



Clinical trial results:

A randomized, multi-centre, double-blind, double dummy placebo controlled single-dose cross-over study to demonstrate that 12 and 24 µg of formoterol delivered by Concept1 has a bronchodilator efficacy which is equivalent to the same dose of formoterol delivered by Aerolizer® in adult and adolescent patients with persistent asthma

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-003225-87 |
| Trial protocol | DE |
| Global end of trial date | 21 May 2007 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2018 |
| First version publication date | 06 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CFOR258D2201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00443482 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharmaceuticals AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, +41 613241111, |
| Scientific contact | Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, +41 613241111, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
|--|----|

| | |
|--|----|
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 May 2007 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 May 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the efficacy of two doses of formoterol, 12 microgram (mcg) and 24 mcg, delivered by Concept1 inhaler device with corresponding doses of formoterol delivered by Aerolizer inhaler device, to demonstrate that two doses of formoterol delivered by the Concept1 device are equivalent to the same doses delivered by the Aerolizer for bronchodilator efficacy in subjects with persistent asthma.

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 Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Subjects who experienced an asthma exacerbation following randomisation were withdrawn from the study. The investigator initiated treatment for such asthma exacerbations as he/she best deemed appropriate. Subjects were provided with an identical formulation of inhaled short-acting β_2 -agonist (salbutamol) as rescue medication. Subjects were instructed not to exceed 8 puffs of rescue medication per 24 hour period. If rescue medication was taken within 6 hours prior to visit, then visit was to be rescheduled to next possible day.

Background therapy:

Subjects received regular anti-inflammatory asthma therapy at a fixed dose regimen, for one month prior to start of pre-randomisation/screening and was continued unchanged throughout the study, unless the subject experienced an asthma exacerbation requiring use of additional anti-inflammatory therapy in opinion of investigator.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 19 February 2007 |
| 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 | Germany: 50 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

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) | 42 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 4 centres in Germany.

Pre-assignment

Screening details:

A total of 53 subjects were screened, out of which 50 subjects were randomised into the study.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment Period I |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to different inhalation devices (Concept1 and Aerolizer) that can be readily distinguished. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Formoterol fumarate 12 mcg via Concept1 device |
|------------------|--|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Concept1 device.

| | |
|------------------|--|
| Arm title | Formoterol fumarate 24 mcg via Concept1 device |
|------------------|--|

Arm description:

Subjects inhaled formoterol 24 mcg capsule orally via Concept1 inhaler device.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Concept1 device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 12 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------------------------|
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 24 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device.

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo capsule inhaled orally via Concept1 and Aerolizer device.

| Number of subjects in period 1 | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device |
|---------------------------------------|--|--|---|
| Started | 10 | 10 | 10 |
| Completed | 10 | 10 | 10 |

| Number of subjects in period 1 | Formoterol fumarate 24 mcg via Aerolizer device | Placebo |
|---------------------------------------|---|---------|
| Started | 10 | 10 |
| Completed | 10 | 10 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treatment Period II |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to different inhalation devices (Concept1 and Aerolizer) that can be readily distinguished. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Formoterol fumarate 12 mcg via Concept1 device |

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Concept1 device.

| | |
|------------------|--|
| Arm title | Formoterol fumarate 24 mcg via Concept1 device |
|------------------|--|

Arm description:

Subjects inhaled formoterol 24 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Concept1 device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 12 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 24 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo capsule inhaled orally via Concept1 and Aerolizer device.

| Number of subjects in period 2 | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device |
|---------------------------------------|--|--|---|
| Started | 10 | 10 | 10 |
| Completed | 10 | 10 | 10 |

| Number of subjects in period 2 | Formoterol fumarate 24 mcg via Aerolizer device | Placebo |
|---------------------------------------|---|---------|
| Started | 10 | 10 |
| Completed | 10 | 10 |

Period 3

| | |
|------------------------------|---|
| Period 3 title | Treatment Period III |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Data analyst, Assessor, Subject |

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to different inhalation devices (Concept1 and Aerolizer) that can be readily distinguished. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study. The treatment period was separated from the next by a washout period of 3 days.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Formoterol fumarate 12 mcg via Concept1 device |
|------------------|--|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------------------|
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
|--|--------------------------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------------|
| Routes of administration | Inhalation use |
|--------------------------|----------------|

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Concept1 device.

| | |
|------------------|--|
| Arm title | Formoterol fumarate 24 mcg via Concept1 device |
|------------------|--|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------------------|
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
|--|--------------------------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------------|
| Routes of administration | Inhalation use |
|--------------------------|----------------|

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Concept1 device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 12 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------------------------|
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
|--|---------------------------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------------|
| Routes of administration | Inhalation use |
|--------------------------|----------------|

Dosage and administration details:

Formoterol capsules 12 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---|
| Arm title | Formoterol fumarate 24 mcg via Aerolizer device |
|------------------|---|

Arm description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------------------------|
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
|--|---------------------------------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

| | |
|--------------------------|----------------|
| Routes of administration | Inhalation use |
|--------------------------|----------------|

Dosage and administration details:

Formoterol capsules 24 mcg inhaled orally via Aerolizer device.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo capsule inhaled orally via Concept1 and Aerolizer device.

| Number of subjects in period 3 | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device |
|---------------------------------------|--|--|---|
| Started | 10 | 10 | 10 |
| Completed | 10 | 10 | 10 |
| Not completed | 0 | 0 | 0 |
| Lost to follow-up | - | - | - |

| Number of subjects in period 3 | Formoterol fumarate 24 mcg via Aerolizer device | Placebo |
|---------------------------------------|---|---------|
| Started | 10 | 10 |
| Completed | 9 | 10 |
| Not completed | 1 | 0 |
| Lost to follow-up | 1 | - |

Period 4

| | |
|------------------------------|---|
| Period 4 title | Treatment Period IV |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Data analyst, Assessor, Subject |

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to different inhalation devices (Concept1 and Aerolizer) that can be readily distinguished. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study. The treatment period was separated from the next by a washout period of 3 days.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|---|---|
| Arm title | Formoterol fumarate 12 mcg via Concept1 device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 12 mcg inhaled orally via Concept1 device. | |
| Arm title | Formoterol fumarate 24 mcg via Concept1 device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 24 mcg inhaled orally via Concept1 device. | |
| Arm title | Formoterol fumarate 12 mcg via Aerolizer device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 12 mcg inhaled orally via Aerolizer device. | |
| Arm title | Formoterol fumarate 24 mcg via Aerolizer device |
| Arm description: Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 24 mcg inhaled orally via Aerolizer device. | |
| Arm title | Placebo |
| Arm description: Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods. | |

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo capsule inhaled orally via Concept1 and Aerolizer device.

| Number of subjects in period 4^[1] | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device |
|---|--|--|---|
| Started | 10 | 10 | 10 |
| Completed | 9 | 10 | 10 |
| Not completed | 1 | 0 | 0 |
| Lost to follow-up | 1 | - | - |
| Joined | 0 | 0 | 0 |
| Transferred in from other group/arm | - | - | - |

| Number of subjects in period 4^[1] | Formoterol fumarate 24 mcg via Aerolizer device | Placebo |
|---|---|---------|
| Started | 9 | 10 |
| Completed | 10 | 10 |
| Not completed | 0 | 0 |
| Lost to follow-up | - | - |
| Joined | 1 | 0 |
| Transferred in from other group/arm | 1 | - |

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Due to the cross-over design of the study, subjects were transferred from one arm of the period to another arm of the next period in a predefined treatment sequence after each period.

Period 5

| | |
|------------------------------|---|
| Period 5 title | Treatment Period V |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

A double-dummy design was used because the identity of the study drugs could not be disguised due to different inhalation devices (Concept1 and Aerolizer) that can be readily distinguished. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study. The treatment period was separated from the next by a washout period of 3 days.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|---|---|
| Arm title | Formoterol fumarate 12 mcg via Concept1 device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 12 mcg inhaled orally via Concept1 device. | |
| Arm title | Formoterol fumarate 24 mcg via Concept1 device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Experimental |
| Investigational medicinal product name | Formoterol fumarate (Concept1) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 24 mcg inhaled orally via Concept1 device. | |
| Arm title | Formoterol fumarate 12 mcg via Aerolizer device |
| Arm description: Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 12 mcg inhaled orally via Aerolizer device. | |
| Arm title | Formoterol fumarate 24 mcg via Aerolizer device |
| Arm description: Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Formoterol fumarate (Aerolizer) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |
| Dosage and administration details: Formoterol capsules 24 mcg inhaled orally via Aerolizer device. | |
| Arm title | Placebo |
| Arm description: Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods. | |

| | |
|--|----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Placebo capsule inhaled orally via Concept1 and Aerolizer device.

| Number of subjects in period 5^[2] | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device |
|---|--|--|---|
| Started | 9 | 10 | 10 |
| Completed | 10 | 10 | 10 |
| Not completed | 0 | 0 | 0 |
| Lost to follow-up | - | - | - |
| Joined | 1 | 0 | 0 |
| Transferred in from other group/arm | 1 | - | - |

| Number of subjects in period 5^[2] | Formoterol fumarate 24 mcg via Aerolizer device | Placebo |
|---|---|---------|
| Started | 10 | 10 |
| Completed | 10 | 9 |
| Not completed | 0 | 1 |
| Lost to follow-up | - | 1 |
| Joined | 0 | 0 |
| Transferred in from other group/arm | - | - |

Notes:

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Due to the cross-over design of the study, subjects were transferred from one arm of the period to another arm of the next period in a predefined treatment sequence after each period.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Treatment Period I |
|-----------------------|--------------------|

Reporting group description: -

| Reporting group values | Treatment Period I | Total | |
|---------------------------------------|--------------------|-------|--|
| Number of subjects | 50 | 50 | |
| Age categorical Units: Subjects | | | |
| Adolescent (18-64 years) | 42 | 42 | |
| Adults (65-74 years) | 8 | 8 | |
| Age continuous Units: years | | | |
| arithmetic mean | 50.1 | | |
| standard deviation | ± 13.24 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 24 | 24 | |
| Male | 26 | 26 | |

End points

End points reporting groups

| | |
|------------------------------|---|
| Reporting group title | Formoterol fumarate 12 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. |
| Reporting group title | Formoterol fumarate 24 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 24 mcg capsule orally via Concept1 inhaler device. |
| Reporting group title | Formoterol fumarate 12 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. |
| Reporting group title | Formoterol fumarate 24 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. |
| Reporting group title | Placebo |
| Reporting group description: | Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. |
| Reporting group title | Formoterol fumarate 12 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 24 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 24 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 12 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 24 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Placebo |
| Reporting group description: | Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 12 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 24 mcg via Concept1 device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 12 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |
| Reporting group title | Formoterol fumarate 24 mcg via Aerolizer device |
| Reporting group description: | Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods. |

days was maintained between two treatment periods.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Formoterol fumarate 12 mcg via Concept1 device |
|-----------------------|--|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Formoterol fumarate 24 mcg via Concept1 device |
|-----------------------|--|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Formoterol fumarate 12 mcg via Aerolizer device |
|-----------------------|---|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Formoterol fumarate 24 mcg via Aerolizer device |
|-----------------------|---|

Reporting group description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Formoterol fumarate 12 mcg via Concept1 device |
|-----------------------|--|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Formoterol fumarate 24 mcg via Concept1 device |
|-----------------------|--|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Formoterol fumarate 12 mcg via Aerolizer device |
|-----------------------|---|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Formoterol fumarate 24 mcg via Aerolizer device |
|-----------------------|---|

Reporting group description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device. A wash-out period of 3 days was maintained between two treatment periods.

| | |
|----------------------------|--|
| Subject analysis set title | Formoterol fumarate 12 mcg via Concept1 device |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received formoterol 12 mcg capsule orally via Concept1 inhaler device in this cross-over study.

| | |
|----------------------------|--|
| Subject analysis set title | Formoterol fumarate 24 mcg via Concept1 device |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received formoterol 24 mcg capsule orally via Concept1 inhaler device in this cross-over study.

| | |
|----------------------------|---|
| Subject analysis set title | Formoterol fumarate 12 mcg via Aerolizer device |
|----------------------------|---|

| | |
|--|---|
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects who received formoterol 12 mcg capsule orally via Aerolizer inhaler device in this cross-over study. | |
| Subject analysis set title | Formoterol fumarate 24 mcg via Aerolizer device |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects who received formoterol 24 mcg capsule orally via Aerolizer inhaler device in this cross-over study. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects who received placebo matching to formoterol capsule orally via Concept1 and Aerolizer inhaler device in this cross-over study. | |

Primary: Area under curve of forced expiratory volume FEV1-AUC(0-12) at 12 hours

| | |
|-----------------|--|
| End point title | Area under curve of forced expiratory volume FEV1-AUC(0-12) at 12 hours ^[1] |
|-----------------|--|

End point description:

FEV1 was defined as the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured using spirometry tests. The FEV1 standardized area under the curve (AUC0-12) was defined as area under the serum concentration-time curve from time 0 to time of the last time point with measurable concentration (0 to 12 hours). AUC of FEV1 followed by single dose of study medication was standardized with respect to length of time completed in the observation period. The primary analysis was performed in Intent-to-treat (ITT) population, defined as all randomized subjects who received at least one treatment. Due to cross-over design of the study, only subjects who received at least two treatments contributed to the primary analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

12 hours

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis for the primary end point has been provided in the attachment.

| End point values | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device | Formoterol fumarate 24 mcg via Aerolizer device |
|-------------------------------------|--|--|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 49 | 50 | 50 | 49 |
| Units: Litre(s) | | | | |
| least squares mean (standard error) | 2.71 (± 0.019) | 2.73 (± 0.019) | 2.67 (± 0.019) | 2.73 (± 0.019) |

| End point values | Placebo | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 49 | | | |
| Units: Litre(s) | | | | |
| least squares mean (standard error) | 2.41 (± 0.019) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area under curve of forced expiratory volume (FEV1-AUC) serial measurement

| | |
|-----------------|--|
| End point title | Area under curve of forced expiratory volume (FEV1-AUC) serial measurement |
|-----------------|--|

End point description:

FEV1 was defined as the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured using spirometry tests. The FEV1-AUC was defined as area under the serum concentration-time curve from time 0 to time of the last time point with measurable concentration. AUC of FEV1 followed by single dose of study medication was standardized with respect to length of time completed in the observation period. The primary analysis was performed in ITT population. Due to cross-over design of the study, only subjects who received at least two treatments contributed to the primary analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 15, 30 minutes, 1, 2, 3, 4, 6, 8, 10, 11 and 12 hours post dosing

| End point values | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device | Formoterol fumarate 24 mcg via Aerolizer device |
|--------------------------------------|--|--|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 49 | 50 | 50 | 49 |
| Units: Litre(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 15 min | 2.7 (± 0.753) | 2.74 (± 0.722) | 2.63 (± 0.706) | 2.69 (± 0.759) |
| 30 min | 2.72 (± 0.778) | 2.78 (± 0.756) | 2.66 (± 0.72) | 2.71 (± 0.774) |
| 1 hour | 2.76 (± 0.787) | 2.81 (± 0.76) | 2.67 (± 0.727) | 2.76 (± 0.802) |
| 2 hours | 2.79 (± 0.775) | 2.82 (± 0.777) | 2.73 (± 0.748) | 2.78 (± 0.808) |
| 3 hours | 2.8 (± 0.802) | 2.83 (± 0.784) | 2.71 (± 0.75) | 2.79 (± 0.799) |
| 4 hours | 2.78 (± 0.794) | 2.82 (± 0.787) | 2.72 (± 0.748) | 2.77 (± 0.811) |
| 6 hours | 2.73 (± 0.806) | 2.76 (± 0.793) | 2.64 (± 0.776) | 2.73 (± 0.801) |
| 8 hours | 2.65 (± 0.829) | 2.7 (± 0.77) | 2.6 (± 0.753) | 2.71 (± 0.798) |
| 10 hours | 2.62 (± 0.842) | 2.65 (± 0.819) | 2.57 (± 0.789) | 2.64 (± 0.809) |
| 11 hours | 2.62 (± 0.816) | 2.64 (± 0.792) | 2.56 (± 0.79) | 2.61 (± 0.814) |
| 12 hours | 2.59 (± 0.846) | 2.61 (± 0.772) | 2.55 (± 0.785) | 2.59 (± 0.825) |

| End point values | Placebo | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 49 | | | |
| Units: Litre(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 15 min | 2.36 (± 0.736) | | | |

| | | | | |
|----------|----------------|--|--|--|
| 30 min | 2.37 (± 0.742) | | | |
| 1 hour | 2.38 (± 0.751) | | | |
| 2 hours | 2.42 (± 0.766) | | | |
| 3 hours | 2.43 (± 0.788) | | | |
| 4 hours | 2.43 (± 0.783) | | | |
| 6 hours | 2.42 (± 0.795) | | | |
| 8 hours | 2.4 (± 0.788) | | | |
| 10 hours | 2.39 (± 0.781) | | | |
| 11 hours | 2.37 (± 0.787) | | | |
| 12 hours | 2.37 (± 0.787) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary excretion of formoterol from 0 to 12 hours (Ae0-12)

| | |
|-----------------|---|
| End point title | Urinary excretion of formoterol from 0 to 12 hours (Ae0-12) |
|-----------------|---|

End point description:

Urinary excretion of formoterol from 0 to 12 hours (Ae0-12) was defined as amount of unchanged formoterol excreted in urine within the 0 to 12 h post-dose collection interval. Ae0-12 was calculated from the formoterol concentrations in urine and the urine volumes using non-compartmental method(s) with WinNonlin Pro (version 5.01). Ae0-12 is reported in nanomoles (nmol) of formoterol free base. Formoterol was measured in urine using Liquid Chromatography–Mass Spectrometry (LC-MS)/MS method. The limit of quantification for urine formoterol was 0.0174 nmol/L. The analysis was performed in the PK population, defined as all completed subjects with quantifiable PK measurements.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 15, 30 minutes, 1, 2, 3, 4, 6, 8, 10, 11 and 12 hours post dosing

| End point values | Formoterol fumarate 12 mcg via Concept1 device | Formoterol fumarate 24 mcg via Concept1 device | Formoterol fumarate 12 mcg via Aerolizer device | Formoterol fumarate 24 mcg via Aerolizer device |
|--------------------------------------|--|--|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 45 | 46 | 41 | 46 |
| Units: nanomole(s) | | | | |
| arithmetic mean (standard deviation) | 1.22 (± 0.42) | 2.46 (± 0.805) | 1.3 (± 0.505) | 2.25 (± 0.77) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until Last Subject Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Formoterol Concept1 12 mcg |
|-----------------------|----------------------------|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Concept1 inhaler device.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Formoterol Aerolizer 24 mcg |
|-----------------------|-----------------------------|

Reporting group description:

Subjects inhaled formoterol 24 mcg capsule orally via Aerolizer inhaler device.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects inhaled placebo matching to formoterol capsule orally via Concept1 and Aerolizer device.

| | |
|-----------------------|----------------------------|
| Reporting group title | Formoterol Concept1 24 mcg |
|-----------------------|----------------------------|

Reporting group description:

Subjects inhaled formoterol 24 mcg capsule orally via Concept1 inhaler device.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Formoterol Aerolizer 12 mcg |
|-----------------------|-----------------------------|

Reporting group description:

Subjects inhaled formoterol 12 mcg capsule orally via Aerolizer inhaler device.

| Serious adverse events | Formoterol Concept1 12 mcg | Formoterol Aerolizer 24 mcg | Placebo |
|---|-------------------------------|--------------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 49 (0.00%) | 0 / 49 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Formoterol Concept1 24 mcg | Formoterol Aerolizer 12 mcg | |
|---|-------------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (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: 2 %

| Non-serious adverse events | Formoterol Concept1 12 mcg | Formoterol Aerolizer 24 mcg | Placebo |
|--|-------------------------------|--------------------------------|----------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 49 (4.08%) | 5 / 49 (10.20%) | 2 / 49 (4.08%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 49 (4.08%) | 2 / 49 (4.08%) |
| occurrences (all) | 1 | 2 | 2 |
| Tremor | | | |
| subjects affected / exposed | 1 / 49 (2.04%) | 2 / 49 (4.08%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 1 / 49 (2.04%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 49 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 49 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Formoterol Concept1 24 mcg | Formoterol Aerolizer 12 mcg | |
|--|-------------------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 50 (6.00%) | 3 / 50 (6.00%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 50 (2.00%) | |
| occurrences (all) | 1 | 1 | |
| Tremor | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 1 / 50 (2.00%) 1 | |
| General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 | |
| Psychiatric disorders Restlessness subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 0 / 50 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 June 2006 | Adolescent subjects were excluded from the study. |
| 19 December 2006 | PK sampling and analysis was included to the protocol as requested by the Food and Drug Administration (FDA). The exclusion criteria was updated to exclude severe asthmatic subjects as per recommendation from German Ethics Committee. |
| 24 January 2007 | Updated urine collection procedures. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> for complete trial results.

Notes: