



## 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 |
|-----------------------|----------|

##### 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 |
|------------------------------|----|

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Crizotinib cMS1 250 mg (Treatment A) |
|------------------|--------------------------------------|

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) |
|------------------|--------------------------------------|

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) |
|------------------|------------------------------------|

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 |
|----------|--------------|

|                                                                                                                                                                                                                                                                    |                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| 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) |
|------------------|-----------------------------------------------------|

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 |
|---------------------------------------|------------------------------------|----------------------------------|----------------------------------|
|                                       |                                    |                                  |                                  |

|                          |    | (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 |
|-----------------------|---------------|

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

## Statistical analyses

| Statistical analysis title | Comparison for AUCinf |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

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 |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

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> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib CMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(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 |
|----------------------------|------------------------|

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) |
|-------------------|---------------------------------------------------------------------------|

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| 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 |
|-----------------------------------|------------------------|

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> |
|-----------------|------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(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 |
|-----------------|-----------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib OS<br>250 mg<br>(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 (±<br>24.689)                       | 23.245 (±<br>24.289)                       | 70.416 (±<br>29.768)                     |  |
| 5MIN                                 | 32.919 (±<br>27.577)                       | 24.228 (±<br>24.196)                       | 54.000 (±<br>31.093)                     |  |
| 10MIN                                | 26.261 (±<br>20.578)                       | 23.246 (±<br>23.155)                       | 46.521 (±<br>29.487)                     |  |
| 20MIN                                | 26.136 (±<br>20.727)                       | 19.566 (±<br>20.969)                       | 41.636 (±<br>28.956)                     |  |

### Statistical analyses

|                            |                                                |
|----------------------------|------------------------------------------------|
| Statistical analysis title | Comparison for Overall Liking - Timepoint 1MIN |
|----------------------------|------------------------------------------------|

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>[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 |
|-----------------------------------|------------------------------------------------|

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 |
|-----------------------------------|-------------------------------------------------|

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>[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 |
|-----------------------------------|-------------------------------------------------|

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 |
|-----------------------------------|------------------------------------------------|

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>[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 |
|-----------------------------------|------------------------------------------------|

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 |
|-----------------------------------|-------------------------------------------------|

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>[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 |
|-----------------------------------|-------------------------------------------------|

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> |
|-----------------|-----------------------------------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib OS<br>250 mg<br>(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 (±<br>25.642)                       | 24.525 (±<br>25.377)                       | 63.792 (±<br>28.018)                     |  |
| 5MIN                                 | 33.913 (±<br>27.184)                       | 26.537 (±<br>26.083)                       | 50.728 (±<br>26.601)                     |  |
| 10MIN                                | 26.833 (±<br>21.178)                       | 21.898 (±<br>23.788)                       | 38.754 (±<br>27.664)                     |  |
| 20MIN                                | 25.516 (±<br>22.293)                       | 15.771 (±<br>16.847)                       | 36.336 (±<br>26.011)                     |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                  | Comparison for Bitterness - Timepoint 1MIN                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Statistical analysis description:<br>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:<br>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 |
|-----------------------------------|--------------------------------------------|

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 |
|-----------------------------------|--------------------------------------------|

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>[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 |
|-----------------------------------|---------------------------------------------|

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 |
|-----------------------------------|---------------------------------------------|

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>[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 |
|-----------------|---------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib OS<br>250 mg<br>(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 (±<br>24.056)                       | 20.776 (±<br>21.025)                       | 58.338 (±<br>28.736)                     |  |
| 5MIN                                 | 24.198 (±<br>18.085)                       | 20.159 (±<br>20.840)                       | 47.326 (±<br>29.334)                     |  |
| 10MIN                                | 19.055 (±<br>17.900)                       | 19.863 (±<br>21.053)                       | 38.727 (±<br>27.786)                     |  |
| 20MIN                                | 17.192 (±<br>16.028)                       | 15.978 (±<br>16.439)                       | 32.804 (±<br>23.028)                     |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                  | Comparison for Mouth Feel - Timepoint 1MIN                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Statistical analysis description:<br>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:<br>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:<br>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 |
|-----------------------------------|---------------------------------------------|

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 |
|-----------------------------------|--------------------------------------------|

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>[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 |
|-----------------------------------|--------------------------------------------|

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 |
|-----------------------------------|---------------------------------------------|

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>[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 |
|-----------------------------------|---------------------------------------------|

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> |
|-----------------|--------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib OS<br>250 mg<br>(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 (±<br>23.830)                       | 21.394 (±<br>28.553)                       | 36.960 (±<br>29.910)                     |  |
| 5MIN                                 | 19.601 (±<br>23.969)                       | 15.062 (±<br>19.950)                       | 33.195 (±<br>30.228)                     |  |
| 10MIN                                | 14.534 (±<br>17.706)                       | 15.428 (±<br>20.074)                       | 25.844 (±<br>27.356)                     |  |
| 20MIN                                | 20.297 (±<br>26.175)                       | 12.480 (±<br>16.224)                       | 24.856 (±<br>26.188)                     |  |

## Statistical analyses

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

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 |
|-----------------------------------|---------------------------------------------------|

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>[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 |
|-----------------------------------|----------------------------------------------------|

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 |
|-----------------------------------|----------------------------------------------------|

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>[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 |
|-----------------|----------------------------------------------------|

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 |
|----------------|---------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib OS<br>250 mg<br>(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:<br>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:<br>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:<br>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 |
|-----------------------------------|---------------------------------------------|

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 |
|-----------------------------------|----------------------------------------------|

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>[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 |
|-----------------------------------|----------------------------------------------|

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 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib OS<br>250 mg<br>(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<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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 |
|-----------------|-------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

End point timeframe:

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

| End point values                              | Crizotinib cMS1<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib OS<br>250 mg<br>(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)<br>30<=Chg<60 | 0                                          | 0                                          | 0                                        | 0                                        |

| End point values                              | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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)<br>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) |
|-----------------|-------------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib OS<br>250 mg<br>(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<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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> |
|-----------------|-----------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(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 |
|----------------------------|-------------------------------------|

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 |
|----------------------------|-------------------------------------|

**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> |
|-----------------|------------------------------------------------------|

**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 |
|----------------|-----------|

**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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(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 |
|-----------------------------------|--------------------------------------|

**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 |
|-----------------------------------|--------------------------------------|

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> |
|-----------------|---------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(Treatment E) | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(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<br>of variation) | 108.9 (± 38)                               | 101.2 (± 43)                               | 82.96 (± 42)                                            | 78.02 (± 32)                                            |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                          | Comparison for Cmax – Food Effect                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Statistical analysis description:<br>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:<br>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> |
|-----------------|----------------------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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 |
|----------------------------|------------------------------------|

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) |
|-------------------|--------------------------------------------------------------------------------------------|

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| 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 |
|-----------------------------------|------------------------------------|

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> |
|-----------------|-----------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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 ( $\pm$ 40)                           | 2311 ( $\pm$ 46)                           | 1677 ( $\pm$ 37)                                             | 1532 ( $\pm$ 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> |
|-----------------|--------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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 |
|----------------------------|----------------------------------|

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<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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<br>10.0)                                  | 6.00 (4.00 to<br>6.03)                                       | 6.00 (4.00 to<br>6.03)                                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Terminal half-life (t<sub>1/2</sub>) for crizotinib

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Terminal half-life (t <sub>1/2</sub> ) for crizotinib <sup>[74]</sup> |
|-----------------|-----------------------------------------------------------------------|

End point description:

t<sub>1/2</sub> 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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(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 (±<br>3.2139)                        | 26.33 (±<br>3.9059)                        | 25.36 (±<br>3.4036)                      | 29.25 (±<br>7.2854)                                     |

| End point values                     | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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 (±<br>7.4028)                                     | 29.44 (±<br>6.4993)                                          | 28.45 (±<br>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> |
|-----------------|---------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(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<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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> |
|-----------------|------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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<br>250 mg<br>(Treatment A) | Crizotinib cMS2<br>250 mg<br>(Treatment B) | Crizotinib FC<br>250 mg<br>(Treatment C) | Crizotinib cMS1<br>250 mg + HF<br>meal<br>(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<br>of variation) | 3710 (± 49)                                | 3770 (± 56)                                | 3476 (± 54)                              | 5295 (± 57)                                             |

| End point values                                       | Crizotinib cMS2<br>250 mg + HF<br>meal<br>(Treatment F) | Crizotinib cMS1<br>250 mg +<br>Esomeprazole<br>(Treatment G) | Crizotinib cMS2<br>250 mg +<br>Esomeprazole<br>(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<br>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 |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### 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 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 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 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 + 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 + HF meal (Treatment E) |
|-----------------------|------------------------------------------------|

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) |
|-----------------------|-----------------------------------------------------|

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) |
|-----------------------|------------------------------------|

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 |
|------------------------------------------------|---|---|---|

| <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<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | 0 / 11 (0.00%)<br>0 | 0 / 11 (0.00%)<br>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                           | 0 / 11 (0.00%)                                      | 0 / 22 (0.00%)                     |  |
| occurrences (all)                                     | 0                                                   | 0                                  |  |
| Nervous system disorders                              |                                                     |                                    |  |
| Dizziness                                             |                                                     |                                    |  |
| subjects affected / exposed                           | 0 / 11 (0.00%)                                      | 0 / 22 (0.00%)                     |  |
| occurrences (all)                                     | 0                                                   | 0                                  |  |
| Headache                                              |                                                     |                                    |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)                                      | 1 / 22 (4.55%)                     |  |
| occurrences (all)                                     | 1                                                   | 1                                  |  |
| Lethargy                                              |                                                     |                                    |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)                                      | 1 / 22 (4.55%)                     |  |
| occurrences (all)                                     | 1                                                   | 1                                  |  |
| Eye disorders                                         |                                                     |                                    |  |
| Ocular hyperaemia                                     |                                                     |                                    |  |
| subjects affected / exposed                           | 0 / 11 (0.00%)                                      | 0 / 22 (0.00%)                     |  |
| occurrences (all)                                     | 0                                                   | 0                                  |  |
| Gastrointestinal disorders                            |                                                     |                                    |  |
| Abdominal pain                                        |                                                     |                                    |  |
| subjects affected / exposed                           | 0 / 11 (0.00%)                                      | 2 / 22 (9.09%)                     |  |
| occurrences (all)                                     | 0                                                   | 2                                  |  |
| Abdominal pain upper                                  |                                                     |                                    |  |
| subjects affected / exposed                           | 0 / 11 (0.00%)                                      | 0 / 22 (0.00%)                     |  |
| occurrences (all)                                     | 0                                                   | 0                                  |  |
| Constipation                                          |                                                     |                                    |  |
| subjects affected / exposed                           | 1 / 11 (9.09%)                                      | 2 / 22 (9.09%)                     |  |
| occurrences (all)                                     | 3                                                   | 2                                  |  |
| Diarrhoea                                             |                                                     |                                    |  |

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