Clinical trial results:
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

Summary

EudraCT number	2019-000783-15
Trial protocol	GB
Global end of trial date	09 August 2019

Results information

Result version number	v2 (current)
This version publication date	20 September 2020
First version publication date	22 August 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GP41341

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03961100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124., Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objectives for this study were to explore the relative bioavailability of entrectinib from two multi-particulate formulations and the reference F06 capsule formulation under fed conditions (Part 1) and to explore the relative bioavailability of two entrectinib F06 capsule formulations under fasted conditions (Part 2).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single center study conducted in the United Kingdom

Pre-assignment

Screening details:

The study was conducted in healthy volunteers. The screening period was 28 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 T1T2R Sequence

Arm description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Arm type	Experimental
Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 1 (T1)/F15
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T1/F15) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 2 (T2)/F16
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T2/F16) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	reference formulation (R)/F06
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

600 mg (3 x 200 mg) entrectinib (R/F06) hard capsule was administered as a single oral dose under fed condition in each period

Arm title	Part 1 T2RT1 Sequence

Arm description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In

each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Arm type	Experimental
Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 1 (T1)/F15
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T1/F15) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 2 (T2)/F16
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T2/F16) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	reference formulation (R)/F06
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

600 mg (3 x 200 mg) entrectinib (R/F06) hard capsule was administered as a single oral dose under fed condition in each period

Arm title	Part 1 RT1T2 Sequence

Arm description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Arm type	Experimental
Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 1 (T1)/F15
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T1/F15) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation 2 (T2)/F16
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg (240 × 2.5 mg) entrectinib (T2/F16) film-coated mini-tablets were administered as a single oral dose under fed condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	reference formulation (R)/F06
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

600 mg (3 x 200 mg) entrectinib (R/F06) hard capsule was administered as a single oral dose under fed condition in each period

Arm title	Part 2 TR Sequence

Arm description:

Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Arm type	Experimental
Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation (T)/F06 coarse
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg (1 x 200 mg) entrectinib (T/F06 coarse) hydroxypropyl methylcellulose (HPMC) capsule was administered as a single oral dose under fasted condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	reference formulation (R)/F06 fine
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

200 mg (1 x 200 mg) entrectinib (R/F06 fine) hard capsule was administered as a single oral dose under fasted condition in each period

Arm title	Part 2 RT Sequence

Arm description:

Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Arm type	Experimental
Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	test formulation (T)/F06 coarse
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg (1 x 200 mg) entrectinib (T/F06 coarse) hydroxypropyl methylcellulose (HPMC) capsule was administered as a single oral dose under fasted condition in each period

Investigational medicinal product name	entrectinib
Investigational medicinal product code	
Other name	reference formulation (R)/F06 fine
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

200 mg (1 x 200 mg) entrectinib (R/F06 fine) hard capsule was administered as a single oral dose under

fasted condition in each period

Number of subjects in period 1	Part 1 T1T2R Sequence	Part 1 T2RT1 Sequence	Part 1 RT1T2 Sequence
Started	5	5	5
Completed	5	5	5

Number of subjects in period 1	Part 2 TR Sequence	Part 2 RT Sequence
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 T1T2R Sequence
Reporting group description:	
Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.	
Reporting group title	Part 1 T2RT1 Sequence
Reporting group description:	
Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.	
Reporting group title	Part 1 RT1T2 Sequence
Reporting group description:	
Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.	
Reporting group title	Part 2 TR Sequence
Reporting group description:	
Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.	
Reporting group title	Part 2 RT Sequence
Reporting group description:	
Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.	

Reporting group values	Part 1 T1T2R Sequence	Part 1 T2RT1 Sequence	Part 1 RT1T2 Sequence
Number of subjects	5	5	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	5
From 65-84 years	0	0	0

85 years and over	0	0	0

Age Continuous			
Units: Years			
arithmetic mean	38.6	47.2	39.8
standard deviation	± 17.3	± 15.2	± 15.2
Sex: Female, Male			
Units: Participants			
Female	1	2	1
Male	4	3	4
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	0	1
Black or African American	0	0	0
White	5	5	4
Race/Ethnicity, Customized			
Units: Subjects			
Not Hispanic or Latino	5	5	5

Reporting group values	Part 2 TR Sequence	Part 2 RT Sequence	Total
Number of subjects	8	8	31
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	8	31
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	40.6	46.8	
standard deviation	± 11.5	± 15.3	-
Sex: Female, Male			
Units: Participants			
Female	2	4	10
Male	6	4	21
Race/Ethnicity, Customized			
Units: Subjects			
Asian	1	0	2
Black or African American	1	0	1
White	6	8	28
Race/Ethnicity, Customized			
Units: Subjects			
Not Hispanic or Latino	8	8	31

End points

End points reporting groups

Reporting group title	Part 1 T1T2R Sequence

Reporting group description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 1 T2RT1 Sequence

Reporting group description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 1 RT1T2 Sequence

Reporting group description:

Subjects were randomly assigned to one of the three treatment sequences (T1T2R, T2RT1, RT1T2). In each treatment sequences, subjects crossed over to three periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 600 milligram (mg) oral dose under fed condition in three different formulations. Test formulation 1 (T1): film-coated mini-tablet; Test formulation 2 (T2): film-coated mini-tablet; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 2 TR Sequence

Reporting group description:

Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 2 RT Sequence

Reporting group description:

Subjects were randomly assigned to one of the two treatment sequences (TR, RT). In each treatment sequences, subjects crossed over to two periods (each period=7 days) taking different formulations of entrectinib. Entrectinib was administered as a single 200 mg oral dose under fasted condition in two different formulations. Test formulation (T): hydroxypropyl methylcellulose (HPMC) capsule; Reference formulation (R): hard capsule. The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Part 1 T1/F15 (Test formulation 1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received a single oral dose of 600 mg (240 × 2.5 mg) entrectinib film-coated mini-tablets in each period (one period=7 days) sprinkled on to, and mixed with, one tablespoon (15 mL) of yoghurt within 30 minutes of consumption of a standardized light “pediatric” breakfast. The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Part 1 T2/F16 (Test formulation 2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received a single oral dose of 600 mg (240 × 2.5 mg) entrectinib film-coated mini-tablets in each period (one period=7 days) sprinkled on to, and mixed with, one tablespoon (15 mL) of yoghurt within 30 minutes of consumption of a standardized light “pediatric” breakfast. The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Part 1 R/F06 (Reference formulation)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received a single oral dose of 600 mg (3 × 200 mg) entrectinib hard capsule in each

period (one period=7 days) swallowed whole with approximately 240 mL of water within 30 minutes of consumption of a standardized light "pediatric" breakfast. The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Part 2 T/F06 coarse (Test formulation)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received a single oral dose of 1 x 200 mg entrectinib hydroxypropyl methylcellulose (HPMC) capsule in each period (one period=7 days) swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours). The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Part 2 R/F06 fine (Reference formulation)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received a single oral dose of 1 x 200 mg entrectinib hard capsule in each period (one period=7 days) swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours). The washout period between entrectinib doses was at least 14 days.

Subject analysis set title	Safety Analysis Population for each of Parts 1 and 2
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least 1 dose of investigational medicinal product (IMP)

Subject analysis set title	PK Population for each of Parts 1 and 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who had received at least 1 dose of IMP who satisfied the following criteria for at least one profile: no missing samples or invalid postdose analytical results at critical time points e.g., around the Cmax; no relevant protocol deviations which may have impacted the study objectives with respect to the PK endpoints; no relevant AEs, such as vomiting, which suggested that the dose was not absorbed for a particular subject

Primary: Area Under the Concentration-Time Curve from Time 0 to Infinity (AUC0-inf) of Entrectinib

End point title	Area Under the Concentration-Time Curve from Time 0 to Infinity (AUC0-inf) of Entrectinib[1]

End point description:

The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib. Only subjects for whom data were collected are included in the analysis.

End point type	Primary

End point timeframe:

At pre-defined intervals from study Day 1 to Day 5 of each periods (each period=7 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 1 R/F06 (Reference formulation)	Part 2 T/F06 coarse (Test formulation)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	14	15	15
Units: nmol.h/L				
geometric mean (geometric coefficient of variation)	41500 (± 38.2)	46600 (± 34.5)	43400 (± 40.9)	9860 (± 64.7)

End point values	Part 2 R/F06 fine (Reference			

	formulation)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nmol.h/L				
geometric mean (geometric coefficient of variation)	10100 (± 56.0)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-inf of Entrectinib Active Metabolite M5

End point title	AUC0-inf of Entrectinib Active Metabolite M5[2]

End point description:

The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib. Only subjects for whom data were collected are included in the analysis.

End point type	Primary

End point timeframe:

At pre-defined intervals from study Day 1 to Day 5 of each periods (each period=7 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 1 R/F06 (Reference formulation)	Part 2 T/F06 coarse (Test formulation)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	2	5	9
Units: nmol.h/L				
geometric mean (geometric coefficient of variation)	12400 (± 31.1)	12200 (± 20.9)	13600 (± 31.7)	3900 (± 42.8)

End point values	Part 2 R/F06 fine (Reference formulation)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: nmol.h/L				
geometric mean (geometric coefficient of variation)	3780 (± 28.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) of Entrectinib

End point title	Maximum Plasma Concentration (Cmax) of Entrectinib[3]

End point description:

The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib. Only subjects for whom data were collected are included in the analysis.

End point type	Primary

End point timeframe:

At pre-defined intervals from study Day 1 to Day 5 of each periods (each period=7 days)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 1 R/F06 (Reference formulation)	Part 2 T/F06 coarse (Test formulation)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: nmol/L				
geometric mean (geometric coefficient of variation)	1930 (± 24.9)	1940 (± 21.3)	1880 (± 26.1)	494 (± 54.7)

End point values	Part 2 R/F06 fine (Reference formulation)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nmol/L				
geometric mean (geometric coefficient of variation)	522 (± 33.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of Entrectinib Active Metabolite M5

End point title	Cmax of Entrectinib Active Metabolite M5[4]

End point description:

The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib. Only subjects for whom data were collected are included in the analysis.

End point type	Primary

End point timeframe:

At pre-defined intervals from study Day 1 to Day 5 of each periods (each period=7 days)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 1 R/F06 (Reference formulation)	Part 2 T/F06 coarse (Test formulation)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: nmol/L				
geometric mean (geometric coefficient of variation)	398 (± 32.2)	325 (± 32.3)	360 (± 30.1)	100 (± 63.2)

End point values	Part 2 R/F06 fine (Reference formulation)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: nmol/L				
geometric mean (geometric coefficient of variation)	113 (± 42.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Treatment-emergent adverse events (TEAEs) are AEs that were not present before the first dose of study drug or that were present before the first dose of study drug but worsened in intensity during exposure to study drug. The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib.

End point type	Secondary

End point timeframe:

From Day -1 to Day 5 of each periods (each period=7 days)

End point values	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 1 R/F06 (Reference formulation)	Part 2 T/F06 coarse (Test formulation)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	16
Units: Percentage of Subjects				
number (not applicable)	100	93.3	100	31.3

End point values	Part 2 R/F06 fine (Reference formulation)			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: Percentage of Subjects				
number (not applicable)	37.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day -1 through Day 5 of each period in both Part 1 and Part 2 (one period=7 days)

Adverse event reporting additional description:

The analysis population included all subjects in Part 1 and Part 2, who received at least one dose of entrectinib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Part 1 T1/F15 (Test formulation 1)

Reporting group description:

Participants who received a single oral dose of 600 mg (240 × 2.5 mg) entrectinib film-coated mini-tablets in each period (one period=7 days) sprinkled on to, and mixed with, one tablespoon (15 mL) of yoghurt within 30 minutes of consumption of a standardized light "pediatric" breakfast. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 1 T2/F16 (Test formulation 2)

Reporting group description:

Participants who received a single oral dose of 600 mg (240 × 2.5 mg) entrectinib film-coated mini-tablets in each period (one period=7 days) sprinkled on to, and mixed with, one tablespoon (15 mL) of yoghurt within 30 minutes of consumption of a standardized light "pediatric" breakfast. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 2 T/F06 coarse (Test formulation)

Reporting group description:

Participants who received a single oral dose of 1 x 200 mg entrectinib hydroxypropyl methylcellulose (HPMC) capsule in each period (one period=7 days) swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours). The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 1 R/F06 (Reference formulation)

Reporting group description:

Participants who received a single oral dose of 600 mg (3 × 200 mg) entrectinib hard capsule in each period (one period=7 days) swallowed whole with approximately 240 mL of water within 30 minutes of consumption of a standardized light "pediatric" breakfast. The washout period between entrectinib doses was at least 14 days.

Reporting group title	Part 2 R/F06 fine (Reference formulation)

Reporting group description:

Participants who received a single oral dose of 1 x 200 mg entrectinib hard capsule in each period (one period=7 days) swallowed whole with approximately 240 mL of water after an overnight fast (minimum 8 hours). The washout period between entrectinib doses was at least 14 days.

Serious adverse events	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 2 T/F06 coarse (Test formulation)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Part 1 R/F06 (Reference formulation)	Part 2 R/F06 fine (Reference formulation)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1 T1/F15 (Test formulation 1)	Part 1 T2/F16 (Test formulation 2)	Part 2 T/F06 coarse (Test formulation)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	14 / 15 (93.33%)	5 / 16 (31.25%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 15 (13.33%)	2 / 16 (12.50%)
occurrences (all)	2	2	2
Headache			
subjects affected / exposed	3 / 15 (20.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	2 / 15 (13.33%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Tension headache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia teeth			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Lip dry			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	13 / 15 (86.67%)	11 / 15 (73.33%)	2 / 16 (12.50%)
occurrences (all)	13	11	2
Toothache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pain in jaw			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 1 R/F06 (Reference formulation)	Part 2 R/F06 fine (Reference formulation)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	6 / 16 (37.50%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Taste disorder			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Tension headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hyperaesthesia teeth			

subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Lip dry			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	14 / 15 (93.33%)	1 / 16 (6.25%)	
occurrences (all)	14	1	
Toothache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	3 / 15 (20.00%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Pain in jaw			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported