



Clinical trial results:

A Study to Assess the Effect of AF-219 on Cough Reflex Sensitivity in Both Healthy and Chronic Cough Subjects

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-000464-34 |
| Trial protocol | GB |
| Global end of trial date | 16 May 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v2 (current) |
| This version publication date | 30 June 2021 |
| First version publication date | 31 May 2017 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 7264-015 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02397460 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 May 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this double-blind crossover study is to assess the effect of single doses of 50 mg and 300 mg gefapixant (AF-219/MK-7264) on cough reflex sensitivity to capsaicin in both healthy participants and participants with chronic cough. This study will also assess the effect of single doses of gefapixant on cough reflex sensitivity to adenosine triphosphate (ATP) in healthy participants and participants with chronic cough.

Protection of trial subjects:

The Investigators agreed to conduct the study in compliance with the study Protocol, with the International Standard of Good Clinical Practice (GCP) procedures, with all applicable local GCP standards and regulations, and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 29 April 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 50 |
| Worldwide total number of subjects | 50 |
| 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) | 42 |
| From 65 to 84 years | 8 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The main purpose of the 14-day Screening period (Day -14 to Day -1) was to ensure that each participant met all the specified eligibility criteria. In addition, cough sensitivity was measured at Screening by standard clinical methodology using cough challenge in response to capsaicin.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |

Arm description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo (PBO) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received single doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between

treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| Number of subjects in period 1 | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|---------------------------------------|---|---|--|
| Started | 7 | 7 | 6 |
| Completed | 7 | 7 | 6 |

| Number of subjects in period 1 | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|---------------------------------------|--|---|---|
| Started | 6 | 6 | 6 |
| Completed | 6 | 6 | 6 |

| Number of subjects in period 1 | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|---------------------------------------|--|--|
| Started | 6 | 6 |
| Completed | 6 | 6 |

Period 2

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |

Arm description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received single doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between

treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|---|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Gefapixant 50 mg, administered as a single oral dose | |
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |

Arm description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|---|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Gefapixant matching placebo, administered as a single oral dose | |

| Number of subjects in period 2 | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|--------------------------------|---|---|--|
| Started | 7 | 7 | 6 |
| Completed | 7 | 7 | 6 |
| Not completed | 0 | 0 | 0 |
| Adverse event, non-fatal | - | - | - |

| Number of subjects in period 2 | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|--------------------------------|--|---|---|
| Started | 6 | 6 | 6 |
| Completed | 6 | 6 | 6 |
| Not completed | 0 | 0 | 0 |
| Adverse event, non-fatal | - | - | - |

| Number of subjects in period 2 | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|--------------------------------|--|--|
| Started | 6 | 6 |

| | | |
|--------------------------|---|---|
| Completed | 6 | 5 |
| Not completed | 0 | 1 |
| Adverse event, non-fatal | - | 1 |

Period 3

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |

Arm description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received single doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between

treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| Number of subjects in period 3 | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|---------------------------------------|---|---|--|
| Started | 7 | 7 | 6 |
| Completed | 7 | 7 | 6 |

| Number of subjects in period 3 | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|---------------------------------------|--|---|---|
| Started | 6 | 6 | 6 |
| Completed | 6 | 6 | 6 |

| Number of subjects in period 3 | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|---------------------------------------|--|--|
| Started | 6 | 5 |
| Completed | 6 | 5 |

Period 4

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |

Arm description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received single doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between

treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 300 mg, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 50 mg, administered as a single oral dose

| | |
|------------------|--|
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|------------------|--|

Arm description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant matching placebo, administered as a single oral dose

| | |
|------------------|---|
| Arm title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|------------------|---|

Arm description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|--|---|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Gefapixant 50 mg, administered as a single oral dose | |
| Arm title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |

Arm description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|---|-------------------------|
| Arm type | Experimental or placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Gefapixant matching placebo, administered as a single oral dose | |

| Number of subjects in period 4 | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|---------------------------------------|---|---|--|
| Started | 7 | 7 | 6 |
| Completed | 7 | 6 | 6 |
| Not completed | 0 | 1 | 0 |
| Physician decision | - | - | - |
| Adverse event, non-fatal | - | 1 | - |

| Number of subjects in period 4 | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|---------------------------------------|--|---|---|
| Started | 6 | 6 | 5 |
| Completed | 6 | 5 | 5 |
| Not completed | 0 | 1 | 0 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | - | - | - |

| Number of subjects in period 4 | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|---------------------------------------|--|--|
| Started | 6 | 6 |
| Completed | 6 | 6 |
| Not completed | 0 | 0 |
| Physician decision | - | - |
| Adverse event, non-fatal | - | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| Reporting group values | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|---|---|---|--|
| Number of subjects | 7 | 7 | 6 |
| Age Categorical | | | |
| Participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |

| | | | |
|---|---------|--------|--------|
| Age Continuous | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: years | | | |
| arithmetic mean | 34.1 | 40.9 | 61.0 |
| standard deviation | ± 11.87 | ± 6.20 | ± 9.25 |
| Gender Categorical | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 5 |
| Male | 7 | 7 | 1 |

| Reporting group values | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|---|--|---|---|
| Number of subjects | 6 | 6 | 6 |
| Age Categorical | | | |
| Participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age Continuous | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: years | | | |
| arithmetic mean | 59.5 | 35.0 | 34.7 |
| standard deviation | ± 8.38 | ± 8.17 | ± 7.42 |
| Gender Categorical | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |
| Female | 5 | 0 | 0 |
| Male | 1 | 6 | 6 |

| Reporting group values | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC | Total |
|---|--|--|-------|
| Number of subjects | 6 | 6 | 50 |
| Age Categorical | | | |
| Participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|----|
| Age Continuous | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: years | | | |
| arithmetic mean | 60.5 | 55 | |
| standard deviation | ± 6.83 | ± 9.01 | - |
| Gender Categorical | | | |
| Healthy participants who received AF-219 300 mg (Cohort 1), AF-219 50 mg (Cohort 2), or placebo (Cohorts 1 and 2) | | | |
| Units: Subjects | | | |
| Female | 5 | 4 | 19 |
| Male | 1 | 2 | 31 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |
| Reporting group description: Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
| Reporting group description: Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
| Reporting group description: Participants with chronic cough (CC) in Cohort 1/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
| Reporting group description: Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
| Reporting group description: Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
| Reporting group description: Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
| Reporting group description: Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
| Reporting group description: Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods. | |
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |

Reporting group description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of

Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence A received single doses of placebo (PBO) on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 1/Sequence B received single doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: PBOGefapixant 300 mgPBOGefapixant 300 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough (CC) in Cohort 1/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 300 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between

treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Gefapixant 300 mgPBOGefapixant 300 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 1/Sequence B received singles doses of gefapixant 300 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence A received singles doses of placebo on Day 1 of Periods 1 and 3 and single doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/Healthy |
|-----------------------|--|

Reporting group description:

Healthy participants in Cohort 2/Sequence B received single doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and single doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: PBOGefapixant 50 mgPBOGefapixant 50 mg/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence A received singles doses of placebo on Day of Periods 1 and 3 and singles doses of gefapixant 50 mg on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: Gefapixant 50 mgPBOGefapixant 50 mgPBO/CC |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 2/Sequence B received singles doses of gefapixant 50 mg on Day 1 of Periods 1 and 3 and singles doses of placebo on Day 1 of Periods 2 and 4. (Each treatment period consisted of Day 1 and Day 2.) There was a minimum 48-hour washout period between treatment periods.

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | Cohort 1: Gefapixant 300 mg/Healthy |
|----------------------------|-------------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Healthy males and females in Cohort 1 who received single doses of gefapixant 300 mg in Periods 1 and 2 combined

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Cohort 1: Placebo/Healthy |
|----------------------------|---------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Healthy males and females in Cohort 1 who received single doses of placebo in Periods 1 and 2 combined

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 1: Gefapixant 300 mg/Chronic Cough |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Males and females with chronic cough in Cohort 1 who received single doses of gefapixant 300 mg in Periods 1 and 2 combined

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Cohort 1: Placebo/Chronic Cough |
|----------------------------|---------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Males and females in Cohort 1 with chronic cough who received single doses of placebo in Periods 1 and 2 combined

| | |
|----------------------------|------------------------------------|
| Subject analysis set title | Cohort 2: Gefapixant 50 mg/Healthy |
|----------------------------|------------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Healthy males and females who received single doses of gefapixant 50 mg in Periods 1 and 2 combined

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Cohort 2: Placebo/Healthy |
|----------------------------|---------------------------|

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description: Healthy males and females in Cohort 2 who received single doses of placebo in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 2: Gefapixant 50 mg/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Males and females with chronic cough in Cohort 2 who received single doses of gefapixant 50 mg in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 2: Placebo/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Males and females with chronic cough in Cohort 2 who received single doses of placebo in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 1: Gefapixant 300 mg/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 1 who received single doses of gefapixant 300 mg in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 1: Placebo/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 1 who received single doses of placebo in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 2: Gefapixant 50 mg/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 2 who received single doses of gefapixant 50 mg in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 2: Placebo/Chronic Cough |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 2 who received single doses of placebo in Periods 1 and 2 combined | |
| Subject analysis set title | Cohort 1: Gefapixant 300 mg/Healthy |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Healthy participants in Cohort 1 who received single doses of gefapixant 300 mg | |
| Subject analysis set title | Cohort 1: Placebo/Healthy |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Healthy participants in Cohort 1 who received single doses of placebo | |
| Subject analysis set title | Cohort 1: Gefapixant 300 mg/Chronic Cough |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 1 who received single doses of gefapixant 300 mg | |
| Subject analysis set title | Cohort 1: Placebo/Chronic Cough |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 1 who received single doses of placebo | |
| Subject analysis set title | Cohort 2: Gefapixant 50 mg/Healthy |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Healthy participants in Cohort 2 who received single doses of gefapixant 50 mg | |

| | |
|---|--|
| Subject analysis set title | Cohort 2: Placebo/Healthy |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Healthy participants in Cohort 2 who received single doses of placebo | |
| Subject analysis set title | Cohort 2: Gefapixant 50 mg/Chronic Cough |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 2 who received single doses of gefapixant 50 mg | |
| Subject analysis set title | Cohort 2: Placebo/Chronic Cough |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants with chronic cough in Cohort 2 who received single doses of placebo | |
| Subject analysis set title | Placebo/Healthy Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Healthy males who received single doses of placebo in Periods 1 and 2 | |
| Subject analysis set title | Placebo/Chronic Cough Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Males with chronic cough who received single doses of placebo in Periods 1 and 2 | |
| Subject analysis set title | Placebo/Chronic Cough Females |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Females with chronic cough who received single doses of placebo in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 50 mg/Healthy Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Healthy males who received single doses of gefapixant 50 mg in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 50 mg/Chronic Cough Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Males with chronic cough who received single doses of gefapixant 50 mg in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 50 mg/Chronic Cough Females |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Females with chronic cough who received single doses of gefapixant 50 mg in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 300 mg/Healthy Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Healthy males who received single doses of gefapixant 300 mg in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 300 mg/Chronic Cough Males |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Males with chronic cough who received single doses of gefapixant 300 mg in Periods 1 and 2 | |
| Subject analysis set title | Gefapixant 300 mg/Chronic Cough Females |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Females with chronic cough who received single doses of gefapixant 300 mg in Periods 1 and 2 | |

Primary: Cough Reflex Sensitivity to Capsaicin Measured by Maximal Cough Response (Emax)

| | |
|-----------------|---|
| End point title | Cough Reflex Sensitivity to Capsaicin Measured by Maximal Cough Response (Emax) |
|-----------------|---|

End point description:

The effect of single doses of 50 mg and 300 mg gefapixant on cough reflex sensitivity to challenge with capsaicin was assessed. Capsaicin-evoked cough challenge was performed 2 hours post-dose in Periods 1 and 2. For capsaicin challenge, doubling concentrations from 0.49 µM to 1000 µM were prepared by dilution of stock solutions with saline, and were administered by inhalation. The number of explosive cough sounds occurring within the first 15 seconds after inhalation were recorded. Nonlinear mixed-effects modeling was used to estimate the Emax. Population pharmacodynamic modeling was performed in NONMEM 7.3. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. Note: All values presented are model-based. The analysis population included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose primary endpoint assessment of Emax in response to capsaicin challenge.

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

End point timeframe:

2 hours post-dose

| End point values | Placebo/Healthy Males | Placebo/Chronic Cough Males | Placebo/Chronic Cough Females | Gefapixant 50 mg/Healthy Males |
|---------------------------------------|-----------------------|-----------------------------|-------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 5 | 18 | 26 |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 4.14 | 4.14 | 7.57 | 3.66 |

| End point values | Gefapixant 50 mg/Chronic Cough Males | Gefapixant 50 mg/Chronic Cough Females | Gefapixant 300 mg/Healthy Males | Gefapixant 300 mg/Chronic Cough Males |
|---------------------------------------|--------------------------------------|--|---------------------------------|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 18 | 26 | 5 |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 3.37 | 6.17 | 3.66 | 3.37 |

| End point values | Gefapixant 300 mg/Chronic Cough Females | | | |
|---------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 18 | | | |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 6.17 | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Emax Response: Gefapixant vs Placebo |
| Statistical analysis description: | |
| Treatment effects on Emax following capsaicin challenge were modeled for dose dependence and were estimated on the basis of disease status for participants who were healthy or had chronic cough and received gefapixant 50 mg, gefapixant 300 mg, or placebo. | |
| Comparison groups | Placebo/Healthy Males v Placebo/Chronic Cough Males v Placebo/Chronic Cough Females v Gefapixant 50 mg/Healthy Males v Gefapixant 50 mg/Chronic Cough Males v Gefapixant 50 mg/Chronic Cough Females v Gefapixant 300 mg/Healthy Males v Gefapixant 300 mg/Chronic Cough Males v Gefapixant 300 mg/Chronic Cough Females |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |

Primary: Cough Reflex Sensitivity to Capsaicin Measured by the Tussive Concentration Required to Achieve 50% of Emax (ED50)

| | |
|---|--|
| End point title | Cough Reflex Sensitivity to Capsaicin Measured by the Tussive Concentration Required to Achieve 50% of Emax (ED50) |
| End point description: | |
| The effect of single doses of 50 mg and 300 mg gefapixant on cough reflex sensitivity to challenge with capsaicin was assessed. Capsaicin-evoked cough challenge was performed 2 hours post-dose in Periods 1 and 2. The concentration of capsaicin required to induce 50% of the Emax (ED50) was assessed. For capsaicin challenge, doubling concentrations from 0.49 µM to 1000 µM were prepared by dilution of stock solutions with saline, and were administered by inhalation. Nonlinear mixed-effects modeling was used to estimate the ED50. Population pharmacodynamic modeling was performed in NONMEM 7.3 using Laplace estimation method. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. Note: All values presented are model-based. The analysis population included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose primary endpoint assessment of ED50 in response to capsaicin challenge. | |
| End point type | Primary |
| End point timeframe: | |
| 2 hours post-dose | |

| End point values | Placebo/Healthy Males | Placebo/Chronic Cough Males | Placebo/Chronic Cough Females | Gefapixant 50 mg/Healthy Males |
|-----------------------------|-----------------------|-----------------------------|-------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 5 | 18 | 26 |
| Units: µM | | | | |
| number (not applicable) | 33 | 33 | 9.56 | 33 |

| End point values | Gefapixant 50 mg/Chronic Cough Males | Gefapixant 50 mg/Chronic Cough Females | Gefapixant 300 mg/Healthy Males | Gefapixant 300 mg/Chronic Cough Males |
|-----------------------------|--------------------------------------|--|---------------------------------|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 18 | 26 | 5 |

| | | | | |
|-------------------------|----|------|----|----|
| Units: μM | | | | |
| number (not applicable) | 33 | 9.56 | 33 | 33 |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Gefapixant 300 mg/Chronic Cough Females | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 18 | | | |
| Units: μM | | | | |
| number (not applicable) | 9.56 | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | ED50 Response: Gefapixant vs Placebo |
| Statistical analysis description: | |
| Treatment effects following capsaicin challenge were modeled for dose dependence and were estimated on the basis of disease status for participants who had chronic cough and received gefapixant 50 mg, gefapixant 300 mg, or placebo. | |
| Comparison groups | Placebo/Healthy Males v Placebo/Chronic Cough Males v Placebo/Chronic Cough Females v Gefapixant 50 mg/Healthy Males v Gefapixant 50 mg/Chronic Cough Males v Gefapixant 50 mg/Chronic Cough Females v Gefapixant 300 mg/Healthy Males v Gefapixant 300 mg/Chronic Cough Males v Gefapixant 300 mg/Chronic Cough Females |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |

Secondary: Cough Reflex Sensitivity to Adenosine Triphosphate (ATP) Measured by Maximal Cough Response (Emax)

| | |
|---|--|
| End point title | Cough Reflex Sensitivity to Adenosine Triphosphate (ATP) Measured by Maximal Cough Response (Emax) |
| End point description: | |
| The effect of single doses of 50 mg and 300 mg gefapixant on cough reflex sensitivity to challenge with adenosine triphosphate (ATP) was assessed. ATP-evoked cough challenge was performed 2 hours post-dose in Periods 3 and 4. For ATP challenge, doubling concentrations from 0.227 $\mu\text{mol/mL}$ to 929 $\mu\text{mol/mL}$ were prepared from ATP powder dissolved in saline, and were administered by inhalation. The number of explosive cough sounds occurring within the first 15 seconds after inhalation were recorded. Nonlinear mixed-effects modeling was used to estimate the Emax. Population pharmacodynamic modeling was performed in NONMEM 7.3. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. Note: All values presented are model-based. The analysis population included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of Emax in response to ATP challenge. | |
| End point type | Secondary |
| End point timeframe: | |
| 2 hours post-dose | |

| End point values | Placebo/Healthy Males | Placebo/Chronic Cough Males | Placebo/Chronic Cough Females | Gefapixant 50 mg/Healthy Males |
|---------------------------------------|-----------------------|-----------------------------|-------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 4 | 18 | 26 |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 2.35 | 2.35 | 5.4 | 2.35 |

| End point values | Gefapixant 50 mg/Chronic Cough Males | Gefapixant 50 mg/Chronic Cough Females | Gefapixant 300 mg/Healthy Males | Gefapixant 300 mg/Chronic Cough Males |
|---------------------------------------|--------------------------------------|--|---------------------------------|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 18 | 26 | 4 |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 2.35 | 5.4 | 2.35 | 2.35 |

| End point values | Gefapixant 300 mg/Chronic Cough Females | | | |
|---------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 18 | | | |
| Units: Emax (Explosive coughs/15 sec) | | | | |
| number (not applicable) | 5.4 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Reflex Sensitivity to ATP Measured by the Tussive Concentration Required to Achieve 50% of Emax (E50)

| | |
|-----------------|---|
| End point title | Cough Reflex Sensitivity to ATP Measured by the Tussive Concentration Required to Achieve 50% of Emax (E50) |
|-----------------|---|

End point description:

The effect of single doses of 50 mg and 300 mg gefapixant on cough reflex sensitivity to challenge with ATP was assessed. ATP-evoked cough challenge was performed 2 hours post-dose in Periods 3 and 4. The concentration of ATP required to induce 50% of the Emax (ED50) was assessed. For ATP challenge, doubling concentrations from 0.227 µmol/mL to 929 µmol/mL were prepared by dilution of stock solutions with saline, and were administered by inhalation. Nonlinear mixed-effects modeling was used to estimate the ED50. Population pharmacodynamic modeling was performed in NONMEM 7.3 using Laplace estimation method. Data exploration, goodness-of-fit plots, statistical analyses, and simulations were performed in Matlab R2015a. Note: All values presented are model-based. The analysis population included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of ED50 in response to ATP challenge.

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

End point timeframe:

2 hours post-dose

| End point values | Placebo/Healthy Males | Placebo/Chronic Cough Males | Placebo/Chronic Cough Females | Gefapixant 50 mg/Healthy Males |
|-----------------------------|-----------------------|-----------------------------|-------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 14 | 4 | 18 | 26 |
| Units: $\mu\text{mol/mL}$ | | | | |
| number (not applicable) | 54.9 | 54.9 | 8.63 | 119.13 |

| End point values | Gefapixant 50 mg/Chronic Cough Males | Gefapixant 50 mg/Chronic Cough Females | Gefapixant 300 mg/Healthy Males | Gefapixant 300 mg/Chronic Cough Males |
|-----------------------------|--------------------------------------|--|---------------------------------|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 18 | 26 | 4 |
| Units: $\mu\text{mol/mL}$ | | | | |
| number (not applicable) | 155.92 | 24.51 | 119.13 | 192.7 |

| End point values | Gefapixant 300 mg/Chronic Cough Females | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 18 | | | |
| Units: $\mu\text{mol/mL}$ | | | | |
| number (not applicable) | 30.29 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Capsaicin Inducing 2 or More Coughs (C2)

| | |
|-----------------|--|
| End point title | Concentrations of Capsaicin Inducing 2 or More Coughs (C2) |
|-----------------|--|

End point description:

The concentrations of capsaicin inducing 2 or more coughs (C2) in participants were assessed in Periods 1 and 2. For capsaicin challenge, doubling concentrations from 0.49 μM to 1000 μM were prepared by dilution of stock solutions with saline, and were administered by inhalation. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of C2 in response to capsaicin challenge.

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

End point timeframe:

2 hours post-dose

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chroni c Cough |
|-------------------------------|---|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 14 | 10 | 10 |
| Units: μM | | | | |
| median (full range (min-max)) | 31.25 (4 to 1000) | 31.25 (4 to 500) | 3.90 (0 to 16) | 7.81 (0 to 31) |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chroni c Cough |
|-------------------------------|--|----------------------------------|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 10 | 12 |
| Units: μM | | | | |
| median (full range (min-max)) | 15.62 (2 to 63) | 23.44 (8 to 125) | 15.62 (0 to 125) | 5.86 (0 to 250) |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Capsaicin Inducing 5 or More Coughs (C5)

| | |
|---|--|
| End point title | Concentrations of Capsaicin Inducing 5 or More Coughs (C5) |
| End point description: The concentrations of capsaicin inducing 5 or more coughs (C5) in participants were assessed in Periods 1 and 2. For capsaicin challenge, doubling concentrations from 0.49 μM to 1000 μM were prepared by dilution of stock solutions with saline, and were administered by inhalation. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of C5 in response to capsaicin challenge. | |
| End point type | Secondary |
| End point timeframe: 2 hours post-dose | |

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chroni c Cough |
|-------------------------------|---|----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 6 | 10 | 10 |
| Units: μM | | | | |
| median (full range (min-max)) | 31.25 (16 to 250) | 62.50 (16 to 1000) | 3.90 (0 to 31) | 11.72 (0 to 125) |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|-------------------------------|--|----------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 7 | 7 | 10 |
| Units: µM | | | | |
| median (full range (min-max)) | 250.00 (63 to 500) | 125.00 (63 to 500) | 15.62 (2 to 63) | 5.86 (0 to 31) |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of ATP Inducing 2 or More Coughs (C2)

| | |
|--|--|
| End point title | Concentrations of ATP Inducing 2 or More Coughs (C2) |
| End point description: | |
| The concentrations of ATP inducing 2 or more coughs (C2) in participants were assessed in Periods 3 and 4. For ATP challenge, doubling concentrations from 0.227 to 929 µmol/mL were prepared from ATP powder, dissolved and diluted in saline, and administered by inhalation. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of C2 in response to ATP challenge. | |
| End point type | Secondary |
| End point timeframe: | |
| 2 hours post-dose | |

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough |
|-------------------------------|---|----------------------------------|--|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 10 | 11 | 7 | 11 |
| Units: mg/mL | | | | |
| median (full range (min-max)) | 192.00 (8 to 256) | 64.00 (1 to 512) | 8.00 (0 to 64) | 1.00 (0 to 64) |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|-------------------------------|--|----------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 8 | 8 | 9 |
| Units: mg/mL | | | | |
| median (full range (min-max)) | 16.00 (8 to 256) | 24.00 (2 to 512) | 4.25 (0 to 512) | 4.00 (0 to 256) |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of ATP Inducing 5 or More Coughs (C5)

| | |
|-----------------|--|
| End point title | Concentrations of ATP Inducing 5 or More Coughs (C5) |
|-----------------|--|

End point description:

The concentrations of ATP inducing 5 or more coughs (C5) in participants were assessed in Periods 3 and 4. For ATP challenge, doubling concentrations from 0.227 to 929 µmol/mL were prepared from ATP powder, dissolved and diluted in saline, and administered by inhalation. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of C5 in response to ATP challenge.

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

End point timeframe:

2 hours post-dose

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough |
|-------------------------------|---|----------------------------------|--|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 2 | 5 | 7 | 8 |
| Units: mg/mL | | | | |
| median (full range (min-max)) | 192.00 (128 to 256) | 128.0 (64 to 256) | 8.00 (0 to 64) | 16.50 (0 to 512) |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|-------------------------------|--|----------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 4 | 5 | 8 |
| Units: mg/mL | | | | |
| median (full range (min-max)) | 64.00 (32 to 256) | 32.00 (2 to 32) | 128.00 (8 to 512) | 4.00 (0 to 128) |

Statistical analyses

No statistical analyses for this end point

Secondary: Urge-to-Cough in Response to Capsaicin Challenge (Chronic Cough)

Participants Only)

| | |
|-----------------|--|
| End point title | Urge-to-Cough in Response to Capsaicin Challenge (Chronic Cough Participants Only) |
|-----------------|--|

End point description:

In response to capsaicin challenges in Periods 1 and 2, participants with chronic cough completed a visual analogue scale (VAS) at the end of a 4-hour post-dose observation period on Day 1; and at end of 24-hour observation period on Day 2. For both periods, participants were asked to mark on a 100 mm VAS the severity of their urge to cough between 0 mm (no urge-to-cough) and 100 mm (worst urge-to-cough). The analysis population for this endpoint included all randomized participants with chronic cough who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of urge-to-cough in response to capsaicin challenge.

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

End point timeframe:

At the end of a 4-hour post-dose observation period on Day 1; at the end of a 24-hour observation period on Day 2

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 11 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 28.9 (± 29.79) | 38.6 (± 26.82) | 36.6 (± 30.84) | 20.5 (± 11.54) |
| Day 2 | 28.2 (± 32.72) | 46.7 (± 29.20) | 41.8 (± 31.02) | 36.7 (± 23.28) |

Statistical analyses

No statistical analyses for this end point

Secondary: Urge-to-Cough in Response to ATP Challenge (Chronic Cough Participants Only)

| | |
|-----------------|--|
| End point title | Urge-to-Cough in Response to ATP Challenge (Chronic Cough Participants Only) |
|-----------------|--|

End point description:

In response to ATP challenges in Periods 3 and 4, participants with chronic cough completed a VAS at the end of a 4-hour post-dose observation period on Day 1; and at end of 24-hour observation period on Day 2. For both periods, participants were asked to mark on a 100 mm VAS the severity of their urge to cough between 0 mm (no urge-to-cough) and 100 mm (worst urge-to-cough). The analysis population for this endpoint included all randomized participants with chronic cough who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of urge-to-cough in response to ATP challenge.

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

End point timeframe:

At the end of a 4-hour post-dose observation period on Day 1; at the end of a 24-hour observation period on Day 2

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 11 | 11 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 19.8 (± 23.54) | 34.4 (± 26.78) | 21.5 (± 22.45) | 25.3 (± 19.69) |
| Day 2 | 21.6 (± 20.65) | 39.8 (± 26.51) | 27.5 (± 29.54) | 37.5 (± 27.33) |

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity in Response to Capsaicin Challenge (Chronic Cough Participants Only)

| | |
|-----------------|---|
| End point title | Cough Severity in Response to Capsaicin Challenge (Chronic Cough Participants Only) |
|-----------------|---|

End point description:

In response to capsaicin challenges in Periods 1 and 2, participants with chronic cough completed a VAS at the end of a 4-hour post-dose observation period on Day 1; and at end of 24-hour observation period on Day 2. For both periods, participants were asked to mark on a 100 mm VAS their cough severity between 0 mm (no cough) and 100 mm (worst cough). The analysis population for this endpoint included all randomized participants with chronic cough who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of cough severity in response to capsaicin challenge.

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

End point timeframe:

At the end of a 4-hour post-dose observation period; at the end of a 24-hour observation period on Day 2

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 11 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 28.2 (± 30.71) | 35.7 (± 24.32) | 30.9 (± 27.22) | 20.5 (± 12.75) |
| Day 2 | 25.8 (± 30.20) | 44.3 (± 27.43) | 39.8 (± 28.97) | 35.5 (± 22.25) |

Statistical analyses

No statistical analyses for this end point

Secondary: Cough Severity in Response to ATP Challenge (Chronic Cough

Participants Only)

| | |
|-----------------|---|
| End point title | Cough Severity in Response to ATP Challenge (Chronic Cough Participants Only) |
|-----------------|---|

End point description:

In response to ATP challenge in Periods 3 and 4, participants with chronic cough completed a VAS at the end of a 4-hour post-dose observation period on Day 1; and at end of 24-hour observation period on Day 2. For both periods, participants were asked to mark on a 100 mm VAS their cough severity between 0 mm (no cough) and 100 mm (worst cough). The analysis population for this endpoint included all randomized participants with chronic cough who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of cough severity in response to ATP challenge.

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

End point timeframe:

At the end of a 4-hour post-dose observation period on Day 1; at the end of a 24-hour observation period on Day 2

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 11 | 11 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 21.5 (± 27.06) | 32.7 (± 24.23) | 21.2 (± 21.04) | 23.5 (± 16.02) |
| Day 2 | 18.9 (± 18.29) | 36.8 (± 26.50) | 27.5 (± 26.78) | 35.5 (± 24.07) |

Statistical analyses

No statistical analyses for this end point

Secondary: Daytime Cough Frequency in Participants With Chronic Cough Who Underwent Capsaicin Challenge

| | |
|-----------------|--|
| End point title | Daytime Cough Frequency in Participants With Chronic Cough Who Underwent Capsaicin Challenge |
|-----------------|--|

End point description:

Daily cough frequency monitoring was performed in participants with chronic cough, who were attached to a digital sound recorder with 2 microphones (a lapel air microphone attached to the participant's clothing and an adhesive chest wall microphone attached to the skin at the top of the sternum). Participants wore the sound recorder from the start of capsaicin challenge to bedtime on Day 1 in Periods 1 and 2. The resulting recording was processed by software which cut out the majority of speech and background noise but retained cough sounds. The investigator listened to the recording and documented the number of coughs per hour. The analysis population for this endpoint included all randomized participants with chronic cough who received at least 1 dose of study medication and had at least 1 post-dose secondary endpoint assessment of daytime cough frequency in response to capsaicin challenge.

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

End point timeframe:

From start of challenge (2 hours post-dose) to bedtime; up to 12 hours

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: coughs/hour | | | | |
| arithmetic mean (standard deviation) | 13.7 (± 13.85) | 19.1 (± 16.76) | 15.5 (± 16.92) | 20.3 (± 13.27) |

Statistical analyses

No statistical analyses for this end point

Secondary: Daytime Cough Frequency in Participants With Chronic Cough Who Underwent ATP Challenge

| | |
|-----------------|--|
| End point title | Daytime Cough Frequency in Participants With Chronic Cough Who Underwent ATP Challenge |
|-----------------|--|

End point description:

Daily cough frequency monitoring was performed in participants with chronic cough, who were attached to a digital sound recorder with 2 microphones (a lapel air microphone attached to the participant's clothing and an adhesive chest wall microphone attached to the skin at the top of the sternum). Participants wore the sound recorder from the start of ATP challenge to bedtime on Day 1 in Periods 3 and 4. The resulting recording was processed by software which cut out the majority of speech and background noise but retained cough sounds. The investigator listened to the recording and documented the number of coughs per hour. The analysis population for this endpoint included all treated participants with chronic cough who had at least 1 post-dose secondary endpoint assessment of daytime cough frequency in response to ATP challenge.

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

End point timeframe:

From start of challenge (2 hours post-dose) to bedtime; up to 12 hours

| End point values | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|--------------------------------------|--|---------------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 11 | 11 |
| Units: coughs/hour | | | | |
| arithmetic mean (standard deviation) | 10.3 (± 11.65) | 22.3 (± 15.48) | 15.6 (± 17.31) | 26.4 (± 16.75) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced at Least One Adverse Event

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Experienced at Least One Adverse Event |
|-----------------|---|

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication.

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

End point timeframe:

Up to Day 41

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough |
|-----------------------------------|---|----------------------------------|--|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 14 | 14 | 12 | 12 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 100.0 | 35.7 | 100.0 | 58.3 |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|-----------------------------------|--|----------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 11 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 75.0 | 33.3 | 50.0 | 27.3 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Discontinued Study Treatment Due to an Adverse Event |
|-----------------|---|

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The analysis population for this endpoint included all randomized participants who received at least 1 dose of study medication.

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

End point timeframe:

Up to Day 24

| End point values | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Health y | Cohort 1: Gefapixant 300 mg/Chronic Cough | Cohort 1: Placebo/Chronic Cough |
|-----------------------------------|---|----------------------------------|--|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 14 | 14 | 12 | 12 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.0 | 0.0 | 0.0 | 0.0 |

| End point values | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Health y | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough |
|-----------------------------------|--|----------------------------------|---|---------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 11 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.0 | 0.0 | 0.0 | 0.0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 41

Adverse event reporting additional description:

The safety analysis population included all randomized participants who received at least 1 dose of study medication. The analysis population for number of deaths (all causes) included all randomized participants.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Cohort 1: Gefapixant 300 mg/Healthy |
|-----------------------|-------------------------------------|

Reporting group description:

Healthy participants in Cohort 1 who received single doses of gefapixant 300 mg

| | |
|-----------------------|---------------------------|
| Reporting group title | Cohort 1: Placebo/Healthy |
|-----------------------|---------------------------|

Reporting group description:

Healthy participants in Cohort 1 who received single doses of placebo

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Gefapixant 300 mg/Chronic Cough |
|-----------------------|---|

Reporting group description:

Participants with chronic cough in Cohort 1 who received single doses

| | |
|-----------------------|---------------------------------|
| Reporting group title | Cohort 1: Placebo/Chronic Cough |
|-----------------------|---------------------------------|

Reporting group description:

Participants with chronic cough in Cohort 1 who received single doses of placebo

| | |
|-----------------------|------------------------------------|
| Reporting group title | Cohort 2: Gefapixant 50 mg/Healthy |
|-----------------------|------------------------------------|

Reporting group description:

Healthy participants in Cohort 2 who received single doses of gefapixant 50 mg

| | |
|-----------------------|---------------------------|
| Reporting group title | Cohort 2: Placebo/Healthy |
|-----------------------|---------------------------|

Reporting group description:

Healthy participants in Cohort 2 who received single doses of placebo

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Gefapixant 50 mg/Chronic Cough |
|-----------------------|--|

Reporting group description:

Participants with chronic cough in Cohort 2 who received single doses of gefapixant 50 mg

| | |
|-----------------------|---------------------------------|
| Reporting group title | Cohort 2: Placebo/Chronic Cough |
|-----------------------|---------------------------------|

Reporting group description:

Participants with chronic cough in Cohort 2 who received single doses of placebo

| Serious adverse events | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Healthy | Cohort 1: Gefapixant 300 mg/Chronic Cough |
|---|---|------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Healthy |
|---|---------------------------------------|---------------------------------------|------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough | |
|---|--|---------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (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 %

| Non-serious adverse events | Cohort 1: Gefapixant 300 mg/Healthy | Cohort 1: Placebo/Healthy | Cohort 1: Gefapixant 300 mg/Chronic Cough |
|---|---|------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 14 (100.00%) | 5 / 14 (35.71%) | 12 / 12 (100.00%) |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Excoriation | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|------------------------|----------------------|-----------------------|
| Ageusia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 3 / 12 (25.00%) 4 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 13 / 14 (92.86%) 20 | 1 / 14 (7.14%) 1 | 9 / 12 (75.00%) 15 |
| Headache subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 2 / 14 (14.29%) 2 | 5 / 12 (41.67%) 5 |
| Hypogeusia subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 0 / 14 (0.00%) 0 | 3 / 12 (25.00%) 3 |
| VIIth Nerve Paralysis subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 12 (0.00%) 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Dry mouth | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 0 / 14 (0.00%) | 4 / 12 (33.33%) |
| occurrences (all) | 4 | 0 | 4 |
| Reflux gastritis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue coated | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth deposit | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry throat | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Oropharyngeal discomfort | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngeal hypoaesthesia | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 14 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 14 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Cohort 1: Placebo/Chronic Cough | Cohort 2: Gefapixant 50 mg/Healthy | Cohort 2: Placebo/Healthy |
|---|---------------------------------------|---------------------------------------|------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 12 (58.33%) | 9 / 12 (75.00%) | 4 / 12 (33.33%) |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 12 (33.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Dizziness | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 12 (33.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 12 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 2 | 1 |
| Hypogeusia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| VIIth Nerve Paralysis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reflux gastritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tongue coated | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth deposit | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 12 (16.67%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Dry throat | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal discomfort | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | 1 / 12 (8.33%) 1 |
| Pharyngeal hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Wheezing subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Spinal osteoarthritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 |

| | | | |
|-----------------------------------|----------------|----------------|----------------|
| Oral herpes | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Cohort 2: Gefapixant 50 mg/Chronic Cough | Cohort 2: Placebo/Chronic Cough | |
|---|--|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 3 / 11 (27.27%) | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Excoriation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dysgeusia | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 5 | 1 / 11 (9.09%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 11 (18.18%) 2 | |
| Hypogeusia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 11 (0.00%) 0 | |
| VIIth Nerve Paralysis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 2 | |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Hypoaesthesia oral | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reflux gastritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tongue coated | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tooth deposit | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dry throat | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 11 (9.09%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oropharyngeal pain | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Pharyngeal hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Throat irritation subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Wheezing subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Spinal osteoarthritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 11 (9.09%) 1 | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 11 (0.00%) 0 | |

| | | | |
|-----------------------------------|----------------|----------------|--|
| Rhinitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 11 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 11 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 25 February 2015 | Amendment 1: Added steps specifying when and for which treatment group the cough monitor was attached and removed |
| 17 July 2015 | Amendment 2: Clarified that an ambulatory cough recorder chest microphone (in addition to the lapel microphone) would be used for cough participants only |
| 05 August 2015 | Amendment 3: Removed spirometry from the Schedule of Assessments and Procedures |
| 02 September 2015 | Amendment 4: Low Dose Extension (AF-219 50 mg, Cohort 2) added to include up to an additional 24 participants |
| 19 October 2015 | Amendment 5: Time frame of the exclusion criteria for treatment with an investigational drug decreased to facilitate the enrollment of participants in Cohort 1 into Cohort 2 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported