medicinal product
ISF	Investigator Site File
L	flag used for value that is below normal reference range
LOD	limit of detection
LLOQ	lower limit of quantification
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MPR	metabolite to parent ratio
n	number of subjects with an observation
N	number of subjects in the dataset
NA	not applicable
NC	not calculated
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NR	no result
NS	no sample
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
QC	quality control
RAP	reporting and analysis plan
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SF	significant figure
SI	substantial increase in QTcF interval from baseline

SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse events
TFLs	tables, figures and listings
WHO	World Health Organization

3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC201525 (GP41341):

- criteria to be used for the definition of the analysis populations relating to safety and pharmacokinetic (PK) data
- handling of missing data
- proposed tabular, graphical and listing presentation of demographic, dosing, PK, palatability and safety data
- methods for PK parameter estimation and formal statistical analysis

This document has been compiled according to the Quotient standard operating procedure (SOP) "Production of Reporting and Analysis Plans" and has been written based on information contained in the final study protocol (v1.0) dated 02 Apr 2019.

3.1 Responsibilities

The Data Sciences Department at Quotient will be responsible for the production of the following items using Quotient SOPs: CDISC study data tabulation model (SDTM) and analysis data model (ADaM) datasets; PK parameter estimation and output and safety and palatability output; including all summary tables, figures and data listings, and formal statistical analysis; and the clinical study report (CSR).

Quotient will provide three sets of tables, data listings and figures during the study:

- after database close but prior to database lock for Genentech, Inc. (Genentech) review (safety and palatability tables and listings only)
- post database lock TFLs (draft) for Genentech review and
- post-review TFLs (final) for inclusion into the CSR.

Quotient will be responsible for the quality control (QC) of all deliverables prior to the client review (Section 14.2).

3.2 Definitions

3.2.1 Subjects Definitions

During the clinical phase of the study, a subject is considered evaluable if they have sufficient data to ensure the primary objective of the relevant study part is met. This will be monitored during the clinical phase to identify any requirement for replacement subjects. This definition will not be used during the reporting phase, including the identification of analysis populations and datasets.

A randomized subject is defined as a subject who signed the informed consent, qualified per the inclusion/exclusion criteria and was randomized to a treatment sequence (i.e., was allocated a subject number).

3.2.2 Definition of Treatments

Throughout the reporting of the study, treatments will be reported as detailed in Table 1.

Table 1 Study Treatments

Study Part	Treatment	Planned Investigational Drug	Label to be used for reporting purposes
Part 1	Test formulation 1 (T1)	Multi-particulate formulation 1: Entrectinib film-coated mini-tablets, 600 mg (240 x 2.5 mg) (Ro 710-2122/F15)	600 mg F15
	Test formulation 2 (T2)	Multi-particulate formulation 2: Entrectinib film-coated mini-tablets, 600 mg (240 x 2.5 mg) (Ro 710-2122/F16)	600 mg F16
	Reference formulation (R)	F06 capsule formulation: Entrectinib (RXDX-101) F06 hard capsules, 600 mg (3 x 200 mg) (Ro 710-2122/F04)	600 mg F06
Part 2	Test formulation (T)	Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules (coarse active pharmaceutical ingredient [API]), 200 mg)	200 mg F06 coarse
	Reference formulation (R)	Entrectinib (RXDX-101) F06 hard capsules, 200 mg (fine API) (Ro 710-2122/F04)	200 mg F06 fine

Sequences will be reported as "T1T2R", "T2RT1" and "RT1T2" in Part 1 and as "TR" and "RT" in Part 2.

3.2.3 Definition of Visits

For clinical data, visits will be referred to as Day throughout this document and for each study part will be referred to as Screening (Day -28 to -2), Day -1 (Admission) of each treatment period, Day 1 through to Day 5 of each treatment period and Follow-up (12 to 14 days post final dose). Time points within these days are detailed in the schedule of activities in Appendix 1 and in the schedule of PK samples in Appendix 2.

Baseline is defined as the last nominal measurement recorded prior to the first dose of investigational medicinal product (IMP) in each treatment period and each study part.

4 Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objectives

The primary objectives of the 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)
- to explore the relative bioavailability of two entrectinib F06 capsule formulations under fasted conditions (Part 2)

4.1.2 Secondary Objective

The secondary objective of the study is:

- to explore the safety and tolerability of a single oral dose of entrectinib in healthy volunteers (Parts 1 and 2)

4.1.3 Additional Objective

The additional objective of the study is:

- to explore the palatability (taste and acceptability) of coated and uncoated multi-particulate formulations (Part 1)

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint of the study is:

- the geometric mean ratio (GMR) 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 (Parts 1 and 2)

4.2.2 Secondary Endpoints

The secondary endpoints of the study are:

- incidence and severity of adverse events (AEs) (Parts 1 and 2)
- incidence of abnormalities in laboratory safety tests, physical examinations, 12-lead electrocardiograms (ECGs) and vital sign measurements (Parts 1 and 2)

4.2.3 Additional Endpoint

The additional endpoint of the study is:

- completion of palatability questionnaire (Appendix 3) (Part 1)

5 Study Design

5.1 Brief Description

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 min 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 (Appendix 3).

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

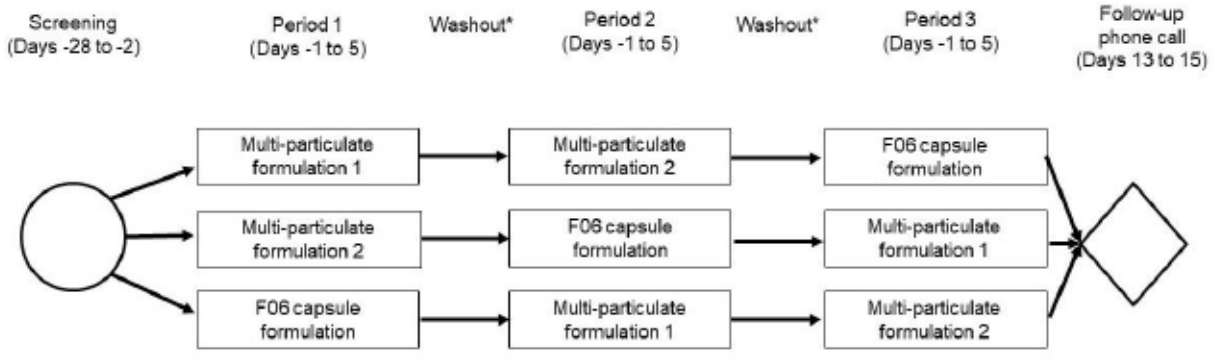
The total duration of the study for each enrolled subject (screening through to end of study) will be up to 10 weeks, divided as follows:

- 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 1 presents an overview of the study design.

Figure 1 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).

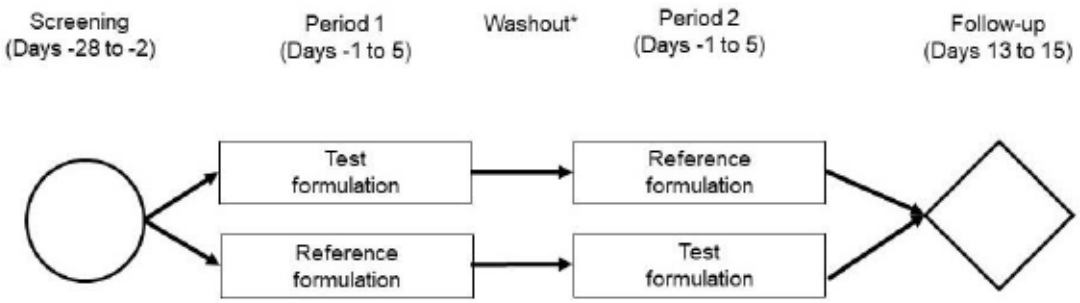
The total duration of the study for each enrolled subject (screening through to end of study) will be up to 8 weeks, divided as follows:

- 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 2 presents an overview of the study design.

Figure 2 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)

5.2 Study Sample Size

It is planned that a 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 principal investigator (PI) to ensure that in each part, 12 subjects complete the study and have evaluable PK data from all treatment periods.

The sample size has been chosen to ensure that the ratios of the geometric means for the PK parameters of entrectinib can be estimated with sufficient precision. In a previous study (Study RXDX-101-15), the within-subject coefficients of variation for $AUC_{0\text{-}inf}$ 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 PK parameters ($AUC_{0\text{-}inf}$ and C_{max}).

5.3 Randomization (Including Replacement Subjects)

Part 1

Using a computer-generated randomization schedule, subject numbers will be allocated to one of three treatment sequences (Table 2) in Part 1. The allocation will be balanced with 5 subjects assigned to each of the treatment sequences.

Table 2 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.

Part 2

Using a computer-generated randomization schedule, subject numbers will be allocated to a treatment sequence (Table 3) in a 1:1 ratio in Part 2. The allocation will be balanced with 8 subjects assigned to each treatment sequence.

Table 3 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]).

5.4 Blinding Issues

This is an open-label study and therefore blinding is not required.

6 Populations for Analysis

6.1 Safety Analysis Population

The safety analysis population will include all subjects who have received at least one dose of IMP.

The safety analysis population will be confirmed by Quotient with approval from Genentech after database lock and will be used for the analysis of demographic and baseline characteristics and all safety and palatability data.

6.2 Pharmacokinetic Population

The PK population will include all subjects who have received at least one dose of IMP and who satisfy the following criteria for at least one profile:

- no missing samples or invalid post-dose analytical results at critical time points e.g., around the C_{max}
- no relevant protocol deviations which may impact the study objectives with respect to the PK endpoints
- no relevant AEs such as vomiting which suggest that the whole dose was not available for absorption for a particular subject

The PK population will be confirmed by Quotient with approval from Genentech following derivation of all PK parameter estimates.

All randomized subjects will be used for the PK data listings and the PK population will be used for the provision of PK summary statistics, summary tables and figures.

If required, a PK analysis dataset or datasets may also be documented by Quotient with approval from Genentech at the same time as the PK population. The PK analysis dataset(s) will be a subset of the PK population. Individual subject profiles (i.e., periods) will be excluded from the PK analysis dataset where deemed appropriate such as if the subject in the study period affected did not meet the bullet point criteria above or other study emergent point related to PK analysis or interpretation.

The PK analysis dataset(s) may be used to generate additional summary tables and figures for the PK concentration and PK parameter data and may be used for the formal statistical analysis of the PK parameter data. Requirements for additional summary tables and figures will be documented at the same time as the PK population.

7 Subject Disposition, Demographics and Baseline Characteristics

No formal statistical testing will be performed on subject disposition or on demographic or baseline data. All data will be listed for all randomized subjects. Summaries of subject disposition and analysis populations will be based on all randomized subjects and summaries of all other data described in this section will be based on the safety population, unless otherwise stated.

Separate summary tables and listings will be produced for each study part.

7.1 Screening Failures

Data for subjects who have failed screening will be databased but will not be cleaned and therefore will not be included in the SDTM or ADaM datasets or any of the tables, figures or data listings.

7.2 Subject Disposition and Withdrawals

The number and percentage of subjects randomized, dosed, completed and discontinued will be presented by treatment sequence and overall. If any subjects discontinued from the study early, then the number of subjects for each reason for discontinuation will be presented by treatment sequence and overall. However, if none of the subjects discontinued from the study early, then the reasons for discontinuation will not be populated in the summary table.

Subject disposition and withdrawal data will be listed, including details of informed consent.

Protocol deviations and any violations of the inclusion/exclusion criteria will also be listed.

7.3 Analysis Populations

A summary table will be produced detailing the number and percentage of subjects in the safety and PK populations for each treatment sequence and overall. The reasons for exclusion from each population will also be included in the summary.

Details of subjects included and excluded in the different analysis populations will be listed.

7.4 Analysis Datasets

If applicable, a summary table will be produced detailing the number and percentage of subjects in each analysis dataset (i.e., PK) for each treatment. The table will be based on the relevant population the dataset is a subset of (i.e., the PK population). The reasons for exclusion from each dataset will also be included in the summary.

Details of subjects included and excluded in the different analysis datasets will be listed.

7.5 Demographic Characteristics and Lifestyle Details

Demographic data (date of birth, ethnicity, race, sex, height [cm], weight [kg] and body mass index [BMI; kg/m^2]) will be recorded at screening. Age will be calculated using the following formula:

$$\text{Age(years)} = \frac{\text{Date of first dose of IMP} - \text{date of birth}}{365.25}$$

and will be rounded down to the nearest year (using the SAS Software floor function). If any subjects are randomized but not dosed and had other assessments recorded, age will be calculated using the date of informed consent.

Summary statistics (mean, standard deviation [SD], median, minimum, maximum and number of subjects with an observation [n]) will be presented for age, height, weight and BMI at screening by treatment sequence and overall. The number and percentage of subjects will be presented by treatment sequence and overall for ethnicity, race and sex. The denominator for the percentage is all subjects in the safety analysis population. If any values are missing, a "missing" row will be presented on the table.

Lifestyle details (i.e., smoking history [does the subject smoke, use e-cigarettes or use nicotine replacement products?] and alcohol consumption) will be summarized by treatment sequence and overall as a categorical variable.

Demographic and lifestyle data will be listed.

7.6 Medical/Surgical History

Medical/surgical history will be recorded for each subject at the screening visit and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v22.0 or most recent version). All medical/surgical history data will be listed by subject, MedDRA system organ class (SOC) and preferred term (PT).

7.7 Prior and Concomitant Medication

Medications (product name) will be coded using the World Health Organization (WHO) Drug Dictionary Global Drug Reference: 2019 Q1 version (or more recent version), using the following Anatomical Therapeutic Chemical (ATC) classification codes:

- product name (Medication)
- preferred name
- drug code
- therapeutic subgroup (ATC 2nd level name and code)
- chemical subgroup (ATC 4th level name and code)

Prior medications are defined as medications that start and stop prior to the first dose of IMP. All other medications will be defined as concomitant medications including those that start prior to the first dose of IMP and continue thereafter. Any medications with an unknown start or stop date will be assumed to be concomitant medications unless a partial start or stop date indicates otherwise.

All medications, including coded terms, and the underlying indication for which the medication was given, will be listed. One combined data listing of prior and concomitant medications will be provided. All prior medications as defined above will be flagged with a "#" symbol. Within this flagged group, medications that started after screening and stopped before dosing of IMP will also be flagged using a "*" symbol.

7.8 Other Baseline Characteristics

All other baseline characteristics, as listed below, at screening and on Day -1 (unless otherwise stated) for each period (as appropriate) will be listed:

- urine drug screen
- alcohol and carbon monoxide breath test

- virology (screening only)
- serum pregnancy test (screening only) and urine pregnancy test (Day -1 of each period only) for female subjects
- follicle stimulating hormone (FSH) test for post-menopausal female subjects (screening only)

8 Efficacy

Not applicable for this Phase I study.

9 Pharmacokinetics

9.1 Pharmacokinetic Parameter Estimation

Where concentrations are provided as ng/mL by the bioanalytical provider for entrectinib and M5, these will be converted in SAS to nmol/L for the calculation of PK parameters, as below:

Entrectinib

Concentration (nmol/L) = concentration (ng/mL) / molecular weight entrectinib (560.65)

M5

Concentration (nmol/L) = concentration (ng/mL) / molecular weight M5 (546.62)

The PK parameters for entrectinib and M5 in plasma will be estimated where possible and appropriate for each subject and treatment by non-compartmental analysis methods using Phoenix WinNonlin software (v8.0 or a more recent version, Certara USA, Inc., USA).

9.1.1 Definition of Pharmacokinetic Parameters

Plasma PK parameter definitions are provided in Table 4.

Table 4 Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tmax	Time of maximum observed concentration	h	DP	2
Cmax	Maximum observed concentration	nmol/L	SF	3
AUC0-t	Area under the curve from 0 time to the last measurable concentration	nmol.h/L	SF	3
AUC0-inf	Area under the curve from 0 time extrapolated to infinity	nmol.h/L	SF	3
%AUCextrap	Percentage of AUC0-inf extrapolated beyond the last measurable concentration	%	DP	2
T1/2	Apparent elimination half-life	h	DP	2
Lambda-z	Slope of the apparent elimination phase	1/h	DP	4
CL/F	Apparent total body clearance calculated after a single extravascular administration where F (fraction of dose	mL/min	SF	3

Parameter	Definition	Unit	DP or SF	No. of DP/SF
	bioavailable) is unknown			
Vz/F	Apparent volume of distribution based on the terminal phase calculated after a single extravascular administration where F (fraction of dose absorbed) is unknown	L	SF	3
Frel AUC0-t	Relative bioavailability based on AUC0-t	%	DP	2
Frel AUC0-inf	Relative bioavailability based on AUC0-inf	%	DP	2
MPR AUC0-inf	Metabolite to parent ratio based on AUC0-inf	NA	DP	2
Lambda-z Lower*	Lower limit on time for values to be included in the calculation of Lambda-z	h	DP	2
Lambda-z Upper*	Upper limit on time for values to be included in the calculation of Lambda-z	h	DP	2

DP=decimal places
SF=significant figures
*=these values should be listed but omitted from the descriptive statistics
NA=not applicable

9.1.2 Rules for Pharmacokinetic Parameter Estimation

The imputation of non-numerical or negative values reported in the input dataset will be performed as follows:

- pre-dose sample times will be entered as zero
- values that are below the limit of quantification (BLQ) obtained prior to the C_{max} will be entered as zero
- values that are BLQ after the C_{max} will be treated as missing
- should partial AUCs be required then values that are BLQ after C_{max} may be imputed as zero for these partial areas if λ_z cannot be determined
- values that are quantifiable after at least 2 consecutive BLQ values after C_{max} will be treated as missing for the calculation of PK parameters
- values that are reported as "No Result" (NR) or "No Sample" (NS) etc. will be treated as missing

PK parameters will be estimated using standard Phoenix WinNonlin methods, details of which may be found in the documentation accompanying the WinNonlin software package. The following constraints will apply:

Parameter Estimation	Constraint
Sampling times	Actual
Trapezoidal method	Lin up log down etc.
Number of points used for λ_z	At least 3, not including C_{max}
Minimum requirements for AUC	At least 3 consecutive quantifiable concentrations
Dose	Nominal
Rounded dose level	0 Decimal Places

Where possible, the terminal elimination rate constant (λ_z) will be calculated for all subjects. The value of λ_z will be determined by the slope of the regression line of the natural log transformed concentrations vs time.

The choice of data points for determination of λ_z will be reviewed by the pharmacokineticist who may adjust the selection in order to provide a more appropriate fit. The choice of data points for determination of λ_z for each profile will be confirmed following a documented peer review.

Relative bioavailability (Frel) will be calculated as follows:

$$\text{Frel} = \left\{\frac{\text{AUC (test)}}{\text{AUC (reference)}}\right\} \times 100$$

Frel will be calculated using $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$. If for any reason the $AUC_{0\text{-}inf}$ is not calculable then an alternative AUC over a partial area may be used.

The following comparisons will be made:

Part 1
- 600 mg F15 vs 600 mg F06
- 600 mg F16 vs 600 mg F06

Part 2
- 200 mg F06 coarse vs 200 mg F06 fine

Metabolite to parent ratios (MPR) after a single dose administration will be calculated as follows using $AUC_{0\text{-}inf}$. If for any reason the $AUC_{0\text{-}inf}$ is not calculable then an alternative AUC such as $AUC_{0\text{-}t}$ or AUC over a partial area may be used:

$$\text{MPR} = \frac{\text{AUC (metabolite)}}{\text{AUC (parent)}}$$

9.2 Pharmacokinetic Parameter Reporting Specifications

The following parameters will be reported for each study part as applicable, according to the rounding specifications provided in Table 4:

Study Parts 1 and 2:
t_{max}, C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, %AUCextrap, $t_{1/2}$, λ_z, λ_z Lower, λ_z Upper, CL/F, V_z/F, MPR (based on $AUC_{0\text{-}inf}$) and Frel (based on $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$).

The following flags/footnotes may be applied to the PK parameters:

Flag	Footnote
a	Rsq of regression was <0.9
b	Period used for regression analysis was less than 2-fold the calculated half-life
c	Extrapolated portion of $AUC_{0\text{-}inf}$ >20%

d	Insufficient post-C_{max} data points for estimation of λ_z
e	Entire profile BLQ, no PK parameters could be calculated
f	Quantifiable pre-dose values were observed, however were considered less than 5% of C_{max}

In the event that the R-squared (Rsq) of regression was <0.9 ("a" flag) or the extrapolated portion of $AUC_{0\text{-}inf}$ >20% ("c" flag), then the parameter estimates derived using λ_z and/or $AUC_{0\text{-}inf}$ will be deemed unreliable and will be listed but excluded from the summary statistics and formal statistical analysis.

In the event that the period used for regression analysis was less than 2-fold the calculated half-life ("b" flag) parameter estimates derived using λ_z will be listed, flagged and included in summary statistics and formal statistical analysis.

In the event that quantifiable pre-dose values less than 5% of C_{max} were observed ("f" flag), all parameter estimates for the profiles affected will be listed, flagged and included in summary statistics and formal statistical analysis.

In the event that quantifiable pre-dose concentrations greater than 5% of C_{max} are observed, requirements for further action will be agreed with Genentech and documented at the same time as the PK population.

Additional flags may be applied based on emerging data.

9.2.1 Bioanalytical and Pharmacokinetic Summary Tables

Summary statistics (i.e., mean, SD, coefficient of variation [CV%], median, minimum, maximum and n) will be calculated at each time point for plasma concentration data by treatment.

Imputation of non-numerical values reported in the plasma concentration data (i.e., values that are BLQ) will be entered as zero for the determination of summary statistics.

Summary statistics (i.e., mean, median, SD, CV%, minimum, maximum, n) will be calculated for all plasma PK parameters. Geometric mean, geometric SD, geometric CV% and geometric n will be presented for all PK parameters except t_{max}.

Separate summary tables will be produced for each study part.

9.2.2 Bioanalytical and Pharmacokinetic Figures

Arithmetic mean plasma concentration vs time curves will be produced on a linear/linear scale and error bars for ± arithmetic SD will be included on the plots.

The arithmetic mean plots will be produced for the following:

- all treatments on the same plot, with separate plots for entrectinib and its metabolite M5
- entrectinib and its metabolite M5 on the same plots, with separate plots for each treatment

Each treatment will be represented on these plots with a different symbol and a legend will be included on the plots to define the symbols used.

Spaghetti plots of individual plasma concentrations against actual sampling times after dosing for each treatment will be produced on both a linear/linear and log10/linear scale. Each subject's concentration profile will be represented on these plots with a different letter or symbol and a legend will be included on the plots to define the letters/symbols used. These data will be plotted for entrectinib and its metabolite M5 on different plots.

Plots of individual plasma concentrations against actual sampling times after dosing for each analyte will also be produced separately for each individual subject with all treatments for that subject overlaid on the same plot. Plots of individual plasma concentrations against actual sampling times after dosing for each treatment will also be produced separately for each individual subject with both analytes for that subject overlaid on the same plot. These plots will be produced on both a linear/linear and log10/linear scale.

For all plots on a linear/linear scale, concentration values reported as BLQ will be set to zero. For all plots on a log 10/linear scale, concentration values reported as BLQ will be set to missing.

Separate figures will be produced for each study part.

9.2.3 Bioanalytical and Pharmacokinetic Listings

The sample collection data (e.g., collection times) for PK samples will be listed. In addition, all plasma concentration data and PK parameters will be listed on a per subject basis. Any flags used will be listed with the appropriate definition.

Separate listings will be produced for each study part.

9.2.4 Statistical Analysis of Pharmacokinetic Parameters

Formal statistical analysis will be performed on the entrectinib and M5 PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} to assess the relative bioavailability between test and reference formulations. The PK parameters will undergo a natural logarithmic transformation and will be analysed using mixed effect modelling techniques. The model will include terms for treatment, period and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect.

The following pairwise treatment comparisons *(test versus reference)* are of interest in Part 1:

- 600 mg F15 vs 600 mg F06
- 600 mg F16 vs 600 mg F06

The following pairwise treatment comparison *(test versus reference)* is of interest in Part 2:

- 200 mg F06 coarse vs 200 mg F06 fine

If the number of subjects with reliable estimates of AUC_{0-inf} for any period falls below the planned number of evaluable subjects, then consideration will be given as to whether formal statistical analysis will be performed.

The adjusted means including differences from the pairwise comparisons listed above and their associated 90% CIs obtained from the model will be back transformed on the log scale to obtain adjusted GMRs and 90% CIs of the ratios, where the ratio, defined as

test/reference, will be presented. In addition, these will be presented together with the p-value from the pairwise treatment comparison and the intra-subject variability values (denoted as CVw in the results table), where the null hypothesis is defined as no treatment difference.

The intra-subject variability values will be calculated for all treatments combined and are obtained from the residual term from the SAS Software output. These values are calculated as follows:

$$\mathrm{CVw} = 100 \times [\exp(\text{Mean Square Error}) - 1]^{1/2}$$

The ANOVA table from the model with F-statistic and p-value for the fixed effects will be presented on a separate page.

The statistical analysis will be performed using actual treatment received and planned sequence as detailed on the randomization schedule. The model will be fitted using the SAS Software procedure PROC MIXED, the method will be specified as Restricted Maximum Likelihood and the denominator degrees of freedom for the fixed effects will be calculated using Kenward and Roger's method [1]. The following is an example of the SAS Software code that will be used:

```
PROC MIXED DATA=<input dataset name> METHOD=REML ORDER=INTERNAL;
           CLASS SUBJIDN TRTAN APERIODN TRTSEQPN;
           MODEL LVAR = TRTAN APERIODN TRTSEQPN / OUTP=PRED DDFM=KR;
           RANDOM SUBJIDN(TRTSEQPN);
           ESTIMATE <relevant pairwise treatment comparisons> / CL ALPHA=0.10;
           LSMEANS TRTAN / ALPHA=0.10;
           ODS OUTPUT LSMEANS=MEANS ESTIMATES=EST COVPARMS=CVW;
RUN;
```

where

- LVAR is the natural log transformed PK parameter of interest
- SUBJIDN is the numeric subject identifier variable
- APERIODN is the numeric period variable
- TRTAN is the numeric treatment variable for the actual treatment received
- TRTSEQPN is the numeric sequence variable for the planned sequence received

If there are any deviations from the planned treatment, then the analysis model specified or methods of analysis may be re-evaluated, as appropriate. Details of any deviations from the planned analysis will be documented in the CSR.

For each analysis, distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions for the parametric approach are not satisfied, then additional sensitivity analyses may be performed including the removal of potential outliers or use of non-parametric methods to assess the robustness of the original analysis. In general terms, the results of the original analysis will always be presented in the CSR. This will be documented in the CSR together with the reasoning supporting the most appropriate action taken, if applicable.

9.2.5 Statistical Figures for Analysis of Pharmacokinetic Data

Plots of GMRs obtained from the statistical model will be produced for each of the PK parameters: C_{max}, AUC_{0-t} and AUC_{0-inf} with bars representing the 90% CIs. Plots will include horizontal lines to show representative lower (i.e., 80.00%) and upper (i.e., 125.00%) limits for the ratios.

Separate figures will be produced for each study part and each analyte.

10 Safety Assessments

Safety data summaries will be presented by actual treatment and the safety analysis population will be used throughout.

Separate summary tables and listings will be produced for each study part.

10.1 Extent of Exposure and Treatment Compliance

The number and percentage of subjects dosed with IMP will be presented for each treatment.

Dosing details (including the date and time of all doses administered and any comments) will be listed. Any recorded deviations from the planned dosing treatment will be listed as protocol deviations.

10.2 Meal Details

Meal details, as recorded on the eCRF will be listed. Any recorded deviations from the planned meal times will be listed as protocol deviations.

10.3 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution.

Throughout the study, all AEs will be evaluated by the PI and noted in the AE section of the eCRF. AEs will be monitored from the time the subject signs the informed consent form (ICF) until after the final follow-up call in each period and each study part.

AEs will be coded using MedDRA v22.0 (or most recent version) and reported by SOC and PT.

AEs will be classified into the following categories:

- pre-dose AEs: AEs recorded after informed consent has been obtained and prior to the first dose of IMP. Only Serious Adverse Events (SAEs) caused by protocol mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) will be reported
- treatment-emergent adverse events (TEAEs): AEs that commence during/after the first dose of IMP or commence before first dose of IMP (i.e., a pre-dose AE or existing medical condition) but worsen in intensity during exposure to IMP

Where the severity of a pre-dose AE intensifies during/after dosing this will be defined as a new AE and classified as a TEAE.

TEAEs will be assigned to the treatment of the period in which the AE first occurred. Where the severity of an AE intensifies or symptoms change in a subsequent period, this

will be defined as a new AE and included under the treatment associated with the subsequent period. AEs that occur during the washout period will be assigned to the treatment the subject received during the period immediately before the washout period.

An IMP-related AE is any AE where a causal relationship with the IMP is at least a reasonable possibility. When considering their relationship to IMP, AEs will be classified as "YES" (i.e., 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.) or "NO" (i.e., evidence exists that the adverse event has an etiology other than the study drug [e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication]; and/or the adverse event has no plausible temporal relationship to administration of the study drug [e.g., cancer diagnosed 2 days after first dose of study drug]). Pre-dose AEs will always have the classification of "NO" when considering their relationship to IMP.

The severity of AEs will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v5.0) grading scale when considering their initial and maximum severity separately. All summary tables will be based on maximum severity but relevant listings will include both initial and maximum severity:

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

[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 AE.
[d] Grade 4 and 5 events must be reported as serious AEs.

If the severity or relationship to IMP of a TEAE is missing, the severity/relationship will be tabulated as "missing" in the summary tables.

Where the start date of an AE is missing and the stop date is on or after the day of first dose of IMP or both the start and stop dates are missing then a "worst-case" scenario will be assumed, i.e., the AE is assumed to have occurred post-dose and is therefore considered treatment-emergent. If a partial start date/time is available, then the event will be considered as treatment-emergent unless the partial information suggests otherwise.

10.3.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 10.3) will be excluded from the summary tables but will be listed for all subjects.

Descriptive statistical methods will be used to summarize the TEAE data.

The number and percentage of subjects reporting each TEAE will be summarized for both SOC and PT. For summaries by SOC and PT, with the exception of TEAEs by severity and relationship to IMP, the number of subjects and the number of events will be summarized. For summaries by severity and relationship only the number of subjects will be summarized.

For counts of subjects experiencing events the following will apply:

- a subject experiencing TEAEs in more than one body system, for a treatment, will be counted once in the total number of subjects with TEAEs in that study period;
- a subject with more than 1 TEAE in the same SOC, for a treatment, counts only once at the SOC level;
- a subject with more than 1 TEAE in the same PT, for a treatment, counts only once at the PT level.

For event counts, all events are included.

When it is necessary to calculate percentages, the denominator will be the total number of subjects in the safety analysis population for that treatment or study part/period and the numerator will be the total number of subjects reporting a TEAE within the relevant category.

Summaries presented for SOC and PT will be presented in descending order of frequency overall i.e., most frequently reported SOC in the study and then by most frequently reported PT in the study within each SOC.

10.3.1.1 Overall Summary of Adverse Events

The following will be summarized by treatment:

- number and percentage of subjects reporting at least 1 TEAE
- number and percentage of subjects reporting at least 1 severe TEAE
- number and percentage of subjects reporting at least 1 life-threatening TEAE
- number and percentage of subjects reporting at least 1 IMP-related TEAE
- number and percentage of subjects reporting at least 1 AE of special interest
- number and percentage of subjects reporting at least 1 serious TEAE
- number and percentage of subjects reporting at least 1 TEAE leading to death

- total number of TEAEs
- total number of severe TEAEs
- total number of life-threatening TEAEs
- total number of IMP-related TEAEs
- total number of AEs of special interest
- total number of serious TEAEs
- total number of TEAEs leading to death

10.3.1.2 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

All subjects reporting TEAEs will be summarized by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than one TEAE within a treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting TEAEs will be summarized for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity i.e., subjects experiencing more than one episode of a TEAE within a treatment will be counted only once within each SOC and PT using the most severe episode.

10.3.1.3 Summary of Treatment-Emergent Adverse Events by Severity

All subjects reporting TEAEs will be summarized by severity (i.e., mild, moderate, severe, life-threatening or death) and treatment. Counts will be given for number of subjects, not number of events. Counts will be given by maximum severity (i.e., subjects experiencing more than one TEAE within a treatment will be counted only once using the most severe episode).

Additionally, subjects reporting TEAEs will be summarized for SOC and PT by maximum severity (i.e., mild, moderate, severe, life-threatening or death) and treatment. Counts will be given for total number of subjects, not for events. Counts by maximum severity will be given (i.e., subjects experiencing more than one TEAE within a treatment will be counted only once within each SOC and PT using the most severe episode).

10.3.1.4 Summary of Treatment-Emergent Adverse Events by Relationship to IMP

All subjects reporting TEAEs will be summarized by relationship to IMP (i.e., "YES" and "NO") and treatment. Counts will be given for number of subjects, not number of events. Counts will be given by the closest relationship to IMP (i.e., subjects experiencing more than one TEAE within a treatment will be counted only once using the most closely related event).

Additionally, subjects reporting TEAEs will be summarized for SOC and PT by closest relationship to IMP (i.e., "YES" and "NO") and treatment. Counts will be given for total number of subjects, not for events. Counts by closest relationship will be given (i.e., subjects experiencing more than one TEAE within a treatment will be counted only once within each SOC and PT using the most closely related event).

10.3.1.5 Summary of IMP-related TEAEs

All subjects reporting IMP-related TEAEs will be summarized by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than one IMP-related TEAE within a treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting IMP-related TEAEs will be summarized for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity i.e., subjects experiencing more than one episode of an IMP-related TEAE within a treatment will be counted only once within each SOC and PT using the most severe episode.

10.3.1.6 Summary of Adverse Events of Special Interest

All subjects reporting AEs of special interest will be summarized by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than one AE of special interest within a treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting AEs of special interest will be summarized for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity i.e., subjects experiencing more than one episode of an AE of special interest within a treatment will be counted only once within each SOC and PT using the most severe episode.

10.3.1.7 Summary of Serious Adverse Events

All subjects reporting SAEs will be summarized by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than one SAE within a treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting SAEs will be summarized for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity i.e., subjects experiencing more than one episode of a SAE within a treatment will be counted only once within each SOC and PT using the most severe episode.

10.3.2 Listings for Adverse Events

All pre-dose AEs (as defined in Section 10.3) will be listed, including SOC and PT.

A separate data listing of all TEAEs will be provided including the SOC and PT. In addition, listings of all AEs of special interest and SAEs will be provided.

10.4 Laboratory Evaluations

The details of sample collection for laboratory safety analysis are described in the study protocol.

Where a value is provided by the safety laboratory as either above or below the limit of detection (LOD) this will be set to the LOD itself for summary purposes. No imputations will be made in the individual listings.

10.4.1 Summary Tables for Laboratory Evaluations

Hematology and coagulation, and serum biochemistry will be summarized (mean, SD, median, minimum, maximum and n) for each laboratory parameter at each time point, including changes from baseline (Day -1, Admission in each study period) at each 96 h post-baseline time point by treatment.

Shift tables from baseline to each post-baseline time point (with respect to the number and percentage of subjects with values below, within or above the reference range) will be presented by treatment. Percentages will be based on the number of subjects with measurements at baseline and the relevant 96 h post-baseline time point.

Reference ranges for each laboratory parameter will be presented for the relevant parameter in each summary table.

10.4.2 Listings for Laboratory Evaluations

The sample collection data and comments (e.g., collection times) for laboratory analysis and urinalysis data will be listed.

All individual subject data, for planned hematology and coagulation, serum biochemistry and urinalysis data will be listed, including change from baseline. If applicable, data from unscheduled laboratory tests will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics. In these listings, individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively.

Separate listings by subject of all hematology and coagulation, serum biochemistry and urinalysis values outside their reference ranges will also be provided. References ranges will be supplied by the safety laboratory for hematology and coagulation, and serum biochemistry and per the eCRF for urinalysis (i.e., a positive or negative result) with the exception of the following reference ranges for urinalysis:

- pH: 5.0 to 8.0
- Specific gravity: 1.000 to 1.030

10.5 Vital Signs

The details of measurement of supine vital signs are described in the study protocol.

10.5.1 Summary Tables for Vital Signs

Vital signs data (i.e., systolic and diastolic blood pressure [BP], pulse rate and oral temperature), including change from baseline (Day 1, Pre-dose of each treatment period) will be summarized (i.e., mean, SD, median, minimum, maximum and n) at each post-baseline time point by treatment.

In addition, the number of subjects with 'substantial' increases ("INC") or decreases ("DEC") or no substantial change ("NONE") from baseline in systolic BP (>±20 mmHg), diastolic BP (>±10 mmHg) and pulse rate (>±15 bpm) will be summarized.

10.5.2 Listings for Vital Signs

All individual vital signs data (i.e., systolic and diastolic BP, pulse rate and oral temperature) data will be listed, including change from baseline. Individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively, and subjects with 'substantial' increases or decreases from baseline (as defined in Section 10.5.1) in systolic BP, diastolic BP and pulse rate will be flagged with an "I" (increase) or "D" (decrease), respectively. If applicable, data from unscheduled vital signs assessments will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics.

In addition, a separate listing of all vital signs data outside their reference ranges by subject will also be provided.

The reference ranges taken from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials" for oral body temperature and from the exclusion criteria of the protocol for all other vital signs parameters, as defined in Table 5, will be used.

Table 5 Vital Signs Reference Ranges

Parameter	Lower limit	Upper limit
Systolic BP	90 mmHg	140 mmHg
Diastolic BP	50 mmHg	90 mmHg
Pulse rate	40 bpm	90 bpm
Oral Body Temperature	35.5ºC	37.5ºC

NA=Not applicable

10.6 ECGs

The details of measurement of supine ECG parameters (i.e., ventricular rate, RR interval, uncorrected QT interval, QTcF interval, PR duration, QRS interval, QRS axis, rhythm and interpretation) are described in the study protocol. ECG parameters will be reported in the order given above i.e., both summary tables and data listings.

10.6.1 Summary Tables for ECGs

ECG data, including change from baseline (Day 1, Pre-dose of each treatment period), will be summarized (i.e., mean, SD, median, minimum, maximum and n) at each post-baseline time point by treatment.

The number and percentage of subjects with normal and prolonged QT intervals corrected for heart rate using Fridericia's correction (i.e., QTcF) and increases in QTcF intervals from baseline within the categories defined in Table 6 (based on the International Council on Harmonization [ICH] E14 guideline [2]) will be summarized by time point. Percentages will be based on the number of subjects with measurements at the relevant time point.

Table 6 ICH E14 Ranges for QTcF Intervals

Parameter	ICH E14 Range
QTcF intervals	≤450 msec (normal)
	451-480 msec
	481-500 msec
	>500 msec
Increase in QTcF interval from baseline	<30 msec
	30-60 msec
	>60 msec

10.6.2 Listings for ECGs

All ECG measurements, including derivations such as change from baseline will be listed.

All ECG measurements will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively. If applicable, data from unscheduled ECG assessments will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics.

In addition, subjects with increase in QTcF interval from baseline (30-60 msec) and with 'substantial increases' (>60 msec) will be flagged with 'I' and 'SI', respectively.

A separate listing of all ECG parameters outside their reference range by subject will also be provided.

The reference ranges taken from the exclusion criteria of the protocol for ventricular rate and from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials" for all other ECG parameters, as defined in Table 7, will be used, apart from the reference range for RR interval which is calculated by the following formula:

$$\text{RR interval} = \frac{60000}{\text{heart rate}}$$

Table 7 ECG Reference Ranges

Parameter	Split	Lower limit	Upper limit
Ventricular Rate	NA	40 bpm	90 bpm
RR Interval	NA	600 msec	1500 msec
QT Interval	NA	0 msec	500 msec
QTcF Interval	NA	0 msec	450 msec
PR Interval	NA	120 msec	220 msec
QRS Duration	NA	0 msec	120 msec
QRS Axis	NA	-30°	100°
Rhythm	NA	Sinus rhythm, Sinus bradycardia (rate dependent), Sinus arrhythmia	

HR=heart rate
NA=Not applicable

10.7 Physical Examination Data

All physical examination details and comments on any physical examination findings will be listed.

11 Palatability Evaluations

Palatability will be assessed for each test formulation administered in Part 1 (i.e., T1 and T2) using a palatability questionnaire (Appendix 3), at the time points detailed in Appendix 1. The questionnaire will ask subjects to rate the overall acceptability of palatability, with additional questions asked on specific palatability attributes (e.g., flavour, mouth feel/texture and aftertaste), on a 100 mm VAS scale.

For the purposes of the summaries, acceptability and each palatability attribute will be scored using 0 mm = "I did not like it" through to 100 mm = "I liked it very much" for Questions 1, 3, 4 and 5; 0 mm = "Very gritty/lumpy" through to 100 mm = "Very smooth" for Question 2; 0 mm = "Very difficult" through to 100 mm = "Very easy" for Question 6; 0 mm = "No taste" through to 100 mm = "Very intense taste" for Questions 7 to 11 and 0 mm = "Not at all" through to 100 mm = "Extremely" for Questions 12 to 16.

The safety analysis population will be used for all summary tables described in this section and all randomized subjects will be used for the listings.

11.1 Palatability Evaluations Summary Tables

Palatability data (for all questions on a VAS scale) will be summarized using descriptive statistics (i.e., mean, SD, median, minimum, maximum and n) for each palatability question by test formulation.

11.2 Palatability Evaluations Listings

All palatability data collected (i.e., score for each VAS scale palatability question and comments for all other palatability questions) will be listed.

12 Interim Statistical Analysis

No formal interim statistical analysis is planned for this study.

13 Changes in the Conduct of the Study or Planned Analysis

13.1 Changes in the Conduct of the Study

No changes in the conduct of the study had been reported at the time this document was written.

13.2 Changes to the Planned Analysis

No changes to planned analysis.

13.3 Any Other Relevant Changes

Not applicable.

14 Overall Considerations

14.1 Statistical Programming and Analysis

The Data Sciences Department at Quotient will perform the statistical programming and analysis to produce all analysis datasets, summary tables, figures and data listings using the statistical package SAS (version 9.4 or later).

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, SD, minimum, maximum and n. For PK data CV% will also be presented and for PK parameter data additional statistics including geometric mean, geometric SD, geometric CV% and geometric n will be presented, as appropriate. The geometric n is the number of subjects included in the calculation of the geometric mean, geometric SD and geometric CV%.

The geometric mean is obtained by applying a natural log transformation to the raw data, calculating the arithmetic mean of the transformed values and then back transforming the arithmetic mean.

The following formula will be used to calculate the geometric SD:

$$\text{geometric SD} = \exp\{\text{SD}[\log(\text{raw data})]\}$$

i.e., a natural log transformation is applied to the raw data, the arithmetic SD of the transformed values is calculated, and then the arithmetic SD of the transformed values is back transformed.

The following formula will be used to calculate the geometric CV%:

$$\text{geometric CV\%} = 100 \times (\exp\{\text{SD}[\log(\text{raw data})]\}^2 - 1)^{1/2}$$

i.e., a natural log transformation is applied to the raw data, the arithmetic SD of the transformed values is calculated. This value is then squared. The square value is back

transformed and a value of 1 is subtracted from the back transformed value. A square root is then applied and the resulting value is multiplied by 100.

In general, summary statistics and statistical analysis results will be presented as detailed in Table 8 below, unless otherwise stated:

Table 8 Reporting Conventions for Summary Statistics and Statistical Analysis

Data Type	Statistic	Number of decimal places for reporting (i)
Frequency	Counts (n)	None
	Percentages (%)	1 decimal place
Summary statistic	n	None
	Mean	i + 1 decimal places
	Median	i + 1 decimal places
	SD	i + 1 decimal places
	Min	i decimal places
	Max	i decimal places
	CV%	1 decimal place
	Geometric n	None
	Geometric Mean	i + 1 decimal places
	Geometric SD	i + 1 decimal places
	Geometric CV%	1 decimal place
Statistical analysis	Ratios (%)	2 decimal places
	Confidence intervals (%)	2 decimal places
	p-values	if <0.001: presented as <0.001
		if ≥0.001 and <0.099: presented to 3 decimal places
		all other p-values will be presented to 2 decimal places

i refers to the number of decimal places reported in the eCRF or other appropriate source data for the original data. Where bioanalytical or PK data are received rounded in significant figures rather than decimal places, summary statistics will be supplied to the same precision.

Details of how the PK parameters will be presented are detailed in Section 9.1.1. Where data requires rounding, values ending with 1 to 4 will be rounded down and values ending with 5 to 9 will be rounded up.

All data listings will be based on all randomized subjects. Details of age and sex will be included on all data listings.

All statistical tests relating to PK parameters will be 2-sided and will be performed using a 10% significance level, leading to 90% (2-sided) CIs.

If any baseline measurements relating to demographic, baseline or safety data are found to be missing, then consideration will be given to imputation using the preceding time point (e.g., Screening, Admission, if applicable). Unscheduled assessment may be used if appropriate. Details of any such imputations will be documented as part of the safety analysis population.

There will be no other imputations for the safety data with regard to missing values or study discontinuation (i.e., subjects who do not complete the study). Imputation for PK parameter estimation using WinNonlin is described in Section 9.1.2 and imputations for reporting PK data are described in Section 9.2.1.

If partial dates are available for smoking history, prior medications or medical/surgical history, there will be no date imputations. The data listings will only show the date information for the date part that is available e.g., if only the year part of the date is available then YYYY will be presented in the listing. If the full date information is missing, then this will be presented as missing on the data listing.

Separate summary tables, figures and data listings will be produced for Part 1 and Part 2 of the study, respectively. The different parts will be identified by a sub-title indicating the relevant part. The text in the remainder of this document refers to both parts, unless specified otherwise.

14.2 Quality Control of Summary Tables, Figures and Listings and Statistical Analysis

Isolated data errors detected as a result of the QC checks that are deemed significant (i.e., errors that would impact the interpretation of the results in relation to the study objectives) will be corrected as per the data management plan. Systematic data errors will be investigated further. The data will be corrected if necessary and the appropriate table, figure and/or listing re-generated and then re-checked.

In addition to QC checks, a documented peer review will be performed of all SAS Software-generated report standard summary tables, figures and data listings, including a review of SAS Software code and program log files.

14.2.1 Quality Control - Summary Tables

Manual QC methods (i.e., comparison of results in the table to results calculated by a calculator or spreadsheet) will be used for all analysis and summary tables. All summary tables will be QC'd as follows:

- where tables are presented by treatment/sequence (i.e., no time points), QC will alternate between treatment/sequence to avoid the same treatment/sequence being QC'd every time however, all summary statistics for that treatment/sequence will be checked
- where tables are presented by treatment and time point, QC will alternate between treatment and time point to avoid the same treatment and time point being QC'd every time, however a single treatment at 1 time point in each table will be checked
- where tables are produced using a macro for multiple parameters, a minimum of 3 tables, using different treatments or combinations of treatments and time point as appropriate, will be QC'd
- for AEs, the treatment details will be 100% QC'd against the randomization schedule for all subjects
- AE summary tables will be 100% checked using the relevant data listing

14.2.2 Quality Control - Figures

All figures will be QC'd manually using the corresponding/appropriate summary table or data listing, as follows:

- across all figures, QC will alternate between treatments to avoid the same treatment being QC'd every time
- where a figure presents data from more than 1 treatment, only 1 treatment will be QC'd; however, all data points for that treatment will be checked
- where figures are produced using a macro for individual subjects and/or multiple parameters, a minimum of 3 figures will be QC'd
- mean figures will be QC'd using the corresponding summary table
- figures showing individual data will be QC'd using the corresponding data listing

14.2.3 Quality Control - Data Listings

All data listings will be subjected to a 100% manual check against the eCRF or other appropriate source data for a minimum of 2 subjects for each study part. If appropriate, the subjects checked will include at least one subject who withdrew early from the study.

The study treatment allocation details on the dosing data listing will be 100% QC checked against the study randomization schedule.

14.2.4 Quality Control - Statistical Analysis

QC of statistical analysis will be performed by peer review of program code, log and output. This will be performed by a statistician at Quotient who is not responsible for performing the statistical analysis.

15 SAS Data Transfer

Study data in ADaM dataset format will be transferred to Genentech at the following milestones:

- Pre database close
- Pre database lock
- Post database lock

Data will be provided in SAS dataset format, each dataset will be contained in a respective SAS transport (XPT) file and conform to CDISC ADaM format (SDTM IG 1.1)

The following standards and versions for creation and validation of the Clinical Data Interchange Standards Consortium (CDISC) Standardized Datasets will be used:

- Study Data Tabulation Model (SDTM) Version: 1.4
- SDTM Implementation Guide Version: 3.2
- ADaM: Model 2.1
- Implementation Guide 1.1
- OpenCDISC Version: 2.2.0
- CDISC SDTM Controlled Terminology Version: "2018-06-29 or latest available"
- SDRG (Standard Data Review Guide): 1.2 or latest available
- ADRG (Standard Data Review Guide): 1.1 or latest available
- Define.xml: 2.0> (end of study transfer only)
- SAS v9.4
- Pinnacle 21

A define.xml will be provided to Genentech for ADaM datasets. This will be accompanied by a Data Reviewers Guide (in pdf format) and linked to the ADaM define.xml. Datasets will be provided in SAS transport file format (XPT), each dataset will be in an individual transport file. The define.xml will be issued on finalization of the CSR.

16 Programming Conventions

Quotient standards for layout of tables, figures and data listings and programming conventions will be used as follows:

- courier new, font size 8
- landscape
- US letter size paper

Tables and listings will be produced as MS Word 2013 documents and figures will be produced as PDF files. Listings will be sorted by subject ID number and period.

The mock tables (Section 21), mock figures (Section 22) and mock listings (Section 23) presented are a representation of Quotient reporting standards. However, these are provided for illustrative purposes only. The numbering, titles, formatting, labelling, footnotes and cosmetic appearance of all output may be modified or additional titles, labelling and/or footnotes may need to be added during analysis and reporting, for clarification purposes. Any such changes will not be regarded as changes to planned analysis.

17 Reference List

[1] Applied Mixed Models in Medicine, Brown and Prescott, 242-243, 3rd edition 2015

[2] International Council for Harmonisation (ICH) Topic E 14, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) in May 2005 which came into force November 2005.

18 Index of Tables

Table Number	Table Title
14.2.1.1.1	Plasma Pharmacokinetic Concentrations: Entrectinib (units) Summary Statistics: PK Population Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.2	Plasma Pharmacokinetic Concentrations: M5 (units) Summary Statistics: PK Population Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.2.1	Plasma Pharmacokinetic Parameters: Entrectinib Summary Statistics: PK Population Part 1
14.2.1.2.2	Plasma Pharmacokinetic Parameters: M5 Summary Statistics: PK Population Part 1
14.2.1.3.1	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population/PK Analysis Dataset Part 1
14.2.1.3.2	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – ANOVA Table: PK Population/PK Analysis Dataset Part 1
14.2.1.4.1	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population/PK Analysis Dataset Part 1
14.2.1.4.2	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – ANOVA Table: PK Population/PK Analysis Dataset Part 1
14.2.2.1.1	Plasma Pharmacokinetic Concentrations: Entrectinib (units) Summary Statistics: PK Population Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

Table Number	Table Title
14.2.2.1.2	Plasma Pharmacokinetic Concentrations: M5 (units) Summary Statistics: PK Population Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.2.1	Plasma Pharmacokinetic Parameters: Entrectinib Summary Statistics: PK Population Part 2
14.2.2.2.2	Plasma Pharmacokinetic Parameters: M5 Summary Statistics: PK Population Part 2
14.2.2.3.1	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population/PK Analysis Dataset Part 2
14.2.2.3.2	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – ANOVA Table: PK Population/PK Analysis Dataset Part 2
14.2.2.4.1	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population/PK Analysis Dataset Part 2
14.2.2.4.2	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – ANOVA Table: PK Population/PK Analysis Dataset Part 2
	Adverse Events
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events Summary Statistics: Safety Analysis Population Part 1
14.3.1.2	Treatment-Emergent Adverse Events By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Population Part 1
14.3.1.3	Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Severity Summary Statistics: Safety Analysis Population Part 1
14.3.1.4	Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Relationship to IMP Summary Statistics: Safety Analysis Population Part 1

Table Number	Table Title
14.3.1.5	Treatment-Emergent Adverse Events Related to IMP By MedDRA System Organ Class and Preferred Team Summary Statistics: Safety Analysis Population Part 1
14.3.1.6	Adverse Events of Special Interest By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Population Part 1
14.3.1.7	Serious Adverse Events By MedDRA System Organ Class and Preferred Team Summary Statistics: Safety Analysis Population Part 1
14.3.2.1	Overall Summary of Treatment-Emergent Adverse Events Summary Statistics: Safety Analysis Population Part 2
14.3.2.2	Treatment-Emergent Adverse Events By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Population Part 2
14.3.2.3	Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Severity Summary Statistics: Safety Analysis Population Part 2
14.3.2.4	Treatment-Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Relationship to IMP Summary Statistics: Safety Analysis Population Part 2
14.3.2.5	Treatment-Emergent Adverse Events Related to IMP By MedDRA System Organ Class and Preferred Team Summary Statistics: Safety Analysis Population Part 2
14.3.2.6	Adverse Events of Special Interest By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Population Part 2
14.3.2.7	Serious Adverse Events By MedDRA System Organ Class and Preferred Team Summary Statistics: Safety Analysis Population Part 2
	Laboratory Results
14.4.1.1	Hematology and Coagulation Summary Statistics: Safety Analysis Population Part 1 *<Parameter>*

Table Number	Table Title
14.4.1.2	Hematology and Coagulation Shift Analysis: Safety Analysis Population Part 1 *<Parameter>*
14.4.1.3	Serum Biochemistry Summary Statistics: Safety Analysis Population Part 1 *<Parameter>*
14.4.1.4	Serum Biochemistry Shift Analysis: Safety Analysis Population Part 1 *<Parameter>*
14.4.2.1	Hematology and Coagulation Summary Statistics: Safety Analysis Population Part 2 *<Parameter>*
14.4.2.2	Hematology and Coagulation Shift Analysis: Safety Analysis Population Part 2 *<Parameter>*
14.4.2.3	Serum Biochemistry Summary Statistics: Safety Analysis Population Part 2 *<Parameter>*
14.4.2.4	Serum Biochemistry Shift Analysis: Safety Analysis Population Part 2 *<Parameter>*
	Vital Signs, ECG Results and Palatability Evaluations
14.5.1.1	Vital Signs Summary Statistics: Safety Analysis Population Part 1 *<Parameter>*
14.5.1.2.1	ECGs Summary Statistics: Safety Analysis Population Part 1 <Parameter>
14.5.1.2.2	ECGs QTcF Categorical Data Summary Statistics: Safety Analysis Population Part 1
14.5.1.3	Palatability Evaluations Summary Statistics: Safety Analysis Population *<Palatability Question>* Part 1

Table Number	Table Title
14.5.2.1	Vital Signs Summary Statistics: Safety Analysis Population Part 2 *<Parameter>*
14.5.2.2.1	ECGs Summary Statistics: Safety Analysis Population Part 2 <Parameter>
14.5.2.2.2	ECGs QTcF Categorical Data Summary Statistics: Safety Analysis Population Part 2

19 Index of Figures

Figure Number	Figure Title
14.2.1.1.6	Plasma Pharmacokinetic Concentrations: Entrectinib Log10/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.7	Plasma Pharmacokinetic Concentrations: M5 Log10/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.8	Plasma Pharmacokinetic Concentrations: Entrectinib Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 1 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.9	Plasma Pharmacokinetic Concentrations: M5 Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 1 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.10	Plasma Pharmacokinetic Concentrations: Entrectinib and M5 Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population *Subtitle: <Treatment>* Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

Figure Number	Figure Title
14.2.1.1.11	Plasma Pharmacokinetic Concentrations: Entrectinib Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 1 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.12	Plasma Pharmacokinetic Concentrations: M5 Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 1 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.1.13	Plasma Pharmacokinetic Concentrations: Entrectinib and M5 Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population *Subtitle: <Treatment>* Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.2.1	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population Adjusted Geometric Mean Ratio + 90% CIs <Pairwise Treatment Comparison> Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.1.2.2	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population Adjusted Geometric Mean Ratio + 90% CIs <Pairwise Treatment Comparison> Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

Figure Number	Figure Title
14.2.2.1.1	Plasma Pharmacokinetic Concentrations: Entrectinib Linear/Linear Scale Arithmetic Mean (± Arithmetic SD) Values: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.2	Plasma Pharmacokinetic Concentrations: M5 Linear/Linear Scale Arithmetic Mean (± Arithmetic SD) Values: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.3	Plasma Pharmacokinetic Concentrations: Entrectinib and M5 Linear/Linear Scale Arithmetic Mean (± Arithmetic SD) Values: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.4	Plasma Pharmacokinetic Concentrations: Entrectinib Linear/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.5	Plasma Pharmacokinetic Concentrations: M5 Linear/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

Figure Number	Figure Title
14.2.2.1.6	Plasma Pharmacokinetic Concentrations: Entrectinib Log10/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.7	Plasma Pharmacokinetic Concentrations: M5 Log10/Linear Scale Spaghetti Plots of All Individual Values: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.8	Plasma Pharmacokinetic Concentrations: Entrectinib Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.9	Plasma Pharmacokinetic Concentrations: M5 Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.10	Plasma Pharmacokinetic Concentrations: Entrectinib and M5 Linear/Linear Scale Individual Values for Subject <*xxx*>: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

Figure Number	Figure Title
14.2.2.1.11	Plasma Pharmacokinetic Concentrations: Entrectinib Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.12	Plasma Pharmacokinetic Concentrations: M5 Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population Part 2 *(programming note: all treatments on same plot)* *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.1.13	Plasma Pharmacokinetic Concentrations: Entrectinib and M5 Log10/Linear Scale Individual Values for Subject <*xxx*>: PK Population *Subtitle: <Treatment>* Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.2.1	Plasma Pharmacokinetic Parameters: Entrectinib Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population Adjusted Geometric Mean Ratio + 90% CIs 200 mg F06 coarse vs 200 mg F06 fine Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
14.2.2.2.2	Plasma Pharmacokinetic Parameters: M5 Statistical Analysis Results – Assessment of Relative Bioavailability: PK Population Adjusted Geometric Mean Ratio + 90% CIs 200 mg F06 coarse vs 200 mg F06 fine Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*

20 Index of Listings

Listing Number	Listing Title
	Subject Informed Consent and Completion/Withdrawal
16.2.1.1	Subject Informed Consent and Completion/Withdrawal Individual Values: All Randomized Subjects Part 1
16.2.1.2	Subject Informed Consent and Completion/Withdrawal Individual Values: All Randomized Subjects Part 2
	Protocol Deviations and Inclusion/Exclusion Criteria
16.2.2.1.1	Protocol Deviations Individual Values: All Randomized Subjects Part 1
16.2.2.1.2	Inclusion/Exclusion Criteria Individual Values: All Randomized Subjects Part 1
16.2.2.2.1	Protocol Deviations Individual Values: All Randomized Subjects Part 2
16.2.2.2.2	Inclusion/Exclusion Criteria Individual Values: All Randomized Subjects Part 2
	Analysis Populations and Reasons for Exclusion
16.2.3.1.1	Analysis Populations and Reasons for Exclusion Individual Values: All Randomized Subjects Part 1 *(programming note: If analysis datasets are not required, then this listing will be re-numbered from 16.2.3.1.1 to 16.2.3.1 and Listing 16.2.3.1.2 will not be produced)*
16.2.3.1.2	Analysis Datasets and Reasons for Exclusion Individual Values: All Randomized Subjects Part 1 *(programming note: If analysis datasets are not required, then this listing will not be produced and Listing 16.2.3.1.1 will be re-numbered from 16.2.3.1.1 to 16.2.3.1)*
16.2.3.2.1	Analysis Populations and Reasons for Exclusion Individual Values: All Randomized Subjects Part 2 *(programming note: If analysis datasets are not required, then this listing will be re-numbered from 16.2.3.2.1 to 16.2.3.2 and Listing 16.2.3.2.2 will not be produced)*

Listing Number	Listing Title
16.2.3.2.2	Analysis Datasets and Reasons for Exclusion Individual Values: All Randomized Subjects Part 2 *(Programming note: If analysis datasets are not required, then this listing will not be produced and Listing 16.2.3.2.1 will be re-numbered from 16.2.3.2.1 to 16.2.3.2)*
	Demographic and Baseline Characteristics
16.2.4.1.1	Demographics and Baseline Characteristics Individual Values: All Randomized Subjects Part 1
16.2.4.1.2	Lifestyle Details: Smoking History and Alcohol Consumption Individual Values: All Randomized Subjects Part 1
16.2.4.1.3	Medical/Surgical History Individual Values: All Randomized Subjects Part 1
16.2.4.1.4	Prior and Concomitant Medication Individual Values: All Randomized Subjects Part 1
16.2.4.1.5	Urine Drug Screen Individual Values: All Randomized Subjects Part 1
16.2.4.1.6	Alcohol and Carbon Monoxide Breath Test Individual Values: All Randomized Subjects Part 1
16.2.4.1.7	Virology Individual Values: All Randomized Subjects Part 1
16.2.4.1.8	Urine/Serum Pregnancy Test Individual Values: All Female Subjects Part 1
16.2.4.1.9	Follicle Stimulating Hormone Individual Values: All Post-Menopausal Female Subjects Part 1
16.2.4.2.1	Demographics and Baseline Characteristics Individual Values: All Randomized Subjects Part 2
16.2.4.2.2	Lifestyle Details: Smoking History and Alcohol Consumption Individual Values: All Randomized Subjects Part 2
16.2.4.2.3	Medical/Surgical History Individual Values: All Randomized Subjects Part 2

Listing Number	Listing Title
16.2.4.2.4	Prior and Concomitant Medication Individual Values: All Randomized Subjects Part 2
16.2.4.2.5	Urine Drug Screen Individual Values: All Randomized Subjects Part 2
16.2.4.2.6	Alcohol Breath and Carbon Monoxide Breath Test Individual Values: All Randomized Subjects Part 2
16.2.4.2.7	Virology Individual Values: All Randomized Subjects Part 2
16.2.4.2.8	Urine/Serum Pregnancy Test Individual Values: All Female Subjects Part 2
16.2.4.2.9	Follicle Stimulating Hormone Individual Values: All Post-Menopausal Female Subjects Part 2
	Dosing Details, Meal Details and Plasma Concentrations
16.2.5.1.1	Dosing Details Individual Values: All Randomized Subjects Part 1
16.2.5.1.2	Meal Details Individual Values: All Randomized Subjects Part 1
16.2.5.1.3	Blood Sample Collection Details and Concentrations for Pharmacokinetic Analysis Individual Values: All Randomized Subjects Part 1 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
16.2.5.2.1	Dosing Details Individual Values: All Randomized Subjects Part 2
16.2.5.2.2	Meal Details Individual Values: All Randomized Subjects Part 2

Listing Number	Listing Title
16.2.5.2.3	Blood Sample Collection Details and Concentrations for Pharmacokinetic Analysis Individual Values: All Randomized Subjects Part 2 *(programming note: where concentrations are provided as ng/mL, these will be converted to nmol/L)*
	Plasma Pharmacokinetic Parameter Data
16.2.6.1.1	Plasma Pharmacokinetic Parameters: Entrectinib Individual Values: All Randomized Subjects Part 1
16.2.6.1.2	Plasma Pharmacokinetic Parameters: M5 Individual Values: All Randomized Subjects Part 1
16.2.6.2.1	Plasma Pharmacokinetic Parameters: Entrectinib Individual Values: All Randomized Subjects Part 2
16.2.6.2.2	Plasma Pharmacokinetic Parameters: M5 Individual Values: All Randomized Subjects Part 2
	Adverse Events
16.2.7.1.1	Pre-dose Adverse Events Individual Values: All Randomized Subjects Part 1
16.2.7.1.2	All Treatment-Emergent Adverse Events Individual Values: All Randomized Subjects Part 1
16.2.7.1.3	Adverse Events of Special Interest Individual Values: All Randomized Subjects Part 1
16.2.7.1.4	Serious Adverse Events Individual Values: All Randomized Subjects Part 1
16.2.7.2.1	Pre-dose Adverse Events Individual Values: All Randomized Subjects Part 2
16.2.7.2.2	All Treatment-Emergent Adverse Events Individual Values: All Randomized Subjects Part 2
16.2.7.2.3	Adverse Events of Special Interest Individual Values: All Randomized Subjects Part 2

Listing Number	Listing Title
16.2.7.2.4	Serious Adverse Events Individual Values: All Randomized Subjects Part 2
	Laboratory Data
16.2.8.1.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Randomized Subjects Part 1
16.2.8.1.1.2	Blood Sample Collection Comments Individual Values: All Randomized Subjects Part 1
16.2.8.1.2	Hematology and Coagulation Individual Values: All Randomized Subjects Part 1
16.2.8.1.3	Hematology and Coagulation Individual Values Outside the Reference Range: All Randomized Subjects Part 1
16.2.8.1.4	Serum Biochemistry Individual Values: All Randomized Subjects Part 1
16.2.8.1.5	Serum Biochemistry Individual Values Outside the Reference Range: All Randomized Subjects Part 1
16.2.8.1.6	Urinalysis Sample Collection Individual Values: All Randomized Subjects Part 1
16.2.8.1.7	Urinalysis Individual Values: All Randomized Subjects Part 1
16.2.8.1.8	Urinalysis Individual Values Outside the Reference Range: All Randomized Subjects Part 1
16.2.8.2.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Randomized Subjects Part 2
16.2.8.2.1.2	Blood Sample Collection Comments Individual Values: All Randomized Subjects Part 2
16.2.8.2.2	Hematology and Coagulation Individual Values: All Randomized Subjects Part 2

Listing Number	Listing Title
16.2.8.2.3	Hematology and Coagulation Individual Values Outside the Reference Range: All Randomized Subjects Part 2
16.2.8.2.4	Serum Biochemistry Individual Values: All Randomized Subjects Part 2
16.2.8.2.5	Serum Biochemistry Individual Values Outside the Reference Range: All Randomized Subjects Part 2
16.2.8.2.6	Urinalysis Sample Collection Individual Values: All Randomized Subjects Part 2
16.2.8.2.7	Urinalysis Individual Values: All Randomized Subjects Part 2
16.2.8.2.8	Urinalysis Individual Values Outside the Reference Range: All Randomized Subjects Part 2
	Vital Signs, ECGs and Other Data
16.2.9.1.1.1	Vital Signs Individual Values: All Randomized Subjects Part 1
16.2.9.1.1.2	Vital Signs Individual Values Outside the Reference Range: All Randomized Subjects Part 1
16.2.9.1.2.1	ECGs Individual Values: All Randomized Subjects Part 1
16.2.9.1.2.2	ECGs Individual Values Outside the Reference Range: All Randomized Subjects Part 1
16.2.9.1.3	Physical Examinations Individual Values: All Randomized Subjects Part 1
16.2.9.1.4	Palatability Evaluations Individual Values: All Randomized Subjects <Palatability Question> Part 1

Listing Number	Listing Title
16.2.9.2.1.1	Vital Signs Individual Values: All Randomized Subjects Part 2
16.2.9.2.1.2	Vital Signs Individual Values Outside the Reference Range: All Randomized Subjects Part 2
16.2.9.2.2.1	ECGs Individual Values: All Randomized Subjects Part 2
16.2.9.2.2.2	ECGs Individual Values Outside the Reference Range: All Randomized Subjects Part 2
16.2.9.2.3	Physical Examinations Individual Values: All Randomized Subjects Part 2

21 Mock Tables

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.1.1.1
Subject Disposition by Reason
Summary Statistics: All Randomized Subjects
Part 1

	Treatment Sequence			
	T1T2R (N=XX) n (%)	T2RT1 (N=XX) n (%)	RT1T2 (N=XX) n (%)	OVERALL (N=XX) n (%)
Subjects randomized	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects dosed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects completed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…
<All categories on eCRF>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
T1: 600 mg entrectinib film-coated mini-tablets fed, T2: 600 mg entrectinib film-coated mini-tablets fed, R: 600 mg entrectinib (RXDX-101) F06 hard capsules fed.
A randomized subject is defined as a subject who signed the informed consent, qualified per the inclusion/exclusion criteria and was randomized to a treatment sequence (i.e., allocated a subject number).
A subject may be discontinued for one reason only.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all reasons for discontinuation as recorded on the eCRF. If none of the subjects discontinued from the study early, then reasons for discontinuation will not be populated in the summary table. All percentages are based on the number of subjects who were randomized.)
(Programming note: A similar table will be produced for Part 2 Subject Disposition by Reason, i.e., Table [14.1.2.1]. Treatment sequences will be TR and RT and footnote will state: T: 200 mg F06 HPMC capsules fasted, R: 200 mg entrectinib (RXDX-101) F06 hard capsules fasted.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.1.1.2.1
Analysis Populations
Summary Statistics: All Randomized Subjects
Part 1

	Treatment Sequence			
	T1T2R (N=XX) n (%)	T2RT1 (N=XX) n (%)	RT1T2 (N=XX) n (%)	OVERALL (N=XX) n (%)
Number (%) of subjects in safety analysis population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from safety analysis population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
<All categories on source listing>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…

Note: The data in this table are presented in listing x.x
T1: 600 mg entrectinib film-coated mini-tablets fed, T2: 600 mg entrectinib film-coated mini-tablets fed, R: 600 mg entrectinib (RXDX-101) F06 hard capsules fed.
A subject may be excluded for more than one reason.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: If analysis datasets are not required, then this table will be re-numbered from Table [14.1.1.2.1] to Table [14.1.1.2] and the next table will not be produced. This table will be continued for all reasons for exclusion as recorded on the eCRF, for the PK Population and for the Palatability Population (Part 1) If none of the subjects were excluded from a population, then reasons for exclusion will not be populated in the summary table. All percentages are based on the number of subjects who were randomized.)
(Programming note: A similar table will be produced for Part 2 Analysis Populations, i.e., Table [14.1.2.2.1]. If analysis datasets are not required, then this table will be re-numbered from Table [14.1.2.2.1] to Table [14.1.2.2] and the next table will not be produced. Treatment sequences will be TR and RT and footnote will state: T: 200 mg F06 HPMC capsules fasted, R: 200 mg entrectinib (RXDX-101) F06 hard capsules fasted.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.1.1.2.2
Analysis Datasets
Summary Statistics: PK Population
Part 1

	Treatment		
	600 mg F15 (N=XX) n (%)	600 mg F16 (N=XX) n (%)	600 mg F06 (N=XX) n (%)
Number (%) of subjects in PK analysis dataset	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from PK analysis dataset	xx (xx.x)	xx (xx.x)	xx (xx.x)
<All categories on source listing>	…	…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
A subject may be excluded for more than one reason.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all reasons for exclusion as recorded on the eCRF. If none of the subjects were excluded from an analysis dataset, then reasons for exclusion will not be populated in the summary table. If analysis datasets are not required, then this table will not be produced and the previous table will be re-numbered from Table [14.1.1.2.1] to Table [14.1.1.2].)
(Programming note: A similar table, if required, will be produced for Palatability Population (Part 1), i.e., Table [14.1.1.2.3].)
(Programming note: A similar table will be produced for Part 2 Analysis Datasets, i.e., Table [14.1.2.2.2]. If analysis datasets are not required, then this table will not be produced and the previous table will be re-numbered from Table [14.1.2.2.1] to Table [14.1.2.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.1.1.3
Demographic and Baseline Characteristics
Summary Statistics: Safety Analysis Population
Part 1

		Treatment Sequence			
		T1T2R (N=XX) n (%)	T2RT1 (N=XX) n (%)	RT1T2 (N=XX) n (%)	OVERALL (N=XX) n (%)
Age (years)	Mean	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
	n	xx	xx	xx	xx
Ethnicity n(%)	<All categories on eCRF>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race n(%)	<All categories on eCRF>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex n(%)	Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	…	…	…	…	…
Weight (kg)	…	…	…	…	…
BMI (kg/m^2)	…	…	…	…	…

Note: The data in this table are presented in listing x.x
T1: 600 mg entrectinib film-coated mini-tablets fed, T2: 600 mg entrectinib film-coated mini-tablets fed, R: 600 mg entrectinib (RXDX-101) F06 hard capsules fed.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Height, Weight and BMI will be assessed using the same descriptive statistics as Age. If any values are missing, then a "missing" row will be included in the table, as applicable.)
(Programming note: A similar table will be produced for Part 2 Demographic and Baseline Characteristics, i.e., Table [14.1.2.3]. Treatment sequences will be TR and RT and footnote will state: T: 200 mg F06 HPMC capsules fasted, R: 200 mg entrectinib (RXDX-101) F06 hard capsules fasted.)

Genentech, Inc.
Protocol: GP41341

TABLE 14.1.1.4
Lifestyle Details: Smoking History and Alcohol Consumption at Baseline
Summary Statistics: Safety Analysis Population
Part 1

		Treatment Sequence			
		T1T2R (N=XX) n (%)	T2RT1 (N=XX) n (%)	RT1T2 (N=XX) n (%)	OVERALL (N=XX) n (%)
Does the subject smoke, use e-cigarettes or use nicotine replacement products?	NO	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PREVIOUSLY	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alcohol Consumption	NONE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	YES, NOT REGULAR	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
T1: 600 mg entrectinib film-coated mini-tablets fed, T2: 600 mg entrectinib film-coated mini-tablets fed, R: 600 mg entrectinib (RXDX-101) F06 hard capsules fed.
Anyone who smoked or used e-cigarettes or nicotine replacement products in the last 12 months is excluded from the study. Anyone who regularly consumes alcohol (>21 units per week in males and >14 units per week in females) is excluded from the study. (1 unit = 1/2 pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type.)

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 Lifestyle Details: Smoking History and Alcohol Consumption at Baseline, i.e., Table [14.1.2.4]. Treatment sequences will be TR and RT and footnote will state: T: 200 mg F06 HPMC capsules fasted, R: 200 mg entrectinib (RXDX-101) F06 hard capsules fasted.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.1.1.5
Extent of Exposure
Summary Statistics: Safety Analysis Population
Part 1

Treatment	Number and percentage of subjects Actual Treatment (N=XX) n (%)
600 mg F15 (N=XX)	xx (xx.x)
600 mg F16 (N=XX)	xx (xx.x)
600 mg F06 (N=XX)	xx (xx.x)

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 Extent of Exposure, i.e., Table [14.1.2.5]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.2.1.1.1
Plasma Pharmacokinetic Concentrations: Entrectinib (units)
Summary Statistics: PK Population
Part 1

		Arithmetic							Geometric			
Treatment	Time Point	Mean	SD	CV%	Median	Min	Max	n	Mean	SD	CV%	n
600 mg F15	PRE-DOSE	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx				
(N=XX)	TIME POINT 1	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 2	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	…	…	…	…	…	…	…	…	…	…	…	…
600 mg F16	PRE-DOSE	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx				
(N=XX)	TIME POINT 1	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 2	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	…	…	…	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
For arithmetic summary statistics, concentration values reported as BLQ are set to zero. Geometric summary statistics are not calculated for the pre-dose time point. For calculation of geometric summary statistics, values reported as BLQ are set to ½ × LLOQ.
For all summary statistics, concentration values reported as NR, NS or not calculated (NC) have been set to 'Missing'.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments and all time points.)
(Programming note: A similar table will be produced for M5, i.e., Table [14.2.1.1.2].)
(Programming note: A similar table will be produced for Part 2 Plasma Pharmacokinetic Concentrations: Entrectinib (units), i.e., Table [14.2.2.1.1] and Plasma Pharmacokinetic Concentrations: M5 (units), i.e., Table [14.2.2.1.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.2.1.2.1
Plasma Pharmacokinetic Parameters: Entrectinib
Summary Statistics: PK Population
Part 1

		PK Parameter				
Treatment	Statistic	Parameter 1 (units)	Parameter 2 (units)	Parameter 3 (units)		All Other PK Parameters (units)
600 mg F15 (N=XX)	Mean	xx.x	xx.x	xx.x	…	xx.x
	SD	xx.x	xx.x	xx.x	…	xx.x
	CV%	xx.x	xx.x	xx.x	…	xx.x
	Median	xx.x	xx.x	xx.x	…	xx.x
	Min	xx	xx	xx	…	xx
	Max	xx	xx	xx	…	xx
	n	xx	xx	xx	…	xx
	Geometric Mean	xx.x	xx.x	xx.x	…	xx.x
	Geometric SD	xx.x	xx.x	xx.x	…	xx.x
	Geometric CV%	xx.x	xx.x	xx.x	…	xx.x
	Geometric n	xx	xx	xx	…	xx
…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments and all PK parameters.)
(Programming note: A similar table will be produced for M5, i.e., Table [14.2.1.2.2].)
(Programming note: A similar table will be produced for Part 2 Plasma Pharmacokinetic Parameters: Entrectinib, i.e., Table [14.2.2.2.1] and Plasma Pharmacokinetic Parameters: M5, i.e., Table [14.2.2.2.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.2.1.3.1
Plasma Pharmacokinetic Parameters: Entrectinib
Statistical Analysis Results - Assessment of Relative Bioavailability: PK Population/PK Analysis Dataset
Part 1

		Test		Reference					
Parameter	Test/ Reference	n	Adj Geo Mean (1)	n	Adj Geo Mean (1)	Ratio (%) (2)	90% CI (3)	P-value (4)	CVw(%) (5)
Cmax	600 mg F15/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x
(units)	600 mg F16/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x
AUC0-t	600 mg F15/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x
(units)	600 mg F16/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x
AUC0-inf	600 mg F15/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x
(units)	600 mg F16/600 mg F06	xx	xxx	xx	xxx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.x

Note: The data in this table are presented in listing x.x
T1: 600 mg entrectinib film-coated mini-tablets fed, T2: 600 mg entrectinib film-coated mini-tablets fed, R: 600 mg entrectinib (RXDX-101) F06 hard capsules fed.
Results obtained from mixed effects model of natural log transformed PK parameters including terms for treatment, period and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect. (1) Adj geo mean = adjusted geometric mean from model, (2) Ratio of adj geo means for test/reference, (3) CI = confidence interval for ratio of adj geo means, (4) P-value 2-sided test with null hypothesis that ratio is equal to 100%, (5) CVw = Intra-subject variability.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for M5, i.e., Table [14.2.1.4.1].)
(Programming note: A similar table will be produced for Part 2 Plasma Pharmacokinetic Parameters: Entrectinib, i.e., Table [14.2.2.3.1] and Plasma Pharmacokinetic Parameters: M5, i.e., Table [14.2.2.3.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.2.1.3.2
Plasma Pharmacokinetic Parameters: Entrectinib
Statistical Analysis Results - ANOVA Table: PK Population/PK Analysis Dataset
Part 1

Parameter	Effect (1)	F-statistic (2)	P-value (3)
Cmax (units)	TREATMENT	x.xx	0.xxx
	PERIOD	x.xx	0.xxx
	SEQUENCE	x.xx	0.xxx
AUC0-t (units)	TREATMENT	x.xx	0.xxx
	PERIOD	x.xx	0.xxx
	SEQUENCE	x.xx	0.xxx
AUC0-inf (units)	TREATMENT	x.xx	0.xxx
	PERIOD	x.xx	0.xxx
	SEQUENCE	x.xx	0.xxx

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Results obtained from mixed effects model of natural log transformed PK parameters including terms for treatment, period and sequence fitted as fixed effects and subject nested within sequence fitted as a random effect. (1) Fixed effects from the model, (2) F-statistic from the model for the relevant fixed effect, (3) P-value (2-sided test) for the relevant fixed effect

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for M5, i.e., Table [14.2.1.4.2].)
(Programming note: A similar table will be produced for Part 2 Plasma Pharmacokinetic Parameters: Entrectinib, i.e., Table [14.2.2.4.1] and Plasma Pharmacokinetic Parameters: M5, i.e., Table [14.2.2.4.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Analysis Population
Part 1

	600 mg F15 (N=XX) n (%)
Number (%) of subjects reporting at least 1 TEAE	xx (xx.x)
Number (%) of subjects reporting at least 1 severe TEAE	xx (xx.x)
Number (%) of subjects reporting at least 1 life-threatening TEAE	xx (xx.x)
…	…
Total number of TEAEs	xx
Total number of severe TEAEs	xx
Total number of life-threatening TEAEs	xx
…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Adverse events are coded using MedDRA vXX.X
An IMP-related AE is any AE where a causal relationship with the IMP is at least a reasonable possibility, i.e., "YES" (i.e., there is a plausible temporal relationship between the onset of the AE and administratio of the study drug, and the AE cannot be readily explained by the subject s clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.)

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments and all bullet points from Section [10.3.1.1] of the RAP.)
(Programming note: A similar table will be produced for Part 2 Overall Summary of Treatment-Emergent Adverse Events, i.e., Table [14.3.2.1]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.3.1.2
Treatment-Emergent Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Population
Part 1

System Organ Class Preferred Term	600 mg F15 n(%)	Events n	600 mg F16 n(%)	Events n	600 mg F06 n(%)	Events n
Subjects reporting TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
…	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts of number of subjects are by maximum severity, i.e., subjects experiencing more than 1 episode of a TEAE are counted only once within each SOC and PT using the most severe episode.
Event is the total number of TEAEs within the relevant SOC and PT.
If severity is missing, then the 'Missing' column will be tabulated.
n is the number of subjects reporting at least 1 event.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Similar tables will be produced for IMP-related TEAEs, i.e., Table [14.3.1.5], AEs of Special Interest, i.e., Table [14.3.1.6] and SAEs, i.e., Table [14.3.1.7] and will be continued for all SOC and all PT.)
(Programming note: A similar table will be produced for Part 2 Treatment-Emergent Adverse Events, i.e., Table [14.3.2.2], IMP-related TEAEs, i.e., Table [14.3.2.5], AEs of Special Interest, i.e., Table [14.3.2.6] and SAEs, i.e., Table [14.3.2.7]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.3.1.3
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Severity
Summary Statistics: Safety Analysis Population
Part 1

	600 mg F15 (N=XX)					
System Organ Class Preferred Term	Mild (Grade 1) n(%)	Moderate (Grade 2) n(%)	Severe (Grade 3) n(%)	Life-threatening (Grade 4) n(%)	Death (Grade 5) n(%)	
Subjects reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts of number of subjects are by maximum severity, i.e., subjects experiencing more than 1 episode of a TEAE are counted only once within each SOC and PT using the most severe episode.
If severity is missing, then the 'Missing' column will be tabulated.
n is the number of subjects reporting at least 1 event.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments.)
(Programming note: A similar table will be produced for Part 2 Treatment-Emergent Adverse Events, i.e., Table [14.3.2.3]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.3.1.4
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to IMP
Summary Statistics: Safety Analysis Population
Part 1

	600 mg F15 (N=XX)		600 mg F16 (N=XX)		600 mg F06 (N=XX)	
System Organ Class Preferred Term	Yes n(%)	No n(%)	Yes n(%)	No n(%)	Yes n(%)	No n(%)
Subjects reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts of number of subjects are by closest relationship i.e., subjects experiencing more than 1 episode of a TEAE are counted only once within each SOC and PT using the most closely related event.
If relationship is missing, then the 'Missing' column will be tabulated.
"YES" = there is a plausible temporal relationship between the onset of the AE and the administration of the study drug.
"NO" = the AE has no plausible temporal relationship to the administration of the study drug
n is the number of subjects reporting at least 1 event.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 Treatment-Emergent Adverse Events, i.e., Table [14.3.2.4]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.4.1.1
Hematology and Coagulation
Summary Statistics: Safety Analysis Population
Part 1
<Parameter> (<units>) [ref range xxx - xxx (male)/ xxx - xxx (female)]

		Result						Change from Baseline					
Treatment	Time Point	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n
600 mg F15	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
600 mg F16	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
600 mg F06	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
BASELINE is defined as Day -1, Admission for each treatment period.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all parameters.)
(Programming note: A similar table will be produced for Serum Biochemistry, i.e., Table [14.4.1.3].)
(Programming note: A similar table will be produced for Part 2 Hematology and Coagulation, i.e., Table [14.4.2.1] and Serum Biochemistry, i.e., Table [14.4.2.3]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.4.1.2
Hematology and Coagulation
Shift Analysis: Safety Analysis Population
Part 1
<Parameter> (<units>)

Time Point Assessment	N#	600 mg F15 Baseline			600 mg F16 Baseline			600 mg F06 Baseline		
		Below n(%)	Within n(%)	Above n(%)	Below n(%)	Within n(%)	Above n(%)	Below n(%)	Within n(%)	Above n(%)
96 H	xx									
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
BASELINE is defined as Day -1, Admission for each treatment period.
N# is the total number of subjects in the relevant treatment and is used as the denominator for calculating the percentages of subjects, n indicates the number of subjects with a baseline and a post baseline assessment at the time point indicated. Below/within/above indicate the n (%) of subjects with assessments below/within/above the normal reference range.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all parameters.)
(Programming note: A similar table will be produced for Serum Biochemistry, i.e., Table [14.4.1.4].)
(Programming note: A similar table will be produced for Part 2 Hematology and Coagulation, i.e., Table [14.4.2.2] and Serum Biochemistry, i.e., Table [14.4.2.4]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.5.1.1
Vital Signs
Summary Statistics: Safety Analysis Population
Part 1
<Parameter> (<units>)

		Result						Change from Baseline						Substantial Change		
Treatment	Time Point	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n	DEC	NONE	INC
600 mg F15	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx									
(N=XX)	2 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	6 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	48 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
600 mg F16	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx									
(N=XX)	2 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	6 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	48 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
BASELINE is defined as Day 1, Pre-dose for each treatment period.
Substantial change is defined as: increase/decrease > ± 20 mmHg Systolic BP, > ± 10 mmHg Diastolic BP and > ± 15 bpm HR.
DEC: number of subjects with substantial decrease from baseline, NONE: number of subjects with no substantial change from baseline, INC: number of subjects with substantial increase from baseline.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments and all parameters.)
(Programming note: A similar table will be produced for Part 2 Vital Signs, i.e., Table [14.5.2.1]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state. The order of Vital Signs parameters is to be as per RAP Section [10.5.2].)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.5.1.2.1
ECGs
Summary Statistics: Safety Analysis Population
Part 1
<Parameter> (<units>)

Treatment	Time Point	Result						Change from Baseline					
		Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n
600 mg F15	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	2 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	6 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	48 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
600 mg F16	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	2 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	6 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	48 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
	96 H	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
BASELINE is defined as Day 1, Pre-dose for each treatment period.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments and all parameters.)
(Programming note: A similar table will be produced for Part 2 ECGs, i.e., Table [14.5.2.2.1]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state. The order of ECG parameters is to be as per RAP Section [10.6.2].)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.5.1.2.2
ECGs
QTcF Categorical Data
Summary Statistics: Safety Analysis Population
Part 1

			QTcF Interval				QTcF Interval Increase		
Treatment	Time Point	N#	<=450 msec n(%)	451-480 msec n(%)	481-500 msec n(%)	>500 msec n(%)	<30 msec n(%)	30-60 msec n(%)	>60 msec n(%)
600 mg F15 (N=XX)	BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
	2 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	6 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	48 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	96 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
600 mg F16 (N=XX)	BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
	2 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	6 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	48 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	96 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
BASELINE is defined as Day 1, Pre-dose for each treatment period.
Categories for QTcF interval and QTcF interval increases are based on ICH E14 guidelines.
N# is the total number of subjects in the relevant treatment and is used as the denominator for the percentages of subjects, n indicates the number of subjects with observations at the given time point.

PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all treatments.)
(Programming note: A similar table will be produced for Part 2 ECGs, i.e., Table [14.5.2.2.2]. Treatments will be 200 mg F06 coarse and 200 mg F06 fine and footnote will state: Each treatment comprised of a 200 mg oral of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

TABLE 14.5.1.3
Palatability Evaluations
Summary Statistics: Safety Analysis Population
<Palatability Question>
Part 1

Statistic	600 mg F15 (N=XX) n (%)	600 mg F16 (N=XX) n (%)	600 mg F06 (N=XX) n (%)
Mean	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
Min	xx	xx	xx
Max	xx	xx	xx
n	xx	xx	xx

Note: The data in this table are presented in listing x.x
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Acceptability and each palatability attribute will be scored using 0 mm = "I did not like it" through to 100 mm = "I liked it very much".

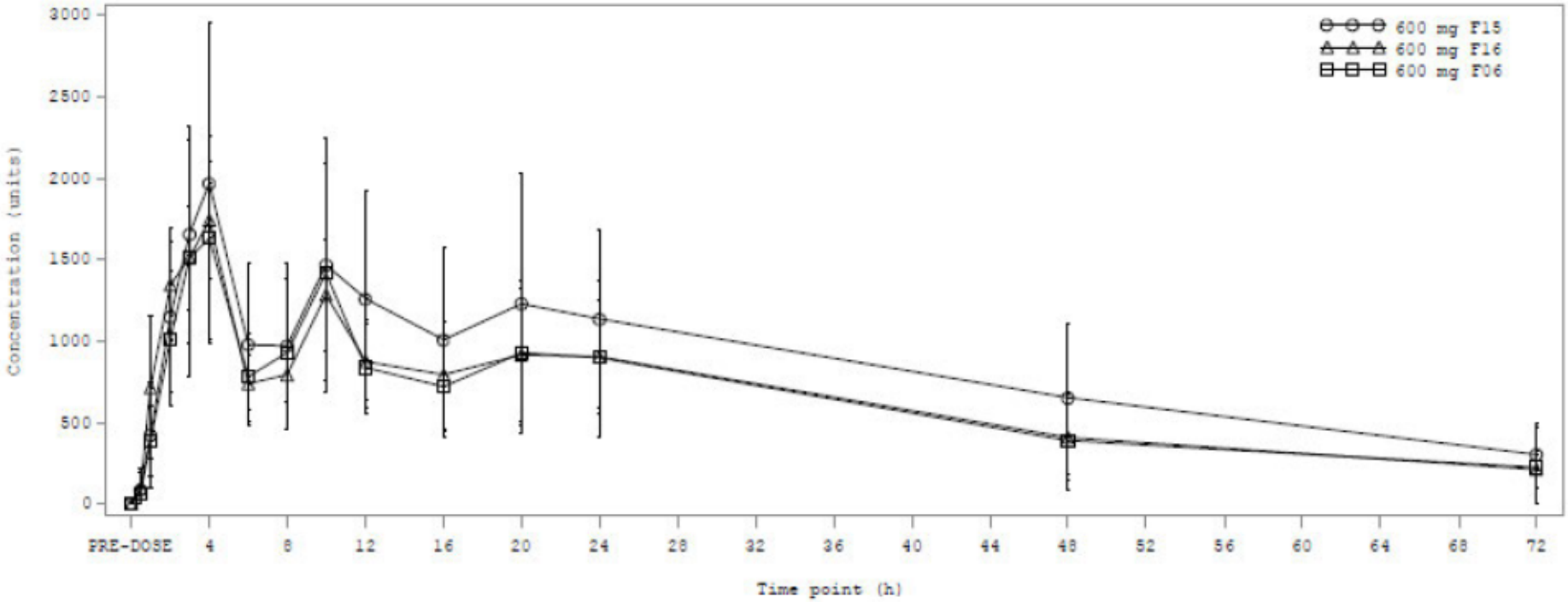
PROGRAM PATH: X:\~\QSC201525\\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A separate page will be used for each palatability question with the relevant subheading. Footnote on scoring will require to be updated based on question from questionnaire.)

22 Mock Figures

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.1.1
Plasma Pharmacokinetic Concentrations: Entrectinib
Linear/Linear Scale
Arithmetic Mean (± Arithmetic SD) Values: PK Population
Part 1



Note: Data in the above graph are presented in listing 16.2.5.1.4
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Concentration values reported as BLQ have been set to 0 (LLOQ = XX units).

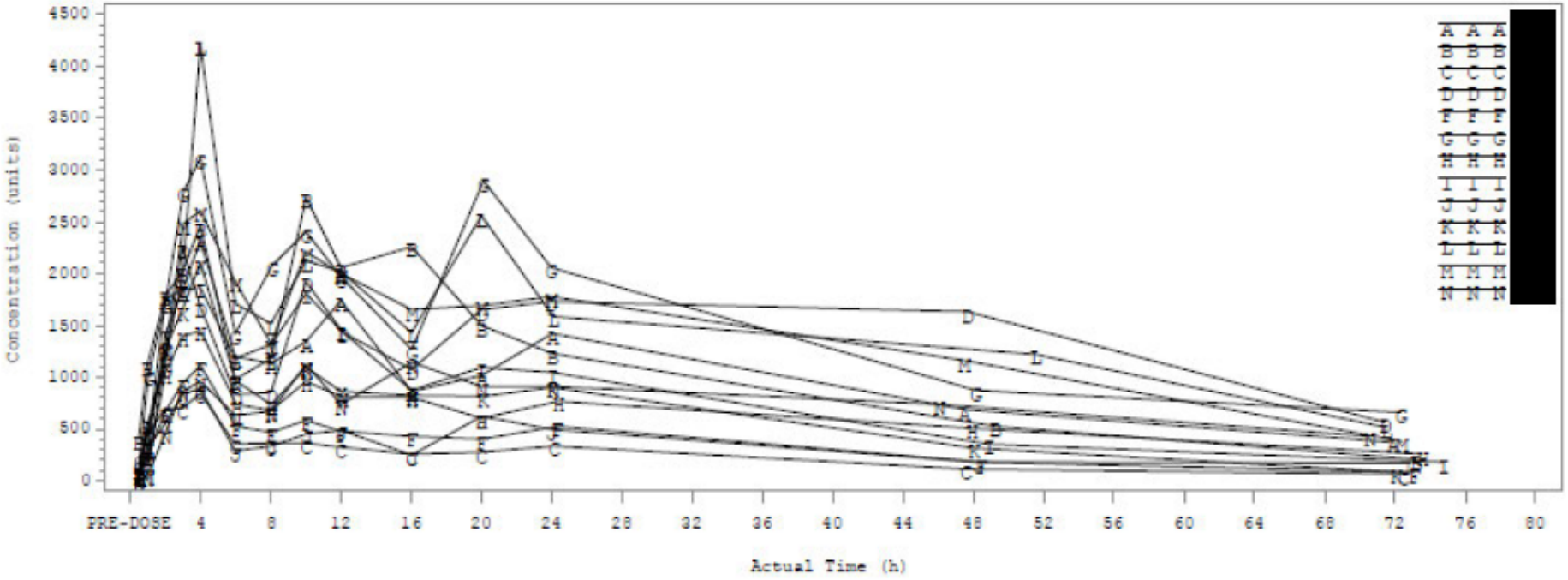
PROGRAM PATH: X:\~\QCL118151\~\TFLS\PRODUCTION\FIG_MEAN1

DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1.1.2], [14.2.1.1.3], [14.2.2.1.1], [14.2.2.1.2] and [14.2.2.1.3]. Part 2 footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.1.4
Plasma Pharmacokinetic Concentrations: Entrectinib
Linear/Linear Scale
Spaghetti Plots of All Individual Values: PK Population
600 mg F15
Part 1



Note: Data in the above graph are presented in listing 16.2.5.1.4
600 mg F15: Entrectinib film-coated mini-tablets, (Ro 710 2122/F15), in the fed state. Concentration values reported as BLQ have been set to 0 (LLOQ = XX units).

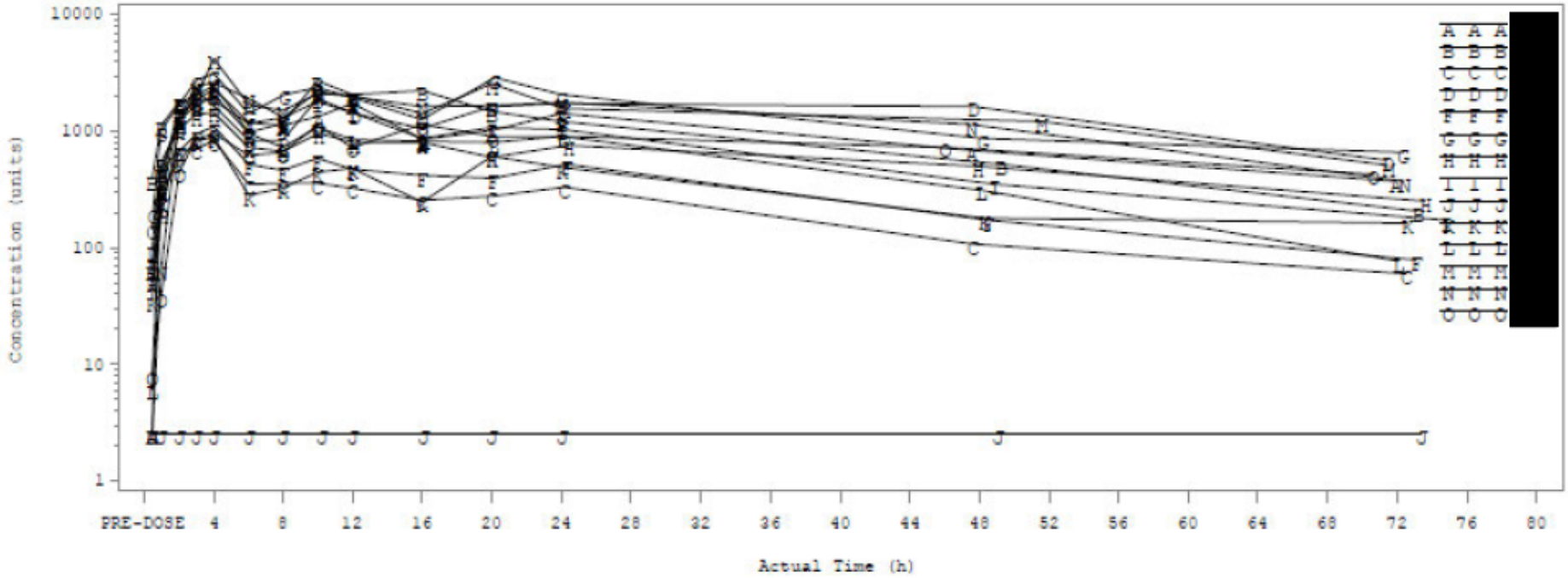
PROGRAM PATH: X:\~\QSC201525\~\TFLS\PRODUCTION\FIG_SPAG

DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1. 1. 5], [14.2.2.1.4] and [14.2.2.1.5]. Part 2 footnote will state:
200 mg F06 coarse: Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules, in the fasted state. Figures for all other treatments will be produced on separate pages.

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.1.6
Plasma Pharmacokinetic Concentrations: Entrectinib
Log10/Linear Scale
Spaghetti Plots of All Individual Values: PK Population
600 mg F15
Part 1



Note: Data in the above graph are presented in listing 16.2.5.1.4
600 mg F15: Entrectinib film-coated mini-tablets, (Ro 710 2122/F15), in the fed state.
Concentration values reported as BLQ have been set to missing.

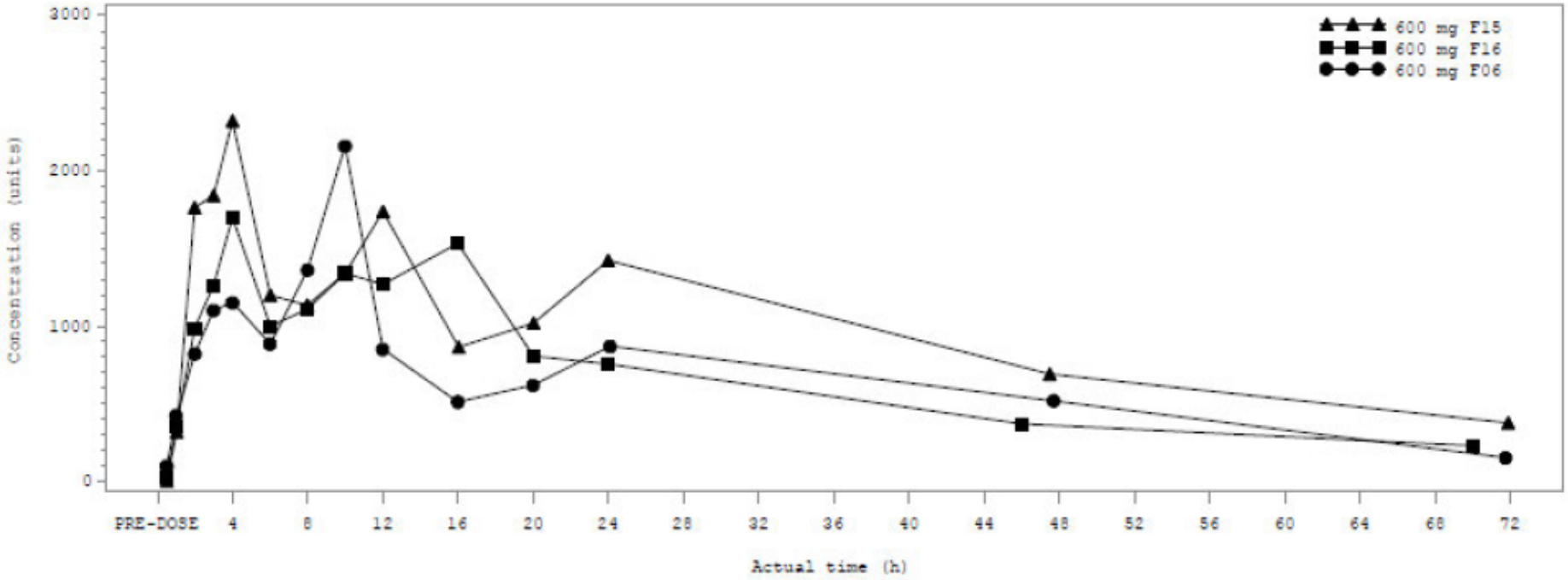
PROGRAM PATH: X:\~\QSC201525\~\TFLS\PRODUCTION\FIG_SPAG

DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1.1 .7], [14.2.2.1.6] and [14.2.2.1.7]. Part 2 footnote will state:
200 mg F06 coarse: Entrectinib F06 hydroxypropyl methylcellulose (HPMC) capsules, in the fasted state. Figures for all other treatments will be produced on separate pages.

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.1.8
Plasma Pharmacokinetic Concentrations: Entrectinib
Linear/Linear Scale
Individual Values for Subject [redacted]: PK Population
Part 1



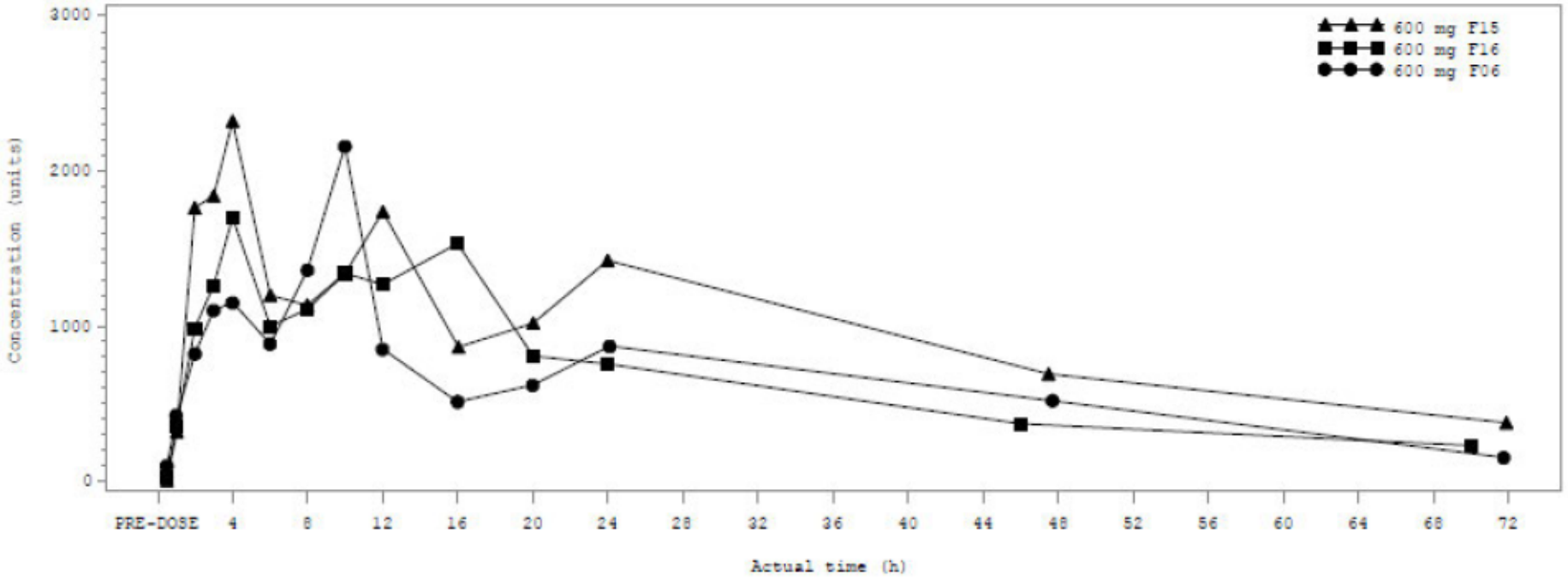
Note: Data in the above graph are presented in listing 16.2.5.1.4
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Concentration values reported as BLQ have been set to 0 (LLOQ = XX units).

PROGRAM PATH: X:\~\QSC201525\~\TFLS\PRODUCTION\FIG_INDIV DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1.1. 9], [14.2.1.1.10], [14.2.2.1.8], [14.2.2.1.9] and [14.2.2.1.10]. Part 2 footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state. Figures for all other subjects will be produced on separate pages.

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.1.11
Plasma Pharmacokinetic Concentrations: Entrectinib
Log10/Linear Scale
Individual Values for Subject [redacted]: PK Population
Part 1



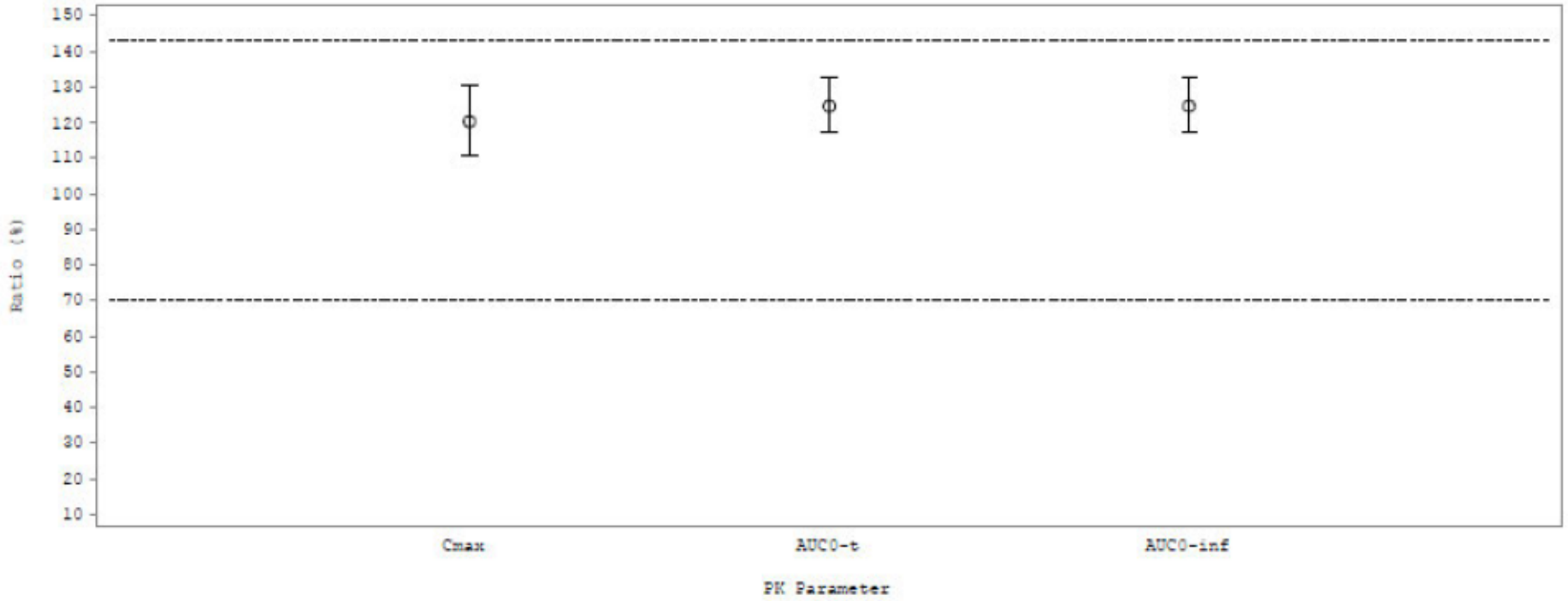
Note: Data in the above graph are presented in listing 16.2.5.1.4
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Concentration values reported as BLQ have been set to missing.

PROGRAM PATH: X:\~\QSC201525\~\TFLS\PRODUCTION\FIG_INDIV DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1.1. 12], [14.2.1.1.13], [14.2.2.1.11], [14.2.2.1.12] and [14.2.2.1.13]. Part 2 footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.
Figures for all other subjects will be produced on separate pages.

Genentech, Inc.
Protocol: GP41341

FIGURE 14.2.1.2.1
Plasma Pharmacokinetic Parameters: Entrectinib
Statistical Analysis Results - Assessment of Relative Bioavailability: PK Population
Adjusted Geometric Mean Ratio + 90% CIs
600 mg F15 vs 600 mg F06
Part 1



Note: Data in the above graph are presented in listing 16.2.6.1.1
Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Dashed lines represent illustrative lower and upper limits, i.e. 80.00% and 125.00%, respectively.

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\FIG_MEAN1 DDMMMYYYY HH:MM

Programming note: Similar figures will be produced for Figure [14.2.1.2.2], [14.2.2.2.1] and [14.2.2.2.2]. Footnote will state:
Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.

23 Mock Listings

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.1.1
Subject Informed Consent and Completion/Withdrawal
Individual Values: All Randomized Subjects
Part 1

		Informed Consent					
Subject ID	Sex/ Age	Date Signed	Time Signed	Version Number	Did Subject Complete Study?	Completion/ Withdrawal Date	Reason for Withdrawal
XXX	[redacted]	DDMMMYYYY	HH:MM	XX	YES	DDMMMYYYY	
XXX		DDMMMYYYY	HH:MM	XX	NO	DDMMMYYYY	XXXX
XXX		DDMMMYYYY	HH:MM	XX	YES	DDMMMYYYY	
…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: If no subjects withdraw, then 'Withdrawal Date' and 'Reason for Withdrawal' will not be presented.)
(Programming note: A similar listing will be produced for Part 2 Subject Informed Consent and Completion/Withdrawal, i.e., Listing [16.2.1.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.2.1.1
Protocol Deviations
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Time Point	Deviation Date	Deviation Category/ Description of Deviation	Impact Assessment/ Impact Comment
XXX	[redacted]	SCREENING		DDMMMYYYY	XXXX/XXXX	XXXX/XXXX
XXX		DAY -1	ADMISSION	DDMMMYYYY	XXXX/XXXX	XXXX/XXXX
XXX		DAY 1	3 H	DDMMMYYYY	XXXX/XXXX	XXXX/XXXX
…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: 'Impact Assessment' will not be presented if Impact of Deviation is assessed as Minor.)
(Programming note: A similar listing will be produced for Part 2 Protocol Deviations, i.e., Listing [16.2.2.2.1]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.2.1.2
Inclusion/Exclusion Criteria
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	All of Inclusion and None of Exclusion Criteria?	Criteria Not Met	Criteria Description
XXX	[redacted]	YES	INCLUSION	XXXX
XXX		YES	INCLUSION	XXXX
XXX		NO	EXCLUSION	XXXX
…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: If all subjects met the inclusion/exclusion criteria, then a listing that states "ALL SUBJECTS MET ELIGIBILITY CRITERIA" will be produced.)
(Programming note: A similar listing will be produced for Part 2 Inclusion/Exclusion Criteria, i.e., Listing [16.2.2.2.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.3.1.1
Analysis Populations and Reasons for Exclusion
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Population	Included in Population	Reason for Exclusion from Population
XXX	[redacted]	SAFETY	YES	
		PK	YES	
XXX		SAFETY	YES	
		PK	YES	
XXX		SAFETY	NO	XXXX
		PK	NO	XXXX
…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Analysis Datasets and Reasons for Exclusion, i.e., Listing [16.2.3.1.2]. If analysis datasets are not required, then this listing will be re-numbered to [16.2.3.1] and the listing Analysis Datasets and Reasons for Exclusion [16.2.3.1.2] will not be produced.)
(Programming note: A similar listing will be produced for Part 2 Analysis Populations and Reasons for Exclusion, i.e., Listing [16.2.3.2.1]. If analysis datasets are not required, then this listing will be re-numbered from Listing [16.2.3.2.1] to Listing [16.2.3.2] and the listing Analysis Datasets and Reasons for Exclusion [16.2.3.2.2] will not be produced. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.4.1.1
Demographic and Baseline Characteristics
Individual Values: All Randomized Subjects
Part 1

Subject ID	Screening Date	Date of Birth	Age (years)	Ethnicity	Race	Sex	Height (m)	Weight (kg)	BMI (kg/m²)
XXX	DDMMMYYYY	DDMMMYYYY	XX	XXXX	XXXX	[redacted]	XXX.X	XX.X	XX.X
XXX	DDMMMYYYY	DDMMMYYYY	XX	XXXX	XXXX		XXX.X	XX.X	XX.X
XXX	DDMMMYYYY	DDMMMYYYY	XX	XXXX	XXXX		XXX.X	XX.X	XX.X
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Age (years) = (Date of first dose of IMP - date of birth)/365.25, rounded down to the nearest year.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: If any values are missing, then a "missing" row will be presented.)
(Programming note: Other race will be added, where required.)
(Programming note: A similar listing will be produced for Part 2 Demographic and Baseline Characteristics, i.e., Listing [16.2.4.2.1].
Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.4.1.2
Lifestyle Details: Smoking History and Alcohol Consumption
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Does Subject Smoke?	Date Stopped	Does Subject Drink Alcohol?	Units per Week
XXX	[redacted]	PREVIOUSLY	DDMMMYYYY	YES	XX
XXX		NO		YES	XX
XXX		NO		YES	XX
…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Anyone who smoked or used e-cigarettes or nicotine replacement products in the last 12 months is excluded from the study. Anyone who regularly consumes alcohol (> 21 units per week in males and > 14 units per week in females) is excluded from the study. (1 unit = 1/2 pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type.)

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Part 2 Lifestyle Details: Smoking History and Alcohol Consumption, i.e., Listing [16.2.4.2.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.4.1.3
Medical/Surgical History
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Sequence	Category/ Description	System Organ Class/ Preferred Term/ Lower Level Term	Date of Onset/ Date of Resolution
XXX	[redacted]	T1T2R	NEUROLOGICAL	INFECTIONS AND INFESTATIONS/ MENINGITIS VIRAL/ MENINGITIS VIRAL	DDMMMYYYY
XXX		RT1T2	REPRODUCTIVE	SURGICAL AND MEDICAL PROCEDURES/ FEMALE STERILISATION/ TUBAL LIGATION	DDMMMYYYY
…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Part 2 Medical/Surgical History, i.e., Listing [16.2.4.2.3]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.4.1.4
Prior and Concomitant Medication
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	M: Medication PT: Preferred Name ATC2: ATC Level 2 ATC4: ATC Level 4 I: Indication	R: Route D: Dosage U: Units FRQ: Frequency AE No: AE Number	S: Start E: End O: Ongoing
XXX	[redacted]	M: XXXXXXXXXXX PT: XXXXXXXXXXX ATC2: XXXXXXXXXX ATC4: XXXXXXXX I: XXXXXXXX	R: XX D: XXX U: XX FRQ: XXXXX XXXXX AE No: X	S: DDMMMYYYY HH:MM E: DDMMMYYYY HH:MM O: NO
…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Medications are coded using the WHODrug Dictionary Global Drug Reference: Q1 2019 version (or most recent version).
Prior medications that start and stop prior to the first dose of IMP are flagged with a "#" symbol. Within this flagged group, medications that started after screening and stopped before dosing of IMP will also be flagged using a "*" symbol.
ATC = Anatomical Therapeutic Classification.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: If no medications will be required from 14 days before IMP administration until discharge, then a listing that states "NO SUBJECTS REPORTED ANY PRIOR AND/OR CONCOMITANT MEDICATION" will be produced.)
(Programming note: A similar listing will be produced for Part 2 Prior and Concomitant Medication, i.e., Listing [16.2.4.2.4]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.4.1.5
Urine Drug Screen
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Sample Date	Sample Time	Parameter 1	Parameter 2		All Urine Drug Parameters
XXX	[redacted]	SCREENING	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
		DAY -1	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
XXX		SCREENING	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
		DAY -1	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
XXX		SCREENING	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
		DAY -1	DDMMMYYYY	HH:MM	XXXX	XXXX	…	XXXX
…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all parameters and subjects.)
(Programming note: A similar listing will be produced for Part 2 Urine Drug Screen, i.e., Listing [16.2.4.2.5]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

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Protocol: GP41341

LISTING 16.2.4.1.6
Alcohol and Carbon Monoxide Breath Test
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Sample Date	Sample Time	Alcohol Breath Test	Carbon Monoxide Test (ppm)
XXX	[redacted]	SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	XX
		DAY -1	DDMMMYYYY	HH:MM	NEGATIVE	XX
XXX		SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	XX
		DAY -1	DDMMMYYYY	HH:MM	NEGATIVE	XX
XXX		SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	XX
		DAY -1	DDMMMYYYY	HH:MM	NEGATIVE	XX
…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Part 2 Alcohol Breath and Carbon Monoxide Test, i.e., Listing [16.2.4.2.6]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.4.1.7
Virology
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Sample		HIV	Hepatitis B Surface Antigen (HBsAg)	Anti-HCV
			Date	Time			
XXX	[redacted]	SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	NEGATIVE	NEGATIVE
XXX		SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	NEGATIVE	NEGATIVE
XXX		SCREENING	DDMMMYYYY	HH:MM	NEGATIVE	NEGATIVE	NEGATIVE
…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Part 2 Virology, i.e., Listing [16.2.4.2.7]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.4.1.8
Urine/Serum Pregnancy Test
Individual Values: All Female Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Sample Date	Sample Time	Serum Pregnancy Test	Urine Pregnancy Test
XXX	F/[redacted]		SCREENING			DDMMMYYYY	HH:MM	NEGATIVE	
		PERIOD 1	DAY -1	ADMISSION	600 mg F15	DDMMMYYYY	HH:MM		NEGATIVE
			DAY 5	96 H		DDMMMYYYY	HH:MM		NEGATIVE
		PERIOD 2	DAY -1	ADMISSION	600 mg F16	DDMMMYYYY	HH:MM		NEGATIVE
			DAY 5	96 H		DDMMMYYYY	HH:MM		NEGATIVE
		PERIOD 3	DAY -1	ADMISSION	600 mg F06	DDMMMYYYY	HH:MM		NEGATIVE
			DAY 5	96 H		DDMMMYYYY	HH:MM		NEGATIVE
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all female subjects.)
(Programming note: A similar listing will be produced for Part 2 Urine/Serum Pregnancy Test, i.e., Listing [16.2.4.2.8]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

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Protocol: GP41341

LISTING 16.2.4.1.9
Follicle Stimulating Hormone
Individual Values: All Post-Menopausal Female Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Sample		Follicle Stimulating Hormone (IU/L)
			Date	Time	
XXX	F/[redacted]	SCREENING	DDMMMYYYY	HH:MM	XX.X
XXX	F/[redacted]	SCREENING	DDMMMYYYY	HH:MM	XX.X
XXX	F/[redacted]	SCREENING	DDMMMYYYY	HH:MM	XX.X
…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all post-menopausal female subjects.)
(Programming note: A similar listing will be produced for Part 2 Follicle Stimulating Hormone, i.e., Listing [16.2.4.2.9]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

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Protocol: GP41341

LISTING 16.2.5.1.1
Dosing Details
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Treatment	Dosing Date	Dosing Start Time	Dosing End Time	Dose Route	Dose Form	Dose Frequency
XXX	[redacted]	PERIOD 1	600 mg F15	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
		PERIOD 2	600 mg F16	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
		PERIOD 3	600 mg F06	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
XXX		PERIOD 1	600 mg F06	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
		PERIOD 2	600 mg F15	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
		PERIOD 3	600 mg F16	DDMMMYYYY	HH:MM	HH:MM	XXXX	XXXX	XXXX
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: This listing will include extent of exposure details.)
(Programming note: A similar listing will be produced for Part 2 Dosing Details, i.e., Listing [16.2.5.2.1]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.5.1.2
Meal Details
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Meal Description	Meal Date	Meal Start Time	Meal End Time	Comments
XXX	[redacted]	PERIOD 1	XXXX	XXXX	DDMMMYYYY	HH:MM	HH:MM	XXXX XXXX
…	…	…	…	…	…	…	…	…
XXX		PERIOD 1	XXXX	XXXX	DDMMMYYYY	HH:MM	HH:MM	XXXX XXXX
…	…	…	…	…	…	…	…	…
XXX		PERIOD 1	XXXX	XXXX	DDMMMYYYY	HH:MM	HH:MM	XXXX XXXX
…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all periods and subjects.)
(Programming note: A similar listing will be produced for Part 2 Meal Details, i.e., Listing [16.2.5.2.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.5.1.3
Blood Sample Collection Details and Concentrations for Pharmacokinetic Analysis
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Treatment	Study Visit	Time Point	Sample Date	Sample Time	Entrectinib (units)	M5 (units)
XXX	[redacted]	PERIOD 1	600 mg F15	DAY 1	PRE-DOSE	DDMMMYYYY	HH:MM	XX.XX	XX.XX
					0.5 H	DDMMMYYYY	HH:MM	XX.XX	XX.XX
					1 H	DDMMMYYYY	HH:MM	XX.XX	XX.XX
				…	…	…	…	…	…
		PERIOD 2	600 mg F16	DAY 1	PRE-DOSE	DDMMMYYYY	HH:MM	XX.XX	XX.XX
					0.5 H	DDMMMYYYY	HH:MM	XX.XX	XX.XX
					1 H	DDMMMYYYY	HH:MM	XX.XX	XX.XX
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods, treatments and time points.)
(Programming note: A similar listing will be produced for Part 2 Blood Sample Collection Details and Concentrations for Pharmacokinetic Analysis, i.e., Listing [16.2.5.2.3]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state..)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.6.1.1
Plasma Pharmacokinetic Parameters: Entrectinib
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Treatment	PK Parameter 1 (units)		All PK Parameters
XXX	[redacted]	PERIOD 1	600 mg F15	XXXX	…	XXXX
		PERIOD 2	600 mg F16	XXXX	…	XXXX
		PERIOD 3	600 mg F06	XXXX	…	XXXX
XXX		PERIOD 1	600 mg F06	XXXX	…	XXXX
		PERIOD 2	600 mg F15	XXXX	…	XXXX
		PERIOD 3	600 mg F16	XXXX	…	XXXX
…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Flags: a = Rsq of regression was <0.9, b = Period used for regression analysis was less than 2-fold the calculated half-life, c = Extrapolated portion of AUC(0-inf)>20%, d = Insufficient post-Cmax data points for estimation of lambda-z, e = Entire profile BLQ, no PK parameters could be calculated.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all parameters and subjects.)
(Programming note: A similar listing will be produced for Plasma Pharmacokinetic Parameters: M5, i.e., Listing [16.2.6.1.2].)
(Programming note: Similar listings will be produced for Part 2 Plasma Pharmacokinetic Parameters: Entrectinib, i.e., Listing [16.2.6.2.1] and for Part 2 Plasma Pharmacokinetic Parameters: M5, i.e., Listing [16.2.6.2.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

Page x of y

LISTING 16.2.7.1.1
Pre-dose Adverse Events
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Treatment	AE No	System Organ Class/ Preferred Term/ Reported Term/ Nature of Event/ Comment	Onset Date Time/ End Date Time/ Outcome	Serious/ Severity/ Relationship/ Cause if Not Related	Action Taken
XXX	[redacted]	PERIOD 1	600 mg F15	XX	GASTROINTESTINAL DISORDERS/ ABDOMINAL PAIN/ ABDOMINAL ACHE (MILD)/ NO NAUSEA SLIGHT PAIN IN UPPER ABDOMEN	DDMMMYYYY HH: MM/ DDMMMYYYY HH: MM/ RECOVERED/RESOLVED	NO/ MILD/ NOT RELATED/ HEADACHE	N/A
…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
AEs are coded using MedDRA vXX.X

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods and treatments.)
(Programming note: A similar listing will be produced for All Treatment-Emergent Adverse Events, i.e., Listing [16.2.7.1.2], AEs of Special Interest, i.e., Listing [16.2.7.1.3] and SAEs, i.e., Listing [16.2.7.1.4]. If no subjects experienced any pre-dose adverse events, then a listing that states "NO SUBJECTS REPORTED ANY PRE-DOSE ADVERSE EVENTS" will be produced. If no subjects experienced any TEAEs, then Listing [16.2.7.1.2] will state "NO SUBJECTS REPORTED ANY TREATMENT-EMERGENT ADVERSE EVENTS". If no subjects experienced any AEs of Special Interest, then Listing [16.2.7.1.3] will state "NO SUBJECTS REPORTED ANY ADVERSE EVENTS OF . SPECIAL INTEREST". If no subjects experienced any SAEs, then Listing [16.2.7.1.4] will state "NO SUBJECTS REPORTED ANY SERIOUS ADVERSE EVENTS".)
(Programming note: Similar listings will be produced for Part 2 Pre-dose Adverse Events, i.e., Listing [16.2.7.2.1], All TEAEs, i.e., Listing [16.2.7.2.2], AEs of Special Interest, i.e., Listing [16.2.7.2.3] and SAEs, i.e., Listing [16.2.7.2.4]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.8.1.1.1
Blood Sample Collection Details for Laboratory Analysis
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Treatment	Study Visit	Time Point	Sample Date	Sample Time	Samples Obtained
XXX	[redacted]	PERIOD 1	600 mg F15	DAY 1	PRE-DOSE	DDMMMYYYY	HH:MM	ABC
					0.5 H	DDMMMYYYY	HH:MM	AB
					1 H	DDMMMYYYY	HH:MM	AB
				…	…	…	…	…
		PERIOD 2	600 mg F16	DAY 1	PRE-DOSE	DDMMMYYYY	HH:MM	ABC
					0.5 H	DDMMMYYYY	HH:MM	A
					1 H	DDMMMYYYY	HH:MM	A
…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
"#" indicates sample outside of scheduled time window.
Sample Obtained: A = Serum Biochemistry, B = Hematology and Coagulation, C = Virology.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods, treatments and time points.)
(Programming note: A similar listing will be produced for Part 2 Blood Sample Collection Details for Laboratory Analysis, i.e., Listing [16.2.8.2.1.1]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.8.1.1.2
Blood Sample Collection Comments
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Time Point	Sample Date	Sample Time	Parameter	Comments
XXX	[redacted]	PRE-DOSE	DDMMMYYYY	HH:MM	XXX	XXXX XXXX
		0.5 H	DDMMMYYYY	HH:MM	XXX	XXXX XXXX
		…	…	…	…	…
XXX		PRE-DOSE	DDMMMYYYY	HH:MM	XXX	XXXX XXXX
		0.5 H	DDMMMYYYY	HH:MM	XXX	XXXX XXXX
…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
"#" indicates sample outside of scheduled time window.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all time points and subjects.)
(Programming note: A similar listing will be produced for Part 2 Blood Sample Collection Comments, i.e., Listing [16.2.8.2.1.2].
Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.8.1.2
Hematology and Coagulation
Individual Values: All Randomized Subjects
Part 1

						Sample		Parameter (Reference Range)	
Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Date	Time	Value (units)	Change (units)
XXX	[redacted]		SCREENING			DDMMMYYYY	HH:MM	XX.X	
		PERIOD 1	DAY -1	ADMISSION	600 mg F15	DDMMMYYYY	HH:MM	XX.X H	
			DAY 5	96 H		DDMMMYYYY	HH:MM	XX.X L	XX.X
		PERIOD 2	DAY -1	ADMISSION	600 mg F16	DDMMMYYYY	HH:MM	XX.X H	
			DAY 5	96 H		DDMMMYYYY	HH:MM	XX.X L	XX.X
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
H = Higher than normal reference range, L = Lower than normal reference range.
"#" indicates sample outside of scheduled time window.
Change is defined as change from baseline and baseline is defined as Day -1, Admission.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods, treatments and parameters.)
(Programming note: Similar listings will be produced for Serum Biochemistry, i.e., Listing [16.2.8.1.4] and Urinalysis, i.e., Listing [16.2.8.1.7].)
(Programming note: Similar listings will be produced for Part 2 Hematology and Coagulation, i.e., Listing [16.2.8.2.2], Serum Biochemistry, i.e., Listing [16.2.8.2.4] and Urinalysis, i.e., Listing [16.2.8.2.7]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.8.1.3
Hematology and Coagulation
Individual Values Outside the Reference Range: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Sample Date	Sample Time	Parameter (units)	Result	Reference Range (units)
XXX	[redacted]		SCREENING			DDMMMYYYY	HH:MM	XXXX	XX.X H	XX - XX
		PERIOD 1	DAY -1	ADMISSION	600 mg F15	DDMMMYYYY	HH:MM	XXXX	XX.X L	XX - XX
			DAY 5	96 H		DDMMMYYYY	HH:MM	XXXX	XX.X H	XX - XX
		PERIOD 2	DAY -1	ADMISSION	600 mg F16	DDMMMYYYY	HH:MM	XXXX	XX.X H	XX - XX
			DAY 5	96 H		DDMMMYYYY	HH:MM	XXXX	XX.X H	XX - XX
…	…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
H = Higher than normal reference range, L = Lower than normal reference range.
"#" indicates sample outside of scheduled time window.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods and treatments.)
(Programming note: Similar listings will be produced for Serum Biochemistry, i.e., Listing [16.2.8.1.5] and Urinalysis, i.e., Listing [16.2.8.1.8].)
(Programming note: Similar listings will be produced for Part 2 Hematology and Coagulation, i.e., Listing [16.2.8.2.3], Serum Biochemistry, i.e., Listing [16.2.8.2.5] and Urinalysis, i.e., Listing [16.2.8.2.8]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.8.1.6
Urinalysis Sample Collection
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Sample Date	Sample Time	Samples Obtained	Comments
XXX	[redacted]		SCREENING			DDMMMYYYY	HH:MM	EF	XXXX XXX
		PERIOD 1	DAY -1	ADMISSION	600 mg F15	DDMMMYYYY	HH:MM	E	XXXX XXX
			DAY 5	96 H		DDMMMYYYY	HH:MM	F	XXXX XXX
		PERIOD 2	DAY -1	ADMISSION	600 mg F16	DDMMMYYYY	HH:MM	F	XXXX XXX
			DAY 5	96 H		DDMMMYYYY	HH:MM	EF	XXXX XXX
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Sample Obtained: E = Urine Drug Screen, F = Urinalysis.
"#" indicates sample outside of scheduled collection period.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods and treatments.)
(Programming note: A similar listing will be produced for Part 2 Urinalysis Sample Collection, i.e., Listing [16.2.8.2.6].
Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

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Protocol: GP41341

LISTING 16.2.9.1.1.1
Vital Signs
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Reading Date	Reading Time	Parameter Value (units)	Parameter Change (units)
XXX	[redacted]		SCREENING			DDMMMYYYY	HH:MM	XXX	
		PERIOD 1	DAY 1	PRE-DOSE	600 mg F15	DDMMMYYYY	HH:MM	XXX H	
				2 H		DDMMMYYYY	HH:MM	XXX	XXX
				6 H		DDMMMYYYY	HH:MM	XXX	XXX
			DAY 3	48 H		DDMMMYYYY	HH:MM	XXX	XXX
			DAY 5	96 H		DDMMMYYYY	HH:MM	XXX	XXX
		PERIOD 2	DAY 1	PRE-DOSE	600 mg F16	DDMMMYYYY	HH:MM	XXX	XXX
				2 H		DDMMMYYYY	HH:MM	XXX	XXX
…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
H = Higher than normal reference range, L = Lower than normal reference range.
Reference Ranges: Parameter 1 xx - xx <(units)> (xx-xx years), yy - yy <(units)> (yy-yy years),
Parameter 2 xx - xx <(units)>, Parameter 3 xx - xx <(units)> (xx-xx years), yy - yy <(units)> (yy-yy years).
Substantial change defined as increases/decreases from baseline: Parameter 1 ± >xx <units>,
Parameter 2 ± >xx <units>, Parameter 3 ± >xx <units>.
Baseline is defined as Day 1, Pre-dose for each treatment period.
"#" indicates sample outside of scheduled time window.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods, treatments, parameters and time points.)
(Programming note: The order of Vital Signs parameters is to be as per RAP Section [10.5.2]. This listing will be continued for all time points and subjects. A similar listing will be produced for ECGs, i.e., Listing [16.2.9.1.2.1]. The order of ECG parameters is to be as per RAP Section [10.6.2].)
(Programming note: Similar listings will be produced for Part 2 Vital Signs, i.e., Listing [16.2.9.2.1.1] and ECGs, i.e., Listing [16.2.9.2.2.1]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

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LISTING 16.2.9.1.1.2
Vital Signs
Individual Values Outside the Reference Range: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Reading Date	Reading Time	Parameter (units)	Result	Reference Range
XXX	[redacted]		SCREENING			DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
		PERIOD 1	DAY 1	PRE-DOSE	600 mg F15	DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
				2 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
				6 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
			DAY 3	48 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
			DAY 5	96 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
		PERIOD 2	DAY 1	PRE-DOSE	600 mg F16	DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
				2 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
				6 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
			DAY 3	48 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
			DAY 5	96 H		DDMMMYYYY	HH:MM	XXXX	XXXX	XX - XX
…	…	…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
H = Higher than normal reference range, L = Lower than normal reference range.
Listing contains all data outside the normal reference range for all vital signs parameters at the relevant time points.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects, periods, treatments and parameters.)
(Programming note: The order of Vital Signs parameters is to be as per RAP Section [10.5.2]. This listing will be continued for all time points and subjects. A similar listing will be produced for ECGs, i.e., Listing [16.2.9.1.2.2]. The order of ECG parameters is to be as per RAP Section [10.6.2].)
(Programming note: This listing will be continued for all data outside the reference range, for all relevant vital sign parameters and for all time points, as applicable. If no values were recorded outside of the reference range, then a listing that states "NO VALUES OUTSIDE THE REFERENCE RANGE WERE RECORDED" will be produced.)
(Programming note: Similar listings will be produced for Part 2 Vital Signs, i.e., Listing [16.2.9.2.1.2] and ECGs, i.e., Listing [16.2.9.2.2.2]. Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc.
Protocol: GP41341

LISTING 16.2.9.1.3
Physical Examinations
Individual Values: All Randomized Subjects
Part 1

Subject ID	Sex/ Age	Study Visit	Physical Examination Date	Physical Examination Performed	Body System	Any Clinically Significant Findings
XXX	[redacted]	SCREENING	DDMMMYYYY	XXX	ALL	XXX
		DAY -1	DDMMMYYYY	XXX	MUSCULOSKELETAL	XXX
…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: A similar listing will be produced for Part 2 Physical Examination Data, i.e., Listing [16.2.9.2.3].
Footnote will state: Each treatment comprised of a 200 mg oral dose of entrectinib administered in the fasted state.)

Genentech, Inc. Page x of y
Protocol: GP41341

LISTING 16.2.9.1.4
Palatability Evaluations
Individual Values: All Randomized Subjects
<Palatability Question>
Part 1

Subject ID	Sex/ Age	Period	Study Visit	Time Point	Treatment	Palatability Test		
						Date	Time	VAS Score
XXX	[redacted]	PERIOD 1	DAY 1	0.5 H	600 mg F15	DDMMMYYYY	HH:MM	XX
		PERIOD 2	DAY 1	0.5 H	600 mg F16	DDMMMYYYY	HH:MM	XX
XXX		PERIOD 1	DAY 1	0.5 H	600 mg F15	DDMMMYYYY	HH:MM	XX
		PERIOD 3	DAY 1	0.5 H	600 mg F16	DDMMMYYYY	HH:MM	XX
XXX		PERIOD 2	DAY 1	0.5 H	600 mg F16	DDMMMYYYY	HH:MM	XX
		PERIOD 3	DAY 1	0.5 H	600 mg F15	DDMMMYYYY	HH:MM	XX
…	…	…	…	…	…	…	…	…

Note: Each treatment comprised of a 600 mg oral dose of entrectinib administered in the fed state.
Acceptability and each palatability attribute will be scored using 0 mm = "I did not like it" through to 100 mm = "I liked it very much".

PROGRAM PATH: X:\Studies-Operations\201551-201750\QSC201525\~\TFLS\PRODUCTION\LIS_XX DDMMMYYYY HH:MM

(Programming note: This listing will be continued for all subjects.)
(Programming note: For palatability questions which are not on a VAS scale, the subject s response/comment will be listed.)
(Programming note: Footnote on scoring will require to be updated based on question from questionnaire.)

Appendix 1: Schedule of activities

Study Day	-28 to -2	-1	1											2		3	4	5	13 to 15
			Times After Dosing (h)																Follow-Up call[a]
	Screening	Admission	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 drug administration				X															
Blood Sampling for entrectinib and M5 PK[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 PK Samples

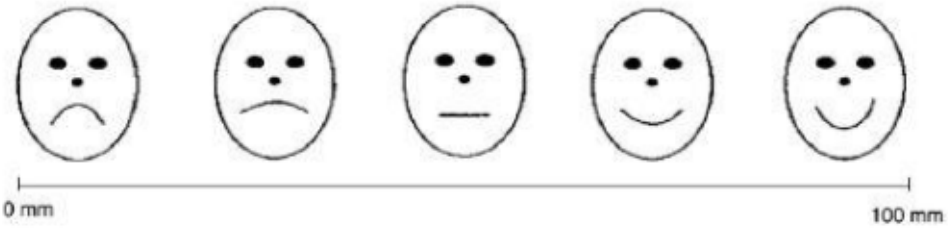
Visit[a]	Time point[a]	Sample Type
Day 1	Predose - 0.5 h	Entrectinib and M5 PK (plasma)
	0.5 h post-dose	Entrectinib and M5 PK (plasma)
	1.0	Entrectinib and M5 PK (plasma)
	2.0	Entrectinib and M5 PK (plasma)
	3.0	Entrectinib and M5 PK (plasma)
	4.0	Entrectinib and M5 PK (plasma)
	5.0	Entrectinib and 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

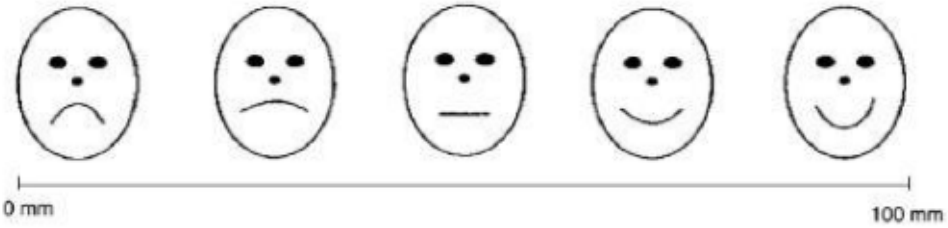
To be completed immediately after taking the multi-particulate with yoghurt.
Please indicate your answer to the following questions by making a **mark on the line**.

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



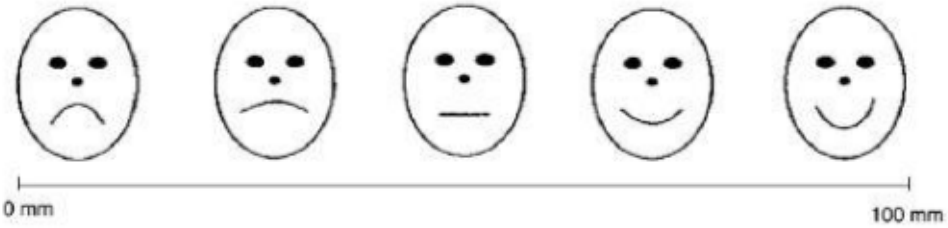
I did not like it — I liked it very much

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



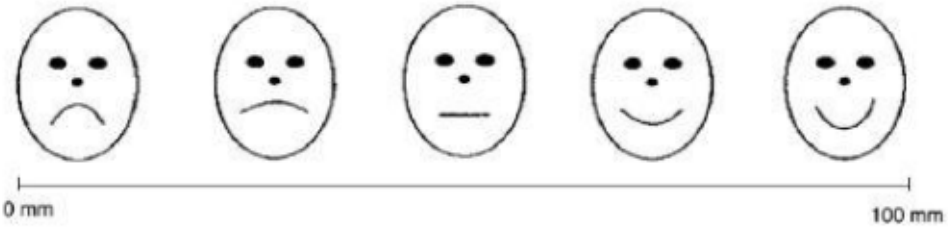
Very gritty/lumpy — Very smooth

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



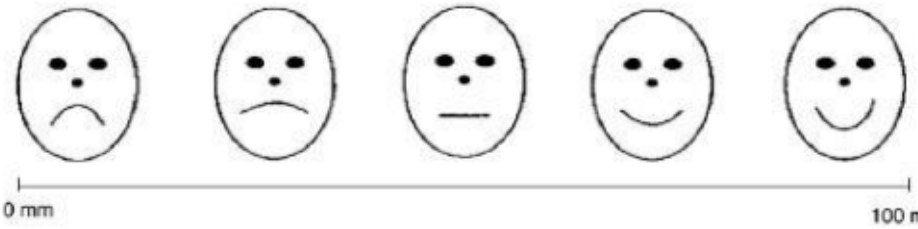
I did not like it — I liked it very much

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?

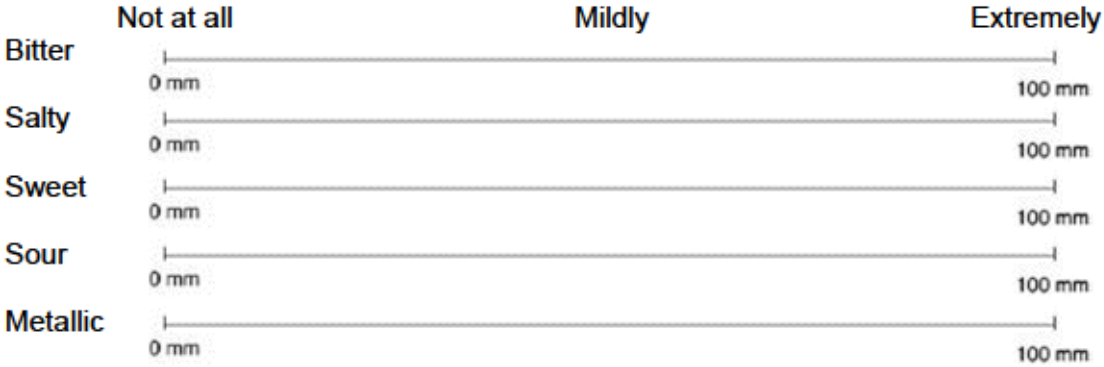
Very difficult Very easy

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?

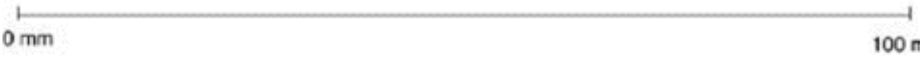


If you experienced another taste or flavour, please describe

.....

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

.....

.....