



## Clinical trial results:

### A Phase 1, Open Label, Crossover Study to Evaluate Palatability and Relative Bioavailability of Two Pediatric Microsphere Formulations of Crizotinib in Healthy Participants

#### Summary

EudraCT number	2021-003805-23
Trial protocol	Outside EU/EEA
Global end of trial date	17 October 2019

#### Results information

Result version number	v1 (current)
This version publication date	25 September 2021
First version publication date	25 September 2021

#### Trial information

##### Trial identification

Sponsor protocol code	A8081069
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03978143
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Pfizer Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc, 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc, 001 1-800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001493-PIP03-18
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	26 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2019
Global end of trial reached?	Yes
Global end of trial date	17 October 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Pharmacokinetics: To estimate the relative bioavailability of 2 new crizotinib formulations (coated microsphere 1 [cMS1] and coated microsphere 2 [cMS2]) to the commercially available crizotinib formulated capsule (FC) at a 250 mg dose administered under fasted conditions in adult healthy participants.

Taste: To evaluate the palatability of 2 new crizotinib formulations (cMS1 and cMS2) using a 250 mg dose in comparison with the crizotinib oral solution (OS) using a 250 mg dose by a taste questionnaire in adult healthy participants.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 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 States: 25
Worldwide total number of subjects	25
EEA total number of subjects	0

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)	25

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Twenty-five subjects were randomised and all received at least 1 study treatment.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Crizotinib cMS1 250 mg (Treatment A)
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Arm description:

Subjects received a single dose of crizotinib 250 mg as cMS1 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS1 dosing.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

A single dose of crizotinib 250 mg as cMS1 was administered on each morning of Day 1 after an overnight fast of at least 10 hours in Periods 1, 2, 3.

<b>Arm title</b>	Crizotinib cMS2 250 mg (Treatment B)
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Arm description:

Subjects received a single dose of crizotinib 250 mg as cMS2 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS2 dosing.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

A single dose of crizotinib 250 mg as cMS2 was administered on each morning of Day 1 after an overnight fast of at least 10 hours in Periods 1, 2, 3.

<b>Arm title</b>	Crizotinib FC 250 mg (Treatment C)
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Arm description:

Subjects received a single dose of crizotinib 250 mg as FC under fasted condition on each Day 1 of Periods 1, 2, 3.

Arm type	Experimental
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Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
A single dose of crizotinib 250 mg as FC was administered on each morning of Day 1 after an overnight fast of at least 10 hours in Periods 1, 2, 3.	
<b>Arm title</b>	Crizotinib OS 250 mg (Treatment D)
Arm description:	
Subjects received a single dose of crizotinib 250 mg as OS under fasted condition on Period 4 Day 1. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib OS dosing.	
Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
A single dose of crizotinib 250 mg as OC was administered on the morning of Period 4 Day 1 after an overnight fast of at least 10 hours.	
<b>Arm title</b>	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Arm description:	
Subjects received a single dose of crizotinib 250 mg as cMS1 with high-fat (HF) meal on Period 5 Day 1.	
Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use
Dosage and administration details:	
A single dose of crizotinib 250 mg as cMS1 was administered with high-fat, high-calorie meal after an overnight fast of at least 10 hours on Period 5 Day 1.	
<b>Arm title</b>	Crizotinib cMS2 250 mg + HF meal (Treatment F)
Arm description:	
Subjects received a single dose of crizotinib 250 mg as cMS2 with HF meal on Period 5 Day 1.	
Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use
Dosage and administration details:	
A single dose of crizotinib 250 mg as cMS2 was administered with high-fat, high-calorie meal after an overnight fast of at least 10 hours on Period 5 Day 1.	
<b>Arm title</b>	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
Arm description:	
Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS1 on Day 1 of Period 6.	
Arm type	Experimental

Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During Period 6, 40 mg delayed release esomeprazole was administered daily 1 hour prior to dinner on Day -5 through Day -1.

Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

A single dose of crizotinib 250 mg as cMS1 was administered on the morning of Period 6 Day 1 after an overnight fast of at least 10 hours.

<b>Arm title</b>	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
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Arm description:

Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS2 on Day 1 of Period 6.

Arm type	Experimental
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	PF-02341066
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

A single dose of crizotinib 250 mg as cMS2 was administered on the morning of Period 6 Day 1 after an overnight fast of at least 10 hours.

Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During Period 6, 40 mg delayed release esomeprazole was administered daily 1 hour prior to dinner on Day -5 through Day -1.

<b>Number of subjects in period 1</b>	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)
Started	25	25	25
Completed	22	23	23
Not completed	3	2	2
Physician decision	-	1	-
Adverse event, non-fatal	1	1	-
Not Treated	2	-	2

<b>Number of subjects in period 1</b>	Crizotinib OS 250 mg (Treatment D)	Crizotinib cMS1 250 mg + HF meal	Crizotinib cMS2 250 mg + HF meal
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		(Treatment E)	(Treatment F)
Started	25	12	13
Completed	22	11	11
Not completed	3	1	2
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Not Treated	3	1	2

<b>Number of subjects in period 1</b>	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Started	12	13
Completed	11	11
Not completed	1	2
Physician decision	-	-
Adverse event, non-fatal	-	-
Not Treated	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
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Reporting group description:

All subjects who were randomised and received at least 1 study treatment.

Reporting group values	Overall Study	Total	
Number of subjects	25	25	
Age Categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	41.28		
standard deviation	± 8.79	-	
Gender Categorical			
Units: Subjects			
Female	2	2	
Male	23	23	
Race Categorical			
Units: Subjects			
White	11	11	
Black or African American	13	13	
Asian	1	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	8	8	
Not Hispanic or Latino	17	17	
Height			
Units: centimeter (cm)			
arithmetic mean	172.4		
standard deviation	± 7.02	-	
Weight			
Units: kilogram (kg)			
arithmetic mean	77.2		
standard deviation	± 11.67	-	
Body Mass Index			
Units: kilogram/metre^2 (kg/m^2)			



arithmetic mean	25.9		
standard deviation	$\pm 3.04$	-	

## End points

### End points reporting groups

Reporting group title	Crizotinib cMS1 250 mg (Treatment A)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as cMS1 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS1 dosing.	
Reporting group title	Crizotinib cMS2 250 mg (Treatment B)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as cMS2 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS2 dosing.	
Reporting group title	Crizotinib FC 250 mg (Treatment C)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as FC under fasted condition on each Day 1 of Periods 1, 2, 3.	
Reporting group title	Crizotinib OS 250 mg (Treatment D)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as OS under fasted condition on Period 4 Day 1. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib OS dosing.	
Reporting group title	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as cMS1 with high-fat (HF) meal on Period 5 Day 1.	
Reporting group title	Crizotinib cMS2 250 mg + HF meal (Treatment F)
Reporting group description: Subjects received a single dose of crizotinib 250 mg as cMS2 with HF meal on Period 5 Day 1.	
Reporting group title	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
Reporting group description: Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS1 on Day 1 of Period 6.	
Reporting group title	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Reporting group description: Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS2 on Day 1 of Period 6.	

### Primary: Area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUCinf) for crizotinib - relative bioavailability

End point title	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUCinf) for crizotinib - relative bioavailability <sup>[1]</sup>
End point description: AUCinf was defined as area under the plasma concentration-time profile from time 0 extrapolated to infinite time. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to estimate the relative bioavailability of 2 new crizotinib formulations (cMS1 and cMS2) to the commercially available crizotinib FC.	
End point type	Primary
End point timeframe: 0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours post crizotinib dose in Periods 1 to 3 in Treatments A, B and C.	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	23	
Units: nanogram.hour per millilitre (ng.hr/mL)				
geometric mean (geometric coefficient of variation)	2483 (± 39)	2496 (± 45)	2610 (± 44)	

## Statistical analyses

Statistical analysis title	Comparison for AUCinf
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Statistical analysis description:

Natural log transformed crizotinib AUCinf was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib FC 250 mg (Treatment C) v Crizotinib cMS1 250 mg (Treatment A)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	96.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.9
upper limit	105.09

Notes:

[2] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 24 and not 46 as stated below.

Statistical analysis title	Comparison for AUCinf
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Statistical analysis description:

Natural log transformed crizotinib AUCinf was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib FC 250 mg (Treatment C) v Crizotinib cMS2 250 mg (Treatment B)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	98.49

Confidence interval	
level	90 %
sides	2-sided
lower limit	90.21
upper limit	107.54

Notes:

[3] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 48 as stated below.

**Primary: Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUClast) for crizotinib - relative bioavailability**

End point title	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUClast) for crizotinib - relative bioavailability <sup>[4]</sup>
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End point description:

AUClast was defined as area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast). PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to estimate the relative relative bioavailability of 2 new crizotinib formulations (cMS1 and cMS2) to the commercially available crizotinib FC.

End point type	Primary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours post crizotinib dose in Periods 1 to 3 in Treatments A, B and C.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	23	
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2312 (± 40)	2311 (± 46)	2428 (± 45)	

**Statistical analyses**

Statistical analysis title	Comparison for AUClast
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Statistical analysis description:

Natural log transformed crizotinib AUClast was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib FC 250 mg (Treatment C)
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Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	97.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	89.31
upper limit	107.39

Notes:

[5] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 48 as stated below.

<b>Statistical analysis title</b>	Comparison for AUClast
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Statistical analysis description:

Natural log transformed crizotinib AUClast was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib FC 250 mg (Treatment C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	95.94
Confidence interval	
level	90 %
sides	2-sided
lower limit	87.36
upper limit	105.36

Notes:

[6] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 24 and not 46 as stated below.

### **Primary: Maximum observed concentration (Cmax) for crizotinib - relative bioavailability**

End point title	Maximum observed concentration (Cmax) for crizotinib - relative bioavailability <sup>[7]</sup>
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End point description:

Cmax was defined as maximum observed concentration. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to estimate the relative relative bioavailability of 2 new crizotinib formulations (cMS1 and cMS2) to the commercially available crizotinib FC.

End point type	Primary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours post crizotinib dose in Periods 1 to 3 in Treatments A, B and C.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	23	
Units: nanogram per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	108.9 (± 38)	101.2 (± 43)	106.3 (± 29)	

## Statistical analyses

Statistical analysis title	Comparison for Cmax
Statistical analysis description:	
Natural log transformed crizotinib Cmax was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments B is the Test Treatment.	
Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib FC 250 mg (Treatment C)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other <sup>[8]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	97.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.23
upper limit	106.9

Notes:

[8] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 48 as stated below.

Statistical analysis title	Comparison for Cmax
Statistical analysis description:	
Natural log transformed crizotinib Cmax was analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Treatment C is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib FC 250 mg (Treatment C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	101.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	92.06
upper limit	111.9

Notes:

[9] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 24 and not 46 as stated below.

### Primary: Taste questionnaire score of overall liking of drug formulation

End point title	Taste questionnaire score of overall liking of drug
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End point description:

Analysis of taste sensory attributes (overall liking) using the Taste Questionnaire. Taste sensory attributes data from Periods 1-3, and 4 (Treatments A, B, and D) were analyzed to assess palatability of cMS1, cMS2, and OS. The data used in the analysis were transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Taste Questionnaire. Overall liking of drug formulation was scored by asking subjects the question: "Please indicate how much you like or dislike the product you tasted."

End point type	Primary
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End point timeframe:

1 (immediately after dosing), 5, 10, and 20 minutes after crizotinib administration in Treatments A, B and D.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib OS 250 mg (Treatment D)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	22	
Units: Units on a scale				
arithmetic mean (standard deviation)				
1MIN	28.596 (± 24.689)	23.245 (± 24.289)	70.416 (± 29.768)	
5MIN	32.919 (± 27.577)	24.228 (± 24.196)	54.000 (± 31.093)	
10MIN	26.261 (± 20.578)	23.246 (± 23.155)	46.521 (± 29.487)	
20MIN	26.136 (± 20.727)	19.566 (± 20.969)	41.636 (± 28.956)	

### Statistical analyses

Statistical analysis title	Comparison for Overall Liking - Timepoint 1MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[11]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-41.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	-50.25
upper limit	-32.62

Notes:

[11] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 5MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[12]</sup>
P-value	= 0.0004
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-20.62
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.61
upper limit	-11.63

Notes:

[12] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 10MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[13]</sup>
P-value	= 0.0009
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-20.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.51
upper limit	-10.6

Notes:

[13] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 20MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[14]</sup>
P-value	= 0.0078
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-15.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.32
upper limit	-6.02

Notes:

[14] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 1MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[15]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-45.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	-54.37
upper limit	-36.89

Notes:

[15] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 5MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[16]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-27.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	-36.73
upper limit	-18.9

Notes:

[16] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 10MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[17]</sup>
P-value	= 0.0003
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-21.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	-31.27
upper limit	-12.57

Notes:

[17] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Overall Liking - Timepoint 20MIN
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Statistical analysis description:

Overall liking was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[18]</sup>
P-value	= 0.0004
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-20.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.88
upper limit	-11.77

Notes:

[18] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

### **Primary: Taste questionnaire score of bitterness of drug formulation**

End point title	Taste questionnaire score of bitterness of drug formulation <sup>[19]</sup>
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End point description:

Analysis of taste sensory attributes (bitterness) using the Taste Questionnaire. Taste sensory attributes data from Periods 1-3, and 4 (Treatments A, B, and D) were analyzed to assess palatability of cMS1, cMS2, and OS. The data used in the analysis were transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Taste Questionnaire. Bitterness of drug formulation was scored by asking subjects the question: "Please tell us about the degree of bitterness of the product you tasted."

End point type	Primary
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End point timeframe:

1 (immediately after dosing), 5, 10, and 20 minutes after crizotinib administration in Treatments A, B and D.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib OS 250 mg (Treatment D)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	22	
Units: Units on a scale				
arithmetic mean (standard deviation)				
1MIN	28.870 (± 25.642)	24.525 (± 25.377)	63.792 (± 28.018)	
5MIN	33.913 (± 27.184)	26.537 (± 26.083)	50.728 (± 26.601)	
10MIN	26.833 (± 21.178)	21.898 (± 23.788)	38.754 (± 27.664)	
20MIN	25.516 (± 22.293)	15.771 (± 16.847)	36.336 (± 26.011)	

## Statistical analyses

Statistical analysis title	Comparison for Bitterness - Timepoint 1MIN
Statistical analysis description:	
Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[20]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-34.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	-43.25
upper limit	-25.53

Notes:

[20] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Bitterness - Timepoint 5MIN
Statistical analysis description:	
Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg

	(Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[21]</sup>
P-value	= 0.0019
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-16.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.73
upper limit	-8.05

Notes:

[21] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 10MIN
Statistical analysis description:	
Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[22]</sup>
P-value	= 0.048
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-11.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.47
upper limit	-2.05

Notes:

[22] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 20MIN
Statistical analysis description:	
Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[23]</sup>
P-value	= 0.0274
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-10.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.12
upper limit	-2.75

Notes:

[23] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 1MIN
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Statistical analysis description:

Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[24]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-37.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	-46.47
upper limit	-28.89

Notes:

[24] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 5MIN
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Statistical analysis description:

Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[25]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-22.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	-30.72
upper limit	-14.19

Notes:

[25] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 10MIN
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Statistical analysis description:

Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[26]</sup>
P-value	= 0.0081
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-15.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	-25.41
upper limit	-6.23

Notes:

[26] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Bitterness - Timepoint 20MIN
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Statistical analysis description:

Bitterness was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[27]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-19.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.15
upper limit	-11.91

Notes:

[27] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

### Primary: Taste questionnaire score of mouth feel from drug formulation

End point title	Taste questionnaire score of mouth feel from drug
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End point description:

Analysis of taste sensory attributes (mouth feel) using the Taste Questionnaire. Taste sensory attributes data from Periods 1-3, and 4 (Treatments A, B, and D) were analyzed to assess palatability of cMS1, cMS2, and OS. The data used in the analysis were transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Taste Questionnaire. Mouth feel from drug formulation was scored by asking subjects the question: "Please tell us about the mouth feel (such as grittiness, stickiness, waxiness) of the product you tasted."

End point type	Primary
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End point timeframe:

1 (immediately after dosing), 5, 10, and 20 minutes after crizotinib administration in Treatments A, B and D.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib OS 250 mg (Treatment D)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	22	
Units: Units on a scale				
arithmetic mean (standard deviation)				
1MIN	28.447 (± 24.056)	20.776 (± 21.025)	58.338 (± 28.736)	
5MIN	24.198 (± 18.085)	20.159 (± 20.840)	47.326 (± 29.334)	
10MIN	19.055 (± 17.900)	19.863 (± 21.053)	38.727 (± 27.786)	
20MIN	17.192 (± 16.028)	15.978 (± 16.439)	32.804 (± 23.028)	



## Statistical analyses

Statistical analysis title	Comparison for Mouth Feel - Timepoint 1MIN
Statistical analysis description: Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[29]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-29.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	-38.37
upper limit	-20.58

Notes:

[29] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Mouth Feel - Timepoint 5MIN
Statistical analysis description: Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[30]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-22.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	-31.44
upper limit	-14.18

Notes:

[30] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Mouth Feel - Timepoint 10MIN
Statistical analysis description: Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[31]</sup>
P-value	= 0.0022
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-19.67
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.84
upper limit	-9.49

Notes:

[31] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Mouth Feel - Timepoint 20MIN
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Statistical analysis description:

Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[32]</sup>
P-value	= 0.0007
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-15.37
Confidence interval	
level	90 %
sides	2-sided
lower limit	-22.47
upper limit	-8.27

Notes:

[32] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Mouth Feel - Timepoint 1MIN
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Statistical analysis description:

Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[33]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-36.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	-45.13
upper limit	-27.51

Notes:

[33] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Mouth Feel - Timepoint 5MIN
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Statistical analysis description:

Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[34]</sup>
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-25.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	-34.5
upper limit	-17.42

Notes:

[34] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Mouth Feel - Timepoint 10MIN
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Statistical analysis description:

Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[35]</sup>
P-value	= 0.0039
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-18.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.18
upper limit	-8.15

Notes:

[35] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Mouth Feel - Timepoint 20MIN
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Statistical analysis description:

Mouth feel was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[36]</sup>
P-value	= 0.0004
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-16.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.09
upper limit	-9.02

Notes:

[36] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

### **Primary: Taste questionnaire score of tongue/mouth burn from drug formulation**

End point title	Taste questionnaire score of tongue/mouth burn from drug formulation <sup>[37]</sup>
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End point description:

Analysis of taste sensory attributes (tongue/mouth burn) using the Taste Questionnaire. Taste sensory attributes data from Periods 1-3, and 4 (Treatments A, B, and D) were analyzed to assess palatability of cMS1, cMS2, and OS. The data used in the analysis were transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Taste Questionnaire. Tongue/mouth burn from drug formulation was scored by asking subjects the question: "Please tell us about the degree of tongue/mouth burn of the product you tasted."

End point type	Primary
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End point timeframe:

1 (immediately after dosing), 5, 10, and 20 minutes after crizotinib administration in Treatments A, B and D.

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib OS 250 mg (Treatment D)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	22	
Units: Units on a scale				
arithmetic mean (standard deviation)				
1MIN	21.863 (± 23.830)	21.394 (± 28.553)	36.960 (± 29.910)	
5MIN	19.601 (± 23.969)	15.062 (± 19.950)	33.195 (± 30.228)	
10MIN	14.534 (± 17.706)	15.428 (± 20.074)	25.844 (± 27.356)	
20MIN	20.297 (± 26.175)	12.480 (± 16.224)	24.856 (± 26.188)	

## Statistical analyses

Statistical analysis title	Comparison for Tongue/Mouth Burn - Timepoint 1MIN
Statistical analysis description: Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[38]</sup>
P-value	= 0.0113
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-14.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.68
upper limit	-5.27

Notes:

[38] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Tongue/Mouth Burn - Timepoint 5MIN
Statistical analysis description: Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg

	(Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[39]</sup>
P-value	= 0.0051
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-13.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.5
upper limit	-5.61

Notes:

[39] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 10MIN
Statistical analysis description:	
Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[40]</sup>
P-value	= 0.0238
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-10.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.72
upper limit	-3.08

Notes:

[40] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 20MIN
Statistical analysis description:	
Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[41]</sup>
P-value	= 0.4427
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-4.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.97
upper limit	4.79

Notes:

[41] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 1MIN
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Statistical analysis description:

Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[42]</sup>
P-value	= 0.013
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-14.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.19
upper limit	-4.92

Notes:

[42] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 5MIN
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Statistical analysis description:

Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[43]</sup>
P-value	= 0.0004
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-16.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.3
upper limit	-9.49

Notes:

[43] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 10MIN
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Statistical analysis description:

Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[44]</sup>
P-value	= 0.0487
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-9.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.12
upper limit	-1.6

Notes:

[44] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Tongue/Mouth Burn - Timepoint 20MIN
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Statistical analysis description:

Tongue/mouth burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[45]</sup>
P-value	= 0.0354
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-11.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.13
upper limit	-2.56

Notes:

[45] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

### Primary: Taste questionnaire score of throat burn from drug formulation

End point title	Taste questionnaire score of throat burn from drug
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End point description:

Analysis of taste sensory attributes (throat burn) using the Taste Questionnaire. Taste sensory attributes data from Periods 1-3, and 4 (Treatments A, B, and D) were analyzed to assess palatability of cMS1, cMS2, and OS. The data used in the analysis were transcribed and rescaled to a score from 0 to 100 from the raw measurements on the Taste Questionnaire. Throat burn from drug formulation was scored by asking subjects the question: "Please tell us about the degree of throat burn of the product you tasted."

End point type	Primary
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End point timeframe:

1 (immediately after dosing), 5, 10, and 20 minutes after crizotinib administration in Treatments A, B and D.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib OS 250 mg (Treatment D)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	25	22	
Units: Units on a scale				
arithmetic mean (standard deviation)				
1MIN	19.900 (± 22.287)	23.977 (± 29.753)	38.493 (± 31.383)	
5MIN	19.379 (± 18.710)	17.187 (± 22.791)	36.469 (± 30.695)	
10MIN	20.968 (± 24.354)	14.079 (± 18.150)	32.234 (± 29.027)	
20MIN	20.198 (± 25.583)	13.098 (± 16.455)	27.999 (± 26.550)	

## Statistical analyses

Statistical analysis title	Comparison for Throat Burn - Timepoint 1MIN
Statistical analysis description: Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[47]</sup>
P-value	= 0.0033
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-18.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.8
upper limit	-8.31

Notes:

[47] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Throat Burn - Timepoint 10MIN
Statistical analysis description: Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[48]</sup>
P-value	= 0.0686
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-10.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.89
upper limit	-1.1

Notes:

[48] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

Statistical analysis title	Comparison for Throat Burn - Timepoint 5MIN
Statistical analysis description: Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[49]</sup>
P-value	= 0.0018
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-16.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	-25.13
upper limit	-8.26

Notes:

[49] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Throat Burn - Timepoint 20MIN
Statistical analysis description:	
Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments A is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[50]</sup>
P-value	= 0.202
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-7.54
Confidence interval	
level	90 %
sides	2-sided
lower limit	-17.33
upper limit	2.24

Notes:

[50] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 45 as stated below.

<b>Statistical analysis title</b>	Comparison for Throat Burn - Timepoint 1MIN
Statistical analysis description:	
Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.	
Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[51]</sup>
P-value	= 0.0288
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-13.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-22.68
upper limit	-3.34

Notes:

[51] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Throat Burn - Timepoint 5MIN
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Statistical analysis description:

Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[52]</sup>
P-value	= 0.0008
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-26.37
upper limit	-9.64

Notes:

[52] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Throat Burn - Timepoint 10MIN
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Statistical analysis description:

Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[53]</sup>
P-value	= 0.005
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-17.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-26.94
upper limit	-7.4

Notes:

[53] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

<b>Statistical analysis title</b>	Comparison for Throat Burn - Timepoint 20MIN
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Statistical analysis description:

Throat burn was analyzed using a mixed effect model with sequence, treatment, time and treatment by time interaction as fixed effects and subjects within sequence as a random effect. Treatment D is the Reference Treatment while Treatments B is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib OS 250 mg (Treatment D)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other <sup>[54]</sup>
P-value	= 0.0184
Method	ANOVA
Parameter estimate	Adjusted Mean Differences
Point estimate	-14.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.7
upper limit	-4.4

Notes:

[54] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 47 as stated below.

### **Secondary: Number of subjects with laboratory test abnormalities (without regard to baseline abnormality) meeting pre-specified criteria**

End point title	Number of subjects with laboratory test abnormalities (without regard to baseline abnormality) meeting pre-specified criteria
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End point description:

Pre-specified criteria were established for each laboratory test to define the values that would be identified as of potential clinical importance, including hematology, chemistry and urinalysis. Laboratory data were listed in accordance with the sponsor reporting standards.

End point type	Secondary
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End point timeframe:

From screening through completion of Period 6 (appropriately 88 days) and/or early withdrawal if necessary.

<b>End point values</b>	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib OS 250 mg (Treatment D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	22
Units: Subjects				
Lymphocytes/Leukocytes (%) <0.8 x LLN	3	0	0	0
Lymphocytes/Leukocytes (%) >1.2 x ULN	1	0	0	0
Eosinophils/Leukocytes (%) >1.2 x ULN	0	1	1	0
Monocytes/Leukocytes (%) >1.2 x ULN	2	2	2	1
Bilirubin (mg/dL) >1.5 x ULN	0	1	0	0
Aspartate Aminotransferase (U/L) >3.0 x ULN	1	0	0	0
Alanine Aminotransferase (U/L) >3.0 x ULN	2	0	0	1
Creatinine (mg/dL) >1.3 x ULN	0	0	0	1
Urate (mg/dL) >1.2 x ULN	0	1	0	1
Indirect Bilirubin (mg/dL) >1.5 x ULN	0	1	0	0
Gamma Glutamyl Transferase(U/L) >3.0 x ULN	1	0	0	0
Creatine Kinase (U/L) >2.0 x ULN	0	1	0	0

<b>End point values</b>	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	11
Units: Subjects				
Lymphocytes/Leukocytes (%) <0.8 x LLN	0	1	0	0
Lymphocytes/Leukocytes (%) >1.2 x ULN	0	0	0	0
Eosinophils/Leukocytes (%) >1.2 x ULN	0	0	0	0
Monocytes/Leukocytes (%) >1.2 x ULN	0	1	2	1
Bilirubin (mg/dL) >1.5 x ULN	0	0	1	0
Aspartate Aminotransferase (U/L) >3.0 x ULN	0	0	0	0
Alanine Aminotransferase (U/L) >3.0 x ULN	0	0	0	0
Creatinine (mg/dL) >1.3 x ULN	0	0	0	0
Urate (mg/dL) >1.2 x ULN	1	0	2	0
Indirect Bilirubin (mg/dL) >1.5 x ULN	0	0	0	0
Gamma Glutamyl Transferase(U/L) >3.0 x ULN	0	0	0	0
Creatine Kinase (U/L) >2.0 x ULN	0	1	0	1

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with electrocardiogram (ECG) data meeting pre-specified criteria

End point title	Number of subjects with electrocardiogram (ECG) data meeting pre-specified criteria
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End point description:

Pre-specified criteria were established for ECG values of potential clinical concern, including PR interval (value>280 msec, %Chg>=25%, %Chg>=50%); QRS duration (value>120 msec, %Chg>=50%); QT interval (value>500 msec); QT interval corrected using the Fridericia formula (QTcF) and QT interval corrected using the Bazett's formula (QTcB) interval (450<value<=480, 480<value<=500, value>500 msec); QTcF and QTcB interval (30<=Chg<60, Chg>=60).

End point type	Secondary
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End point timeframe:

From screening through completion of Period 6 (appropriately 88 days) and/or early withdrawal if necessary.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib OS 250 mg (Treatment D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	24	23	22
Units: Subjects				
QTCB INTERVAL, AGGREGATE (MSEC) 30<=Chg<60	0	0	0	0

End point values	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	11
Units: Subjects				
QTCB INTERVAL, AGGREGATE (MSEC) 30<=Chg<60	0	0	1	1

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of subjects with treatment-emergent adverse events (TEAEs)**

End point title	Number of subjects with treatment-emergent adverse events (TEAEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subjects. TEAEs were AEs related to the investigational product. A serious AE was any untoward medical occurrence at any dose that resulted in death; was life-threatening; required hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect or that was considered to be an important medical event. A severe AE was an event that prevented normal everyday activities. The focus of AE summaries was on treatment-emergent AE.

End point type	Secondary
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End point timeframe:

From screening through completion of follow-up period of 28-35 days after the last dose of investigational product (approximately 130 days).

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib OS 250 mg (Treatment D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	22
Units: Subjects				
All-causality TEAEs	12	9	11	6
Treatment-related TEAEs	11	9	9	6
All-causality serious AEs	0	0	0	0
Treatment-related serious AEs	0	0	0	0
All-causality severe AEs	0	0	0	0
Treatment-related severe AEs	0	0	0	0

End point values	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	11
Units: Subjects				
All-causality TEAEs	4	4	4	1
Treatment-related TEAEs	3	4	2	1
All-causality serious AEs	0	0	0	0
Treatment-related serious AEs	0	0	0	0
All-causality severe AEs	0	0	0	0
Treatment-related severe AEs	0	0	0	0

**Statistical analyses**

No statistical analyses for this end point



## Secondary: AUCinf for crizotinib - food effect

End point title	AUCinf for crizotinib - food effect <sup>[55]</sup>
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End point description:

AUCinf was defined as area under the plasma concentration-time profile from time 0 extrapolated to infinite time. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of food on the PK of cMS1 and cMS2.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 5 in Treatments E, F.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2483 (± 39)	2496 (± 45)	1944 (± 38)	1957 (± 39)

## Statistical analyses

Statistical analysis title	Comparison for AUCinf – Food Effect
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Statistical analysis description:

Natural log transformed crizotinib AUCinf was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment F is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + HF meal (Treatment F)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[56]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	71.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	61.75
upper limit	83.51

Notes:

[56] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

Statistical analysis title	Comparison for AUCinf – Food Effect
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**Statistical analysis description:**

Natural log transformed crizotinib AUCinf was analyzed using Analysis of Variance (ANOVA) with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment E is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + HF meal (Treatment E)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[57]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	85.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	73.25
upper limit	99.16

**Notes:**

[57] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

**Secondary: AUClast for crizotinib - food effect**

End point title	AUClast for crizotinib - food effect <sup>[58]</sup>
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**End point description:**

AUClast was defined as area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast). PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of food on the PK of cMS1 and cMS2.

End point type	Secondary
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**End point timeframe:**

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 5 in Treatments E, F.

**Notes:**

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

<b>End point values</b>	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2312 (± 40)	2311 (± 46)	1757 (± 41)	1780 (± 42)

**Statistical analyses**

<b>Statistical analysis title</b>	Comparison for AUClast – Food Effect
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**Statistical analysis description:**

Natural log transformed crizotinib AUClast was analyzed using ANOVA with treatment and sequence as a

fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment E is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + HF meal (Treatment E)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[59]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	82.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	70.63
upper limit	97.3

Notes:

[59] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

<b>Statistical analysis title</b>	Comparison for AUClast – Food Effect
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Statistical analysis description:

Natural log transformed crizotinib AUClast was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment F is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + HF meal (Treatment F)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[60]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	70.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	60.05
upper limit	82.62

Notes:

[60] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

## Secondary: Cmax for crizotinib - food effect

End point title	Cmax for crizotinib - food effect <sup>[61]</sup>
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End point description:

Cmax was defined as maximum observed concentration. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of food on the PK of cMS1 and cMS2.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 5 in Treatments E, F.

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + HF meal (Treatment E)	Crizotinib cMS2 250 mg + HF meal (Treatment F)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng/mL				
geometric mean (geometric coefficient of variation)	108.9 ( $\pm$ 38)	101.2 ( $\pm$ 43)	82.96 ( $\pm$ 42)	78.02 ( $\pm$ 32)

## Statistical analyses

Statistical analysis title	Comparison for Cmax – Food Effect
Statistical analysis description: Natural log transformed crizotinib Cmax was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment F is the Test Treatment.	
Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + HF meal (Treatment F)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[62]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	75.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	63.63
upper limit	90.2

Notes:

[62] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

Statistical analysis title	Comparison for Cmax – Food Effect
Statistical analysis description: Natural log transformed crizotinib Cmax was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment E is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + HF meal (Treatment E)

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[63]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	77.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	64.81
upper limit	92.05

Notes:

[63] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

## Secondary: AUCinf for crizotinib - proton pump inhibitor (PPI) effect

End point title	AUCinf for crizotinib - proton pump inhibitor (PPI) effect <sup>[64]</sup>
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End point description:

AUCinf was defined as area under the plasma concentration-time profile from time 0 extrapolated to infinite time. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of esomeprazole on the PK of cMS1 and cMS2.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 6 in Treatments G, H.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2483 (± 39)	2496 (± 45)	1854 (± 34)	1697 (± 45)

## Statistical analyses

Statistical analysis title	Comparison for AUCinf – PPI Effect
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Statistical analysis description:

Natural log transformed crizotinib AUCinf was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment H is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
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Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[65]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	62.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	53.55
upper limit	72.41

Notes:

[65] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

<b>Statistical analysis title</b>	Comparison for AUCinf – PPI Effect
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Statistical analysis description:

Natural log transformed crizotinib AUCinf was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment G is the Test Treatment.

Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[66]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	81.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	69.85
upper limit	94.57

Notes:

[66] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

### Secondary: AUClast for crizotinib - PPI effect

End point title	AUClast for crizotinib - PPI effect <sup>[67]</sup>
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End point description:

AUClast was defined as area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast). PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of esomeprazole on the PK of cMS1 and cMS2.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 6 in Treatments G, H.

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng.hr/mL				
geometric mean (geometric coefficient of variation)	2312 (± 40)	2311 (± 46)	1677 (± 37)	1532 (± 49)

## Statistical analyses

Statistical analysis title	Comparison for AUClast – PPI Effect
Statistical analysis description:	
Natural log transformed crizotinib AUClast was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment G is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[68]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	79.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	67.4
upper limit	92.85

Notes:

[68] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

Statistical analysis title	Comparison for AUClast – PPI Effect
Statistical analysis description:	
Natural log transformed crizotinib AUClast was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment H is the Test Treatment.	
Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[69]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	60.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	51.69
upper limit	71.12

Notes:

[69] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

## Secondary: Cmax for crizotinib - PPI effect

End point title	Cmax for crizotinib - PPI effect <sup>[70]</sup>
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End point description:

Cmax was defined as maximum observed concentration. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period. This endpoint is to explore the effect of esomeprazole on the PK of cMS1 and cMS2.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Periods 1 to 3 in Treatments A, B and in Period 6 in Treatments G, H.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	11	11
Units: ng/mL				
geometric mean (geometric coefficient of variation)	108.9 (± 38)	101.2 (± 43)	82.36 (± 35)	70.42 (± 47)

## Statistical analyses

Statistical analysis title	Comparison for Cmax – PPI Effect
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Statistical analysis description:

Natural log transformed crizotinib Cmax was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment B is the Reference Treatment while Treatment H is the Test Treatment.

Comparison groups	Crizotinib cMS2 250 mg (Treatment B) v Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other <sup>[71]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	68.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	57.43
upper limit	81.41



Notes:

[71] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 25 and not 36 as stated below.

<b>Statistical analysis title</b>	Comparison for Cmax – PPI Effect
Statistical analysis description:	
Natural log transformed crizotinib Cmax was analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Treatment A is the Reference Treatment while Treatment G is the Test Treatment.	
Comparison groups	Crizotinib cMS1 250 mg (Treatment A) v Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[72]</sup>
Parameter estimate	Ratio of Adjusted Geometric Means
Point estimate	76.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	64.34
upper limit	91.39

Notes:

[72] - As this was a crossover, 6-period, 6-sequence study, the same subjects received different study treatments in separate study periods. Due to limitations in system functionality which cannot be corrected currently, the total number of subjects included in the analysis is 23 and not 34 as stated below.

### Secondary: Time for Cmax (Tmax) for crizotinib

End point title	Time for Cmax (Tmax) for crizotinib <sup>[73]</sup>
End point description:	
Tmax was defined as time for Cmax of crizotinib. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period.	
End point type	Secondary

End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Treatments A, B, C, E, F, G, and H.

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	11
Units: Hour				
median (full range (min-max))	4.00 (1.00 to 6.00)	6.00 (2.00 to 6.25)	4.03 (1.00 to 8.00)	6.00 (4.00 to 8.00)

End point values	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: Hour				
median (full range (min-max))	6.00 (4.00 to 10.0)	6.00 (4.00 to 6.03)	6.00 (4.00 to 6.03)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal half-life (t1/2) for crizotinib

End point title	Terminal half-life (t1/2) for crizotinib <sup>[74]</sup>
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End point description:

t1/2 was defined as terminal half-life of crizotinib. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Treatments A, B, C, E, F, G, and H.

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	11
Units: Hour				
arithmetic mean (standard deviation)	25.72 (± 3.2139)	26.33 (± 3.9059)	25.36 (± 3.4036)	29.25 (± 7.2854)

End point values	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: Hour				
arithmetic mean (standard deviation)	28.52 (± 7.4028)	29.44 (± 6.4993)	28.45 (± 4.9589)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Apparent oral clearance (CL/F) for crizotinib

End point title	Apparent oral clearance (CL/F) for crizotinib <sup>[75]</sup>
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End point description:

CL/F was defined as apparent oral clearance of crizotinib. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Treatments A, B, C, E, F, G, and H.

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	11
Units: Litre per hour (L/hr)				
geometric mean (geometric coefficient of variation)	100.8 (± 39)	100.2 (± 45)	95.78 (± 44)	128.4 (± 38)

End point values	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: Litre per hour (L/hr)				
geometric mean (geometric coefficient of variation)	127.7 (± 39)	134.8 (± 34)	147.5 (± 45)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent volume of distribution (V<sub>z</sub>/F) for crizotinib

End point title	Apparent volume of distribution (V <sub>z</sub> /F) for crizotinib <sup>[76]</sup>
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End point description:

V<sub>z</sub>/F was defined as apparent volume of distribution of crizotinib. PK parameter evaluable analysis set was used to analyze this endpoint, including all subjects randomised and treated who had at least 1 of the PK crizotinib parameters of primary interest in at least 1 period.

End point type	Secondary
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End point timeframe:

0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 24, 48, and 96 hours after crizotinib administration in Treatments A, B, C, E, F, G, and H.

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Analysis was planned only for the arms specified.

End point values	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib cMS2 250 mg (Treatment B)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	25	23	11
Units: Litre (L)				
geometric mean (geometric coefficient of variation)	3710 (± 49)	3770 (± 56)	3476 (± 54)	5295 (± 57)

End point values	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	11	11	
Units: Litre (L)				
geometric mean (geometric coefficient of variation)	5131 (± 59)	5618 (± 54)	5970 (± 63)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening (within 28 days prior to Day 1) up to 35 days after last dose of investigational product, the total duration of the study is approximately 130 days including screening.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Crizotinib cMS1 250 mg (Treatment A)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as cMS1 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS1 dosing.

Reporting group title	Crizotinib FC 250 mg (Treatment C)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as FC under fasted condition on each Day 1 of Periods 1, 2, 3.

Reporting group title	Crizotinib cMS2 250 mg (Treatment B)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as cMS2 under fasted condition on each Day 1 of Periods 1, 2, 3. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib cMS2 dosing.

Reporting group title	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)
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Reporting group description:

Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS1 on Day 1 of Period 6.

Reporting group title	Crizotinib cMS2 250 mg + HF meal (Treatment F)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as cMS2 with HF meal on Period 5 Day 1.

Reporting group title	Crizotinib cMS1 250 mg + HF meal (Treatment E)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as cMS1 with HF meal on Period 5 Day 1.

Reporting group title	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)
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Reporting group description:

Subjects received esomeprazole 40 mg 1 hour prior to dinner on Day -5 through Day -1; then a single dose of crizotinib 250 mg as cMS2 on Day 1 of Period 6.

Reporting group title	Crizotinib OS 250 mg (Treatment D)
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Reporting group description:

Subjects received a single dose of crizotinib 250 mg as OS under fasted condition on Period 4 Day 1. The Taste Questionnaire then was administered at 1 (immediately after crizotinib dosing), 5, 10, and 20 minutes after the completion of crizotinib OS dosing.

Serious adverse events	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS2 250 mg (Treatment B)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
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<b>Serious adverse events</b>	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

<b>Serious adverse events</b>	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	Crizotinib OS 250 mg (Treatment D)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

<b>Non-serious adverse events</b>	Crizotinib cMS1 250 mg (Treatment A)	Crizotinib FC 250 mg (Treatment C)	Crizotinib cMS2 250 mg (Treatment B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)	11 / 23 (47.83%)	9 / 25 (36.00%)
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 23 (13.04%)	2 / 23 (8.70%)	2 / 25 (8.00%)
occurrences (all)	3	2	2
Headache			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Lethargy			
subjects affected / exposed	2 / 23 (8.70%)	3 / 23 (13.04%)	0 / 25 (0.00%)
occurrences (all)	2	4	0

Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 23 (13.04%)	4 / 23 (17.39%)	3 / 25 (12.00%)
occurrences (all)	3	4	3
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	7 / 23 (30.43%)	5 / 23 (21.74%)	6 / 25 (24.00%)
occurrences (all)	8	8	6
Nausea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	2 / 25 (8.00%)
occurrences (all)	2	1	2
Renal and urinary disorders			
Urine odour abnormal			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

<b>Non-serious adverse events</b>	Crizotinib cMS1 250 mg + Esomeprazole (Treatment G)	Crizotinib cMS2 250 mg + HF meal (Treatment F)	Crizotinib cMS1 250 mg + HF meal (Treatment E)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	4 / 11 (36.36%)	4 / 11 (36.36%)
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Lethargy			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	2 / 11 (18.18%)
occurrences (all)	2	3	2
Nausea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Urine odour abnormal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			



Back pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
<b>Non-serious adverse events</b>	Crizotinib cMS2 250 mg + Esomeprazole (Treatment H)	Crizotinib OS 250 mg (Treatment D)	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 11 (9.09%)	6 / 22 (27.27%)	
Injury, poisoning and procedural complications Skin abrasion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 22 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Lethargy subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0  1 / 11 (9.09%) 1  1 / 11 (9.09%) 1	0 / 22 (0.00%) 0  1 / 22 (4.55%) 1  1 / 22 (4.55%) 1	
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 22 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Diarrhoea	0 / 11 (0.00%) 0  0 / 11 (0.00%) 0  1 / 11 (9.09%) 3	2 / 22 (9.09%) 2  0 / 22 (0.00%) 0  2 / 22 (9.09%) 2	

subjects affected / exposed	0 / 11 (0.00%)	3 / 22 (13.64%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Urine odour abnormal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported