# Clinical trial results:
# A Dose Escalation Study to Assess the Efficacy and Tolerance of AF-219 in Subjects with Refractory Chronic Cough

## Summary

| | |
|---|---|
| EudraCT number | 2015-000474-35 |
| Trial protocol | GB |
| Global end of trial date | 09 February 2016 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 31 December 2020 |
| First version publication date | 30 July 2017 |
| Version creation reason | • Correction of full data set<br>Updated for Consistency with ClinicalTrials.gov Results posting |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 7264-010 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02349425 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck study number: MK-7264-010, Afferent study number: AF219-010 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Afferent Pharmaceuticals, Inc. |
| Sponsor organisation address | 2929 Campus Dr #230, San Mateo, CA, United States, 94403 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., 1 8006726372, ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Senior Vice President, Global Clinical Development, Merck Sharp & Dohme Corp., 1 8006726372, 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 | 09 February 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the dose-response of Gefapixant (AF-219) in reducing Awake Objective Cough Frequency and to identify tolerable dose(s) of Gefapixant that reduce Awake Objective Cough Frequency.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 March 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 States: 59 |
| Worldwide total number of subjects | 59 |
| 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) | 31 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited at 12 clinical trial sites in the United States.

### Pre-assignment

Screening details:

29 participants were enrolled, randomized and treated with study drug in Cohort 1 and 30 participants in Cohort 2. Of the 30 participants in Cohort 2, 18 of them were from Cohort 1 and they re-consented, were given new randomization numbers and treated with study drug.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1: Gefapixant>Placebo |

Arm description:

Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 50 mg, 100 mg, 150 mg, or 200 mg oral, administered as 1, 2, 3, or 4 50-mg tablets BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| **Arm title** | Cohort 1: Placebo>Gefapixant |

Arm description:

Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

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

| | |
|---|---|
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 50 mg, 100 mg, 150 mg, or 200 mg oral, administered as 1, 2, 3, or 4 50-mg tablets BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| **Arm title** | Cohort 2: Gefapixant>Placebo |

Arm description:

Gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 7.5 mg, 15 mg, 30 mg, or 50 mg oral, administered as 1, 2, or 4 7.5-mg tablets or 1 50-mg tablet BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| **Arm title** | Cohort 2: Placebo>Gefapixant |

Arm description:

Placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 1 and gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 7.5 mg, 15 mg, 30 mg, or 50 mg oral, administered as 1, 2, or 4 7.5-mg tablets or 1 50-mg tablet BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| **Number of subjects in period 1** | Cohort 1: Gefapixant>Placebo | Cohort 1: Placebo>Gefapixant | Cohort 2: Gefapixant>Placebo |
|---|---|---|---|
| Started | 15 | 14 | 15 |
| Completed | 14 | 13 | 15 |
| Not completed | 1 | 1 | 0 |
| Adverse event, non-fatal | 1 | 1 | - |

| **Number of subjects in period 1** | Cohort 2: Placebo>Gefapixant |
|---|---|
| Started | 15 |
| Completed | 15 |
| Not completed | 0 |
| Adverse event, non-fatal | - |

**Period 2**

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

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1: Gefapixant>Placebo |

Arm description:

Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

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

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 50 mg, 100 mg, 150 mg, or 200 mg oral, administered as 1, 2, 3, or 4 50-mg tablets BID for 4 days

| | |
|---|---|
| **Arm title** | Cohort 1: Placebo>Gefapixant |

Arm description:

Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 50 mg, 100 mg, 150 mg, or 200 mg oral, administered as 1, 2, 3, or 4 50-mg tablets BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| **Arm title** | Cohort 2: Gefapixant>Placebo |

Arm description:

Gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 7.5 mg, 15 mg, 30 mg, or 50 mg oral, administered as 1, 2, or 4 7.5-mg tablets or 1 50-mg tablet BID for 4 days

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| **Arm title** | Cohort 2: Placebo>Gefapixant |

Arm description:

Placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 1 and gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

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

Dosage and administration details:

Placebo to Gefapixant, oral, administered BID for 16 days

| | |
|---|---|
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant: 7.5 mg, 15 mg, 30 mg, or 50 mg oral, administered as 1, 2, or 4 7.5-mg tablets or 1 50-mg tablet BID for 4 days

| **Number of subjects in period 2** | Cohort 1: Gefapixant>Placebo | Cohort 1: Placebo>Gefapixant | Cohort 2: Gefapixant>Placebo |
|---|---|---|---|
| Started | 14 | 13 | 15 |
| Completed | 14 | 12 | 14 |
| Not completed | 0 | 1 | 1 |
| Adverse event, non-fatal | - | 1 | 1 |

| **Number of subjects in period 2** | Cohort 2: Placebo>Gefapixant |
|---|---|
| Started | 15 |
| Completed | 15 |
| Not completed | 0 |
| Adverse event, non-fatal | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant>Placebo |
| Reporting group description: | |
| Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods. | |
| Reporting group title | Cohort 1: Placebo>Gefapixant |
| Reporting group description: | |
| Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods. | |
| Reporting group title | Cohort 2: Gefapixant>Placebo |
| Reporting group description: | |
| Gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods. | |
| Reporting group title | Cohort 2: Placebo>Gefapixant |
| Reporting group description: | |
| Placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 1 and gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods. | |

| Reporting group values | Cohort 1: Gefapixant>Placebo | Cohort 1: Placebo>Gefapixant | Cohort 2: Gefapixant>Placebo |
|---|---|---|---|
| Number of subjects | 15 | 14 | 15 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 6 | 9 | 8 |
| From 65-84 years | 9 | 5 | 7 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 64.5 | 61.7 | 60.7 |
| standard deviation | ± 6.92 | ± 7.77 | ± 9.42 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 13 | 12 | 12 |
| Male | 2 | 2 | 3 |

| | | | |
|---|---|---|---|
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 1 |
| White | 15 | 13 | 13 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 14 | 14 | 14 |
| Unknown or Not Reported | 0 | 0 | 0 |

| **Reporting group values** | Cohort 2: Placebo>Gefapixant | Total | |
|---|---|---|---|
| Number of subjects | 15 | 59 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 8 | 31 | |
| From 65-84 years | 7 | 28 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 59.8 | | |
| standard deviation | ± 12.8 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 12 | 49 | |
| Male | 3 | 10 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 1 | |
| White | 15 | 56 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 3 | |

| | | | |
|---|---|---|---|
| Not Hispanic or Latino | 14 | 56 | |
| Unknown or Not Reported | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant>Placebo |

Reporting group description:

Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 1: Placebo>Gefapixant |

Reporting group description:

Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 2: Gefapixant>Placebo |

Reporting group description:

Gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 2: Placebo>Gefapixant |

Reporting group description:

Placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 1 and gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant>Placebo |

Reporting group description:

Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 1: Placebo>Gefapixant |

Reporting group description:

Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 2: Gefapixant>Placebo |

Reporting group description:

Gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Reporting group title | Cohort 2: Placebo>Gefapixant |

Reporting group description:

Placebo to gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth twice daily for 4 days each in Period 1 and gefapixant 7.5, 15, 30, and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2 there was a 14-21 day washout period between treatment periods.

| | |
|---|---|
| Subject analysis set title | Cohort 1 – Gefapixant>Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7-day washout period between treatment periods.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Placebo>Gefalixant |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo to gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 50, 100, 150, and 200 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 1, there was a 3 to 7 day washout period between treatment periods.

| | |
|---|---|
| Subject analysis set title | Cohort 2 – Gefapixant>Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 7.5, 15, 30 and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and placebo to gefapixant 7.5, 15, 30 and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2, there was a 14 to 21-day washout period between treatment periods.

| | |
|---|---|
| Subject analysis set title | Cohort 2 - Placebo>Gefapixant |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo to gefapixant 7.5, 15, 30 and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 1 and gefapixant 7.5, 15, 30 and 50 mg, tablet(s) administered by mouth, twice daily, for 4 days each in Period 2. For Cohort 2, there was a 14 to 21-day washout period between treatment periods.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 50 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Gefapixant 100 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 100 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 100 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Gefapixant 150 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 150 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 150 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Gefapixant 200 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Gefapixant 200 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 200 mg |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Placebo tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Subject analysis set title | Cohort 2 - Gefapixant 7.5 mg |

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 7.5 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant 15 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 15 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 15 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 30 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 1 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50, 100, 150, and 200 mg tablet(s) administered by mouth BID for 4 days each. | |
| Subject analysis set title | Cohort 1 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 7.5, 15, 30, and 50 mg tablet(s) administered by mouth BID for 4 days each. | |
| Subject analysis set title | Cohort 2 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days each. | |
| Subject analysis set title | Cohort 1 - Gefapixant 50 mg |

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 1 - Gefapixant 100 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 100 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 100 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 150 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 200 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 100 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 100 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 100 mg |

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 150 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 200 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant 7.5 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 7.5 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant 15 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 15 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 15 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Gefapixant 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 30 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 30 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Gefapixant 50 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 2 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 50 mg |

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 50 mg tablet administered by mouth BID for 4 days. | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 50 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 100 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 100 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 100 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 150 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 150 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 200 mg tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Placebo for Gefapixant 200 mg |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 1 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 50, 100, 150, and 200 mg tablet(s) administered by mouth BID for 4 days each. | |
| Subject analysis set title | Cohort 1 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 7.5, 15, 30, and 50 mg tablet(s) administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 2 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 1 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 50, 100, 150, and 200 mg tablet(s) administered by mouth BID for 4 days each. | |
| Subject analysis set title | Cohort 1 - Placebo |

| | |
|---|---|
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days | |
| Subject analysis set title | Cohort 2 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 7.5, 15, 30, and 50 mg tablet(s) administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 2 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 1 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 50, 100, 150, and 200 mg tablet(s) administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 1 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 2 - Gefapixant |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Gefapixant 7.5, 15, 30, and 50 mg tablet(s) administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 2 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days each | |
| Subject analysis set title | Cohort 2 - Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>Placebo tablet administered by mouth BID for 4 days each | |

## Primary: Change in Awake Objective Cough Frequency on Log-transformed Scale - Cohort 1

| | |
|---|---|
| End point title | Change in Awake Objective Cough Frequency on Log-transformed Scale - Cohort 1 |
| End point description:<br>Awake Objective Frequency (per hour) is the total number of cough events during the monitoring period (in general, 24-hr interval) the participant is awake divided by the total duration (in hours) for the monitoring period the participant is awake. 24-hour sound recordings were collected using a digital recording device. | |
| End point type | Primary |
| End point timeframe:<br>Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses | |

| End point values | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 25 | 24 | 25 |
| Units: Log coughs/hour | | | | |
| geometric mean (confidence interval 95%) | 0.56 (0.43 to 0.72) | 0.95 (0.73 to 1.23) | 0.46 (0.34 to 0.61) | 0.95 (0.71 to 1.28) |

| End point values | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 22 | 25 | 25 |
| Units: Log coughs/hour | | | | |
| geometric mean (confidence interval 95%) | 0.48 (0.35 to 0.65) | 0.90 (0.65 to 1.24) | 0.45 (0.33 to 0.63) | 1.06 (0.75 to 1.48) |

**Statistical analyses**

| Statistical analysis title | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0055 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -41.222 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -59.294 |
| upper limit | -15.127 |

| Statistical analysis title | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |

| | |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -51.973 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -68.23 |
| upper limit | -27.397 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0075 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -46.853 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -66.291 |
| upper limit | -16.206 |

| **Statistical analysis title** | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -57.067 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -73.375 |
| upper limit | -30.771 |

## Primary: Change in Awake Objective Cough Frequency on Log-transformed Scale - Cohort 2

| End point title | Change in Awake Objective Cough Frequency on Log-transformed Scale - Cohort 2 |
|---|---|

End point description:

Awake Objective Frequency (per hour) is the total number of cough events during the monitoring period (in general, 24-hr interval) the participant is awake divided by the total duration (in hours) for the monitoring period the participant is awake. 24-hour sound recordings were collected using a digital recording device.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Log coughs/hour | | | | |
| geometric mean (confidence interval 95%) | 0.80 (0.66 to 0.96) | 0.93 (0.77 to 1.13) | 0.67 (0.57 to 0.80) | 0.90 (0.75 to 1.08) |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 29 | 27 |
| Units: Log coughs/hour | | | | |
| geometric mean (confidence interval 95%) | 0.53 (0.40 to 0.69) | 0.84 (0.64 to 1.10) | 0.44 (0.32 to 0.60) | 1.00 (0.72 to 1.38) |

### Statistical analyses

| **Statistical analysis title** | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2542 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -14.691 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -35.307 |
| upper limit | 12.493 |

| **Statistical analysis title** | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0267 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -25.165 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.014 |
| upper limit | -3.421 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0198 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -37.146 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -57.345 |
| upper limit | -7.3821 |

| **Statistical analysis title** | gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Mixed models analysis |
| Parameter estimate | Estimated percent change |
| Point estimate | -55.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -71.923 |
| upper limit | -30.797 |

## Primary: Percent Change from Baseline in Awake Cough Frequency for Cohort 1

| | |
|---|---|
| End point title | Percent Change from Baseline in Awake Cough Frequency for Cohort 1[1] |

End point description:

Awake Objective Cough Frequency (per hour) is the total number of cough events during the monitoring period (in general, 24-hr interval) the participant is awake divided by the total duration (in hours) for the monitoring period the participant is awake. 24-hour sound recordings were collected using a digital recording device. Percent Change in Awake Cough Frequency is the change from baseline in awake cough frequency x 100, divided by baseline awake cough frequency. A negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

Notes:

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

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 25 | 24 | 25 |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -20.6 (± 84.29) | -0.1 (± 33.75) | -31.7 (± 70.27) | 1.9 (± 35.18) |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 22 | 25 | 25 |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -22.0 (± 82.84) | -0.1 (± 39.55) | -27.9 (± 57.03) | 15.1 (± 48.38) |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percent Change from Baseline in Awake Cough Frequency for Cohort 2

| End point title | Percent Change from Baseline in Awake Cough Frequency for Cohort 2[2] |
|---|---|

End point description:

Awake Objective Cough Frequency (per hour) is the total number of cough events during the monitoring period (in general, 24-hr interval) the participant is awake divided by the total duration (in hours) for the monitoring period the participant is awake. 24-hour sound recordings were collected using a digital recording device. Percent Change in Awake Cough Frequency is the change from baseline in awake cough frequency x 100, divided by baseline awake cough frequency. A negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed for this endpoint.

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | 5.0 (± 125.05) | -3.8 (± 36.13) | -21.4 (± 39.32) | -6.4 (± 33.78) |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 29 | 27 |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | -26.3 (± 61.01) | -1.1 (± 64.38) | -28.1 (± 74.90) | 23.1 (± 92.60) |

## Statistical analyses

No statistical analyses for this end point

## Primary: Responder Analysis of Awake Cough Frequency for Cohort 1

| End point title | Responder Analysis of Awake Cough Frequency for Cohort 1[3] |
|---|---|

End point description:

Participants were classified as responders based on the magnitude of the percent change from baseline in Awake Objective cough frequency: 1. ≥70% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤-70.0%; 0 Otherwise; 2. ≥50% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤ -50.0%; 0 Otherwise; 3. ≥30% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤ -30.0%; 0 Otherwise. These responder definitions were not mutually exclusive. A participant who achieved a 1 for ≥70% Reduction for a particular period and dosing interval, were by definition, classified as ≥50% Reduction and ≥ 30% Reduction.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed for this endpoint.

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 25 | 24 | 25 |
| Units: Percent Responders | | | | |
| number (not applicable) | | | | |
| % Reduction ≥70 | 34.6 | 0 | 33.3 | 0 |
| % Reduction ≥50 | 46.2 | 0 | 50.0 | 4.0 |
| % Reduction ≥30 | 53.8 | 12.0 | 66.7 | 16.0 |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 22 | 25 | 25 |
| Units: Percent Responders | | | | |
| number (not applicable) | | | | |
| % Reduction ≥70 | 34.8 | 4.5 | 32.0 | 0 |
| % Reduction ≥50 | 47.8 | 4.5 | 44.0 | 0 |
| % Reduction ≥30 | 65.2 | 22.7 | 56.0 | 16.0 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Responder Analysis of Awake Cough Frequency for Cohort 2

| End point title | Responder Analysis of Awake Cough Frequency for Cohort 2[4] |
|---|---|

End point description:

Participants were classified as responders based on the magnitude of the percent change from baseline in Awake Objective cough frequency: 1. ≥70% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤-70.0%; 0 Otherwise; 2. ≥50% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤ -50.0%; 0 Otherwise; 3. ≥30% Reduction=1 if Percent Change from Baseline in cough frequency at the end of the dosing interval ≤ -30.0%; 0 Otherwise. These responder definitions were not mutually exclusive. A participant who achieved a 1 for ≥70% Reduction for a particular period and dosing interval, were by definition, classified as ≥50% Reduction and ≥ 30% Reduction.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed for this endpoint.

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Percent Responders | | | | |
| number (not applicable) | | | | |
| % Reduction ≥70 | 3.4 | 3.6 | 10.0 | 0 |
| % Reduction ≥50 | 13.8 | 7.1 | 20.0 | 6.9 |
| % Reduction ≥30 | 37.9 | 14.3 | 46.7 | 20.7 |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 29 | 27 |
| Units: Percent Responders | | | | |
| number (not applicable) | | | | |
| % Reduction ≥70 | 20.7 | 3.4 | 31.0 | 3.7 |
| % Reduction ≥50 | 31.0 | 17.2 | 41.4 | 11.1 |
| % Reduction ≥30 | 62.1 | 31.0 | 55.2 | 22.2 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Awake (0-8 Hours) Objective Cough Frequency for Cohort 1

| End point title | Change from Baseline in Awake (0-8 Hours) Objective Cough |
|---|---|

| | |
|---|---|
| | Frequency for Cohort 1 |

End point description:

Awake (0-8 hours) Objective Cough Frequency is the total number of cough events during the monitoring period the participant was awake for the first 8 hours after the participant took their study medication divided by 8 or the total duration (in hours) for the monitoring period the participant was awake whichever is less. 24-hour sound recordings were collected using a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using a mixed model repeated measures (MMRM) to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 0-8 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 0-8 hours after Day 26, 30, 34 and 38 doses

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 25 | 24 | 25 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -24.5 (-33.0 to -15.9) | -5.5 (-14.2 to 3.3) | -24.5 (-33.1 to -15.8) | -0.1 (-8.8 to 8.7) |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 22 | 25 | 25 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -26.5 (-40.3 to -12.8) | 2.7 (-11.4 to 16.9) | -27.5 (-37.9 to -17.0) | 2.2 (-8.5 to 12.8) |

## Statistical analyses

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -19 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.2 |
| upper limit | -6.8 |

| **Statistical analysis title** | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -24.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.7 |
| upper limit | -12.1 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -29.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -49 |
| upper limit | -9.5 |

| **Statistical analysis title** | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |

| | |
|---|---|
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -29.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -44.6 |
| upper limit | -14.7 |

## Secondary: Change from Baseline in Awake (0-8 Hours) Objective Cough Frequency for Cohort 2

| | |
|---|---|
| End point title | Change from Baseline in Awake (0-8 Hours) Objective Cough Frequency for Cohort 2 |

End point description:

Awake (0-8 hours) Objective Cough Frequency is the total number of cough events during the monitoring period the participant was awake for the first 8 hours after the participant took their study medication divided by 8 or the total duration (in hours) for the monitoring period the participant was awake whichever is less. 24-hour sound recordings were collected using a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using a mixed model repeated measures (MMRM) to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1 (while awake): baseline (Day 0) and 0-8 hours after Day 4, 8, 12 & 16 doses; Period 2 (while awake): baseline (Day 22) and 0-8 hours after Day 26, 30, 34 and 38 doses

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -8.0 (-17.9 to 1.9) | -1.1 (-11.1 to 9.0) | -15.2 (-22.1 to -8.3) | -1.7 (-8.8 to 5.3) |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 29 | 27 |

| | | | | |
|---|---|---|---|---|
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -21.7 (-31.9 to -11.5) | 8.5 (-1.8 to 18.8) | -21.9 (-32.8 to -11.0) | 4.7 (-6.5 to 16.0) |

**Statistical analyses**

| **Statistical analysis title** | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.332 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21 |
| upper limit | 7.2 |

| **Statistical analysis title** | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.008 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -13.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.3 |
| upper limit | -3.6 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |

| | |
|---|---|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -30.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -44.7 |
| upper limit | -15.7 |

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -26.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -42.3 |
| upper limit | -11 |

## Secondary: Change from Baseline in Total (24 hours) Cough Frequency - Cohort 1

| End point title | Change from Baseline in Total (24 hours) Cough Frequency - Cohort 1 |
|---|---|

End point description:

Total (0-24 hours) Objective Cough Frequency is the total number of cough events during the monitoring period divided by the total duration (in hours, i.e., 24 hours mostly) for the monitoring period. 24-hour sound recordings were collected using a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1: baseline (Day 0) and 0-24 hours after Day 4, 8, 12 & 16 doses; Period 2: baseline (Day 22) and 0-24 hours after Day 26, 30, 34 and 38 doses

| End point values | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 25 | 24 | 25 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -16.6 (-22.4 to -10.9) | -1.5 (-7.5 to 4.5) | -17.6 (-24.1 to -11.0) | -0.9 (-7.5 to 5.8) |

| End point values | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 22 | 25 | 25 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -18.0 (-26.1 to -9.9) | 1.5 (-6.8 to 9.8) | -17.4 (-25.2 to -9.5) | 3.1 (-4.9 to 11.2) |

**Statistical analyses**

| Statistical analysis title | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -15.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.5 |
| upper limit | -6.8 |

| Statistical analysis title | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |

| | |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -16.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.1 |
| upper limit | -7.4 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -19.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.1 |
| upper limit | -7.8 |

| **Statistical analysis title** | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -20.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.8 |
| upper limit | -9.3 |

## Secondary: Change from Baseline in Total (24 hours) Cough Frequency - Cohort 2

| End point title | Change from Baseline in Total (24 hours) Cough Frequency - Cohort 2 |
|---|---|

End point description:

Total (0-24 hours) Objective Cough Frequency is the total number of cough events during the monitoring period divided by the total duration (in hours, i.e., 24 hours mostly) for the monitoring period. 24-hour sound recordings were collected using a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1: baseline (Day 0) and 0-24 hours after Day 4, 8, 12 & 16 doses; Period 2: baseline (Day 22) and 0-24 hours after Day 26, 30, 34 and 38 doses

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -6.9 (-12.6 to -1.1) | -2.7 (-8.6 to 3.1) | -11.0 (-15.5 to -6.4) | -3.8 (-8.4 to 0.9) |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 29 | 27 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -16.9 (-23.3 to -10.4) | 1.4 (-5.2 to 7.9) | -15.9 (-21.0 to -9.9) | 1.8 (-4.4 to 7.9) |

### Statistical analyses

| **Statistical analysis title** | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.315 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.3 |
| upper limit | 4 |

| **Statistical analysis title** | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.03 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -7.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.7 |
| upper limit | -0.7 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -18.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.4 |
| upper limit | -9.1 |

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -17.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.3 |
| upper limit | -9 |

## Secondary: Change from Baseline in Sleep Cough Frequency - Cohort 1

| | |
|---|---|
| End point title | Change from Baseline in Sleep Cough Frequency - Cohort 1 |

End point description:

Sleep Objective Cough Frequency is the total number of cough events during the monitoring period the participant is asleep divided by the total duration (in hours) for the monitoring period the participant is asleep. 24-hour sound recording were collected with a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1 (while asleep): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while asleep): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 | 24 | 21 | 24 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -3.5 (-7.0 to 0.1) | 0.1 (-3.5 to 3.7) | -3.1 (-6.8 to 0.6) | -0.7 (-4.2 to 2.8) |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 24 | 25 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -2.0 (-4.8 to 0.7) | -0.1 (-2.8 to 2.6) | -3.6 (-7.0 to -0.1) | 0.2 (-3.2 to 3.6) |

**Statistical analyses**

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.169 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.6 |
| upper limit | 1.6 |

| **Statistical analysis title** | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.341 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 2.6 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |

| | |
|---|---|
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.311 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 1.9 |

| **Statistical analysis title** | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.128 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.6 |
| upper limit | 1.1 |

## Secondary: Change from Baseline in Sleep Cough Frequency - Cohort 2

| End point title | Change from Baseline in Sleep Cough Frequency - Cohort 2 |
|---|---|

End point description:

Sleep Objective Cough Frequency is the total number of cough events during the monitoring period the participant is asleep divided by the total duration (in hours) for the monitoring period the participant is asleep. 24-hour sound recording were collected with a digital recording device. Results are change from baseline: a negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency.

Cough frequency was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1 (while asleep): baseline (Day 0) and 24 hours after Day 4, 8, 12 & 16 doses; Period 2 (while asleep): baseline (Day 22) and 24 hours after Day 26, 30, 34 and 38 doses

| End point values | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 28 | 30 | 29 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | 0.6 (-2.7 to 3.9) | -0.6 (-3.9 to 2.8) | -3.1 (-5.6 to -0.5) | -2.5 (-5.1 to 0.2) |

| End point values | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 29 | 29 | 28 | 27 |
| Units: Coughs/hour | | | | |
| least squares mean (confidence interval 95%) | -2.4 (-4.7 to -0.2) | -1.6 (-3.8 to 0.7) | -3.0 (-8.7 to 2.6) | 2.1 (-3.6 to 7.9) |

**Statistical analyses**

| Statistical analysis title | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.613 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5 |
| upper limit | 5.9 |

| Statistical analysis title | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |

| | |
|---|---|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.743 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.3 |
| upper limit | 3.1 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.589 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | 2.3 |

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.205 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -5.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.2 |
| upper limit | 2.9 |

## Secondary: Change from Baseline of the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 1

| End point title | Change from Baseline of the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 1 |
|---|---|

End point description:

The daily CSD Score is calculated using the daily CSD instrument, a 7-item, disease specific, patient-reported outcome measure with a recall period of "today" (the current day). The measure evaluates frequency of cough (3 items); intensity of cough (2 items); and sleep disruption due to cough (2 items). Each of these 7 items is rated on an 11-point scale, ranging from 0 (best) to 10 (worst), with higher scores indicating greater severity. The total daily CSD score is the sum of these 7 item scores (Min=0, Max=70). Baseline CSD score = average of CSD scores at screening and baseline. Results are change from baseline: a negative result indicates a decrease in cough severity, while a positive result indicates an increase in cough severity.

CSD was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Screening; Period 1: baseline (Day 0) and Days 1-17; Period 2: baseline (Day 22) and Days 23-39

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 27 | 26 | 27 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -0.6 (-1.2 to -0.1) | 0.0 (-0.5 to 0.5) | -1.1 (-1.8 to -0.5) | 0.1 (-0.5 to 0.8) |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 27 | 28 | 28 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.5 (-2.2 to -0.8) | 0.1 (-0.6 to 0.8) | -1.6 (-2.4 to -0.8) | 0.1 (-0.7 to 0.9) |

### Statistical analyses

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0811 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0.1 |

| **Statistical analysis title** | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0097 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.3 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0025 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | -0.6 |

| Statistical analysis title | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.8 |
| upper limit | -0.5 |

## Secondary: Change from Baseline of the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 2

| End point title | Change from Baseline of the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 2 |
|---|---|

End point description:

The daily CSD Score is calculated using the daily CSD instrument, a 7-item, disease specific, patient-reported outcome measure with a recall period of "today" (the current day). The measure evaluates frequency of cough (3 items); intensity of cough (2 items); and sleep disruption due to cough (2 items). Each of these 7 items is rated on an 11-point scale, ranging from 0 (best) to 10 (worst), with higher scores indicating greater severity. The total daily CSD score is the sum of these 7 item scores (Min=0, Max=70). Baseline CSD score = average of CSD scores at screening and baseline. Results are change from baseline: a negative result indicates a decrease in cough severity, while a positive result indicates an increase in cough severity.

CSD was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Screening; Period 1: baseline (Day 0) and Days 1-17; Period 2: baseline (Day 22) and Days 23-39

| End point values | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 29 | 30 | 29 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.0 (-1.5 to -0.5) | -0.3 (-0.8 to 0.2) | -1.2 (-1.8 to -0.6) | -0.3 (-0.9 to 0.3) |

| End point values | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 |
|---|---|---|---|---|

| | | mg | | mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 29 | 29 | 29 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.7 (-2.3 to -1.1) | -0.3 (-1.0 to 0.3) | -1.6 (-2.4 to -0.9) | -0.5 (-1.3 to 0.2) |

**Statistical analyses**

| **Statistical analysis title** | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0506 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0 |

| **Statistical analysis title** | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0447 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 0 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |

| | |
|---|---|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0026 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | -0.5 |

| | |
|---|---|
| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0405 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 0 |

## Secondary: Change from Baseline at End of Treatment Period Leicester Cough Questionnaire (LCQ): individual Domain and Total Scores for Cohort 1 and 2

| | |
|---|---|
| End point title | Change from Baseline at End of Treatment Period Leicester Cough Questionnaire (LCQ): individual Domain and Total Scores for Cohort 1 and 2 |

End point description:

The LCQ-Acute is a 19-item health-related quality-of-life (HRQoL) questionnaire specific for acute cough which contains three domains (i.e., physical, psychological, and social). It is calculated as a mean score for each domain ranging from 1 (worst) to 7 (best), and total score ranging from 3 (worst) to 21 (best). Each item on the LCQ-acute assesses symptoms or the impact of symptoms on HRQoL in the last 24 hours using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. Participants' perception of their cough severity was assessed, based on the LCQ-Acute score, at Baseline and last day of dose.

LCQ was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Period 1: Day 0 (baseline) and Day 17; Period 2: Day 22 (baseline) and Day 39

| End point values | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 28 | 30 | 29 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 3.02 (1.61 to 4.42) | -0.82 (-2.19 to 0.55) | 3.57 (2.27 to 4.87) | 0.05 (-1.28 to 1.37) |

**Statistical analyses**

| Statistical analysis title | Gefapixant Vs. Placebo Cohort 1 |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant v Cohort 1 - Placebo |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.88 |
| upper limit | 5.8 |

| Statistical analysis title | Gefapixant vs. Placebo Cohort 2 |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant v Cohort 2 - Placebo |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.66 |
| upper limit | 5.38 |

**Secondary: Change from Baseline of Cough Visual Analogue Scale (VAS) Score for**

**Cohort 1**

| End point title | Change from Baseline of Cough Visual Analogue Scale (VAS) Score for Cohort 1 |
|---|---|

End point description:

Cough VAS is scored from 0 to 100 using a 10 mm visual analogue scale with 0 at 0mm and 100 at 10mm with 0 (no cough) and 100 (most severe cough). Baseline cough VAS is defined as average of screening and baseline cough VAS. Results are change from baseline: a negative result indicates a decrease in cough severity, while a positive result indicates an increase in cough severity.

Cough VAS was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Screening; Period 1: baseline (Day 0) and Day 4, 8, 12 & 16; Period 2: baseline (Day 22) and Day 26, 30, 34, 38 and 39

| **End point values** | Cohort 1 - Gefapixant 50 mg | Cohort 1 - Placebo for Gefapixant 50 mg | Cohort 1 - Gefapixant 100 mg | Cohort 1 - Placebo for Gefapixant 100 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 28 | 27 | 27 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -14.4 (-23.4 to -5.5) | -3.8 (-12.6 to 5.0) | -26.3 (-36.0 to -16.6) | -6.3 (-15.9 to 3.2) |

| **End point values** | Cohort 1 - Gefapixant 150 mg | Cohort 1 - Placebo for Gefapixant 150 mg | Cohort 1 - Gefapixant 200 mg | Cohort 1 - Placebo for Gefapixant 200 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 27 | 26 | 27 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -28.8 (-39.1 to -18.4) | -2.6 (-12.8 to 7.6) | -31.5 (-41.9 to -21.0) | 2.3 (-8.0 to 12.6) |

**Statistical analyses**

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 50 mg v Cohort 1 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.096 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -10.6 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.2 |
| upper limit | 1.9 |

| **Statistical analysis title** | Gefapixant 100 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 100 mg v Cohort 1 - Placebo for Gefapixant 100 mg |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -20 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -33.6 |
| upper limit | -6.3 |

| **Statistical analysis title** | Gefapixant 150 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 150 mg v Cohort 1 - Placebo for Gefapixant 150 mg |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -26.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.7 |
| upper limit | -11.6 |

| **Statistical analysis title** | Gefapixant 200 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 1 - Gefapixant 200 mg v Cohort 1 - Placebo for Gefapixant 200 mg |

| | |
|---|---|
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -33.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -48.4 |
| upper limit | -19.1 |

## Secondary: Change from Baseline of Cough Visual Analogue Scale (VAS) Score for Cohort 2

| | |
|---|---|
| End point title | Change from Baseline of Cough Visual Analogue Scale (VAS) Score for Cohort 2 |

End point description:

Cough VAS is scored from 0 to 100 using a 10 mm visual analogue scale with 0 at 0mm and 100 at 10mm with 0 (no cough) and 100 (most severe cough). Baseline cough VAS is defined as average of screening and baseline cough VAS. Results are change from baseline: a negative result indicates a decrease in cough severity, while a positive result indicates an increase in cough severity.

Cough VAS was analyzed using MMRM to evaluate the results of the 2-period cross-over study. The derived change measured at each dose were the repeated measures.

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

End point timeframe:

Screening; Period 1: baseline (Day 0) and Day 4, 8, 12 & 16; Period 2: baseline (Day 22) and Day 26, 30, 34, 38 and 39

| **End point values** | Cohort 2 - Gefapixant 7.5 mg | Cohort 2 - Placebo for Gefapixant 7.5 mg | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Placebo for Gefapixant 15 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 29 | 30 | 29 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | -12.6 (-21.5 to -3.8) | -6.2 (-15.2 to 2.9) | -17.4 (-26.0 to -8.7) | -10.0 (-18.7 to -1.2) |

| **End point values** | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Placebo for Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg | Cohort 2 - Placebo for Gefapixant 50 mg |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 30 | 29 | 29 | 29 |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval | -23.3 (-31.7 to | -7.7 (-16.2 to | -24.7 (-35.2 to | -9.3 (-19.9 to |

| | | | | |
|---|---|---|---|---|
| 95%) | -14.9) | 0.9) | -14.2) | 1.4) |

**Statistical analyses**

| **Statistical analysis title** | Gefapixant 7.5 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 7.5 mg v Cohort 2 - Placebo for Gefapixant 7.5 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.311 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.1 |
| upper limit | 6.2 |

| **Statistical analysis title** | Gefapixant 15 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 15 mg v Cohort 2 - Placebo for Gefapixant 15 mg |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.232 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -7.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.7 |
| upper limit | 4.9 |

| **Statistical analysis title** | Gefapixant 30 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 30 mg v Cohort 2 - Placebo for Gefapixant 30 mg |

| | |
|---|---|
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -15.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -27.6 |
| upper limit | -3.6 |

| **Statistical analysis title** | Gefapixant 50 mg vs. Placebo |
|---|---|
| Comparison groups | Cohort 2 - Gefapixant 50 mg v Cohort 2 - Placebo for Gefapixant 50 mg |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.043 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -15.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.4 |
| upper limit | -0.5 |

**Other pre-specified: Baseline (Predose) Awake Objective Cough Frequency for Cohort 1 and Cohort 2**

| End point title | Baseline (Predose) Awake Objective Cough Frequency for Cohort 1 and Cohort 2 |
|---|---|

End point description:

Awake Objective Cough Frequency (per hour) is the total number of cough events during the monitoring period (in general, 24-hr interval) the participant is awake divided by the total duration (in hours) for the monitoring period the participant is awake. 24 hour sound recordings were collected using a digital recording device. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

24 hours (while awake) on Days 0 and 22 (Baseline)

| End point values | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 26 | 30 | 29 |
| Units: Coughs/hour | | | | |
| arithmetic mean (standard deviation) | 54.5 (± 41.09) | 52.8 (± 40.44) | 49.6 (± 44.01) | 46.1 (± 39.82) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Baseline (Predose) Awake (0 - 8 hours) Cough Frequency for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) Awake (0 - 8 hours) Cough Frequency for Cohort 1 and Cohort 2 |
|---|---|

End point description:

Awake (0 - 8 hours) Objective Cough Frequency is the total number of cough events during the monitoring period the participant was awake for the first 8 hours after the participant took their study medication divided by 8 or the total duration (in hours) for the monitoring period the participant was awake whichever is less. 24 hour sound recordings were collected with a digital recording device. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

First 8 hours (while awake) on Days 0 and 22 (Baseline)

| End point values | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 26 | 30 | 29 |
| Units: Coughs/hour | | | | |
| arithmetic mean (standard deviation) | 51.8 (± 41.09) | 53.3 (± 42.30) | 47.2 (± 42.09) | 42.2 (± 39.42) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Baseline (Predose) Total (24-hour) Cough Frequency for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) Total (24-hour) Cough Frequency for Cohort 1 and Cohort 2 |
|---|---|

End point description:

Total (0 - 24 hours) Objective Cough Frequency is the total number of cough events during the monitoring period divided by the total duration (in hours) for the monitoring period. 24 hour sound recordings were collected using a digital recording device. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group

(gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

24 hours (while awake) on Days 0 and 22 (Baseline)

| **End point values** | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 26 | 30 | 29 |
| Units: Coughs/hour | | | | |
| arithmetic mean (standard deviation) | 39.7 (± 28.38) | 37.9 (± 27.46) | 36.3 (± 32.28) | 32.2 (± 27.97) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Baseline (Predose) for Sleep Cough Frequency for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) for Sleep Cough Frequency for Cohort 1 and Cohort 2 |
|---|---|

End point description:

Sleep Objective Cough Frequency is the total number of cough events during the monitoring period the participant is asleep divided by the total duration (in hours) for the monitoring period the participant is asleep. 24-hour sound recording were collected with a digital recording device. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

First 8 hours (while asleep) on Days 0 and 22 (Baseline)

| **End point values** | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 26 | 30 | 29 |
| Units: Coughs/hour | | | | |
| arithmetic mean (standard deviation) | 8.3 (± 9.30) | 7.8 (± 9.80) | 10.1 (± 26.77) | 5.6 (± 7.58) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Baseline (Predose) for the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) for the Mean Total Daily Cough Severity Diary (CSD) Score for Cohort 1 and Cohort 2 |
|---|---|

End point description:

The daily CSD Score is calculated using the daily CSD instrument, a 7-item, disease specific, patient-reported outcome measure with a recall period of "today" (the current day). The measure evaluates frequency of cough (3 items); intensity of cough (2 items); and sleep disruption due to cough (2 items). Each of these 7 items is rated on an 11-point scale, ranging from 0 (best) to 10 (worst), with higher scores indicating greater severity. The total daily CSD score is the sum of these 7 item scores (Min=0, Max=70). Baseline CSD score = average of CSD scores at screening and baseline. A negative result indicates a decrease in cough frequency, while a positive result indicates an increase in cough frequency. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline (Days 0 and 22)

| **End point values** | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 28 | 30 | 28 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 4.2 (± 1.89) | 3.7 (± 1.61) | 4.5 (± 1.98) | 4.5 (± 1.93) |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Baseline (Predose) for the Acute Leicester Cough Questionnaire (LCQ) Instrument for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) for the Acute Leicester Cough Questionnaire (LCQ) Instrument for Cohort 1 and Cohort 2 |
|---|---|

End point description:

The LCQ-Acute is a 19-item health-related quality-of-life (HRQoL) questionnaire specific for acute cough which contains three domains (i.e., physical, psychological, and social). It is calculated as a mean score for each domain ranging from 1 (worst) to 7 (best), and total score ranging from 3 (worst) to 21 (best). Each item on the LCQ-acute assesses symptoms or the impact of symptoms on HRQoL in the last 24 hours using a 7-point Likert scale ranging from 1 to 7. Higher scores indicate better HRQoL. As per the Statistical Analysis Plan, each domain and total LCQ score change from baseline were analyzed without the treatment by dose interaction. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Days 0 and 22 (Baseline)

| End point values | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 28 | 30 | 29 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Psychological Domain Score | 3.8 (± 1.21) | 4.1 (± 1.45) | 3.9 (± 1.58) | 4.1 (± 1.56) |
| Physical Domain Score | 4.4 (± 0.99) | 4.7 (± 1.06) | 4.8 (± 1.19) | 5.0 (± 1.00) |
| Social Domain Score | 4.2 (± 1.22) | 4.3 (± 1.21) | 3.9 (± 1.57) | 4.2 (± 1.57) |
| Total Acute Leicester Score | 12.3 (± 3.13) | 13.1 (± 3.41) | 12.6 (± 4.04) | 13.3 (± 3.81) |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Baseline (Predose) for Cough Visual Analogue Scale (VAS) for Cohort 1 and Cohort 2

| End point title | Baseline (Predose) for Cough Visual Analogue Scale (VAS) for Cohort 1 and Cohort 2 |
|---|---|

End point description:

Cough VAS: scored from 0 to 100 using a 10 mm visual analogue scale with 0 (no cough) and 100 (most severe cough) mm. Baseline cough VAS is defined as average of screening and baseline cough VAS. Baseline measurements were not available by individual arm because baseline cough frequencies were measured before participants received the first dose of study drug. Baseline summaries were evaluated based on the participant's randomized group (gefapixant or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Screening, Days 0 and 22 (Baseline)

| End point values | Cohort 1 - Gefapixant | Cohort 1 - Placebo | Cohort 2 - Gefapixant | Cohort 2 - Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 28 | 28 | 30 | 29 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | 58.4 (± 18.66) | 52.2 (± 19.21) | 54.5 (± 24.26) | 57.2 (± 23.71) |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data collection is up to 11 weeks
All-cause mortality is up to 22 weeks

Adverse event reporting additional description:

Analysis population consisted of all randomized participants who received at least 1 dose of study drug

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant 50 mg |

Reporting group description:

Gefapixant 50 mg tablet administered by mouth twice daily (BID) for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant 100 mg |

Reporting group description:

Gefapixant 100 mg tablet administered by mouth BID or 4 days.

| | |
|---|---|
| Reporting group title | Cohort 1 - Gefapixant 150 mg |

Reporting group description:

Gefapixant 150 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 1: Gefapixant 200 mg |

Reporting group description:

Gefapixant 200 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 1 - Placebo |

Reporting group description:

Placebo tablet administered by mouth BID for 4 days each.

| | |
|---|---|
| Reporting group title | Cohort 2 - Gefapixant 7.5 mg |

Reporting group description:

Gefapixant 7.5 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 2 - Gefapixant 15 mg |

Reporting group description:

Gefapixant 15 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 2 - Gefapixant 30 mg |

Reporting group description:

Gefapixant 30 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 2 - Gefapixant 50 mg |

Reporting group description:

Gefapixant 50 mg tablet administered by mouth BID for 4 days.

| | |
|---|---|
| Reporting group title | Cohort 2- Placebo |

Reporting group description:

Placebo tablet administered by mouth BID for 4 days each.

| Serious adverse events | Cohort 1: Gefapixant 50 mg | Cohort 1: Gefapixant 100 mg | Cohort 1 - Gefapixant 150 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 28 (3.57%) | 0 / 26 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 28 (3.57%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 28 (3.57%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 28 (3.57%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 1: Gefapixant 200 mg | Cohort 1 - Placebo | Cohort 2 - Gefapixant 7.5 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 28 (3.57%) | 0 / 30 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 28 (3.57%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 1 / 30 (3.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and | | | |

| | | | |
|---|---|---|---|
| unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 2- Placebo | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Cohort 1: Gefapixant 50 mg | Cohort 1: Gefapixant 100 mg | Cohort 1 - Gefapixant 150 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 28 (60.71%) | 8 / 28 (28.57%) | 4 / 26 (15.38%) |
| Investigations | | | |
| Urine output decreased | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 13 / 28 (46.43%) | 6 / 28 (21.43%) | 4 / 26 (15.38%) |
| occurrences (all) | 13 | 6 | 4 |
| Hypogeusia | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 2 / 28 (7.14%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 2 / 28 (7.14%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 2 / 28 (7.14%) | 1 / 28 (3.57%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Cohort 1: Gefapixant 200 mg | Cohort 1 - Placebo | Cohort 2 - Gefapixant 7.5 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | 4 / 28 (14.29%) | 6 / 30 (20.00%) |
| Investigations | | | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Ageusia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 28 (3.57%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypogeusia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 28 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 28 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Infections and infestations | | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 28 (3.57%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 28 (3.57%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 26 (0.00%) | 2 / 28 (7.14%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| **Non-serious adverse events** | Cohort 2 - Gefapixant 15 mg | Cohort 2 - Gefapixant 30 mg | Cohort 2 - Gefapixant 50 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 13 / 30 (43.33%) | 9 / 30 (30.00%) |
| Investigations | | | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 12 / 30 (40.00%) | 4 / 30 (13.33%) |
| occurrences (all) | 1 | 12 | 4 |
| Hypogeusia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Flank pain | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 4 / 30 (13.33%) |
| occurrences (all) | 0 | 0 | 4 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Cohort 2- Placebo | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| Investigations | | | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypogeusia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Hypoaesthesia oral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | | |
| occurrences (all) | 0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 July 2015 | Amendment 1: Low-Dose Cohort 2 with an additional 30 subjects was added to the trial. |
| 03 September 2015 | Amendment 2: Changes in study objectives and endpoints and elimination of study sites in the United Kingdom. |
| 02 October 2015 | Amendment 3: Changes made to Renal/Urologic Symptom Inventory assessments, wash-out periods, and the follow-up of adverse events. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported