



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Month Study to Evaluate the Efficacy and Safety of MK-7264 in Adult Participants with Chronic Cough (PN027)

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2017-000537-31 |
| Trial protocol | CZ ES FR DK GB PL HU |
| Global end of trial date | 17 August 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 July 2021 |
| First version publication date | 28 July 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 7264-027 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03449134 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 June 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study will be to evaluate the efficacy of gefapixant in reducing cough frequency as measured over a 24-hour period at Week 12, and to evaluate the safety and tolerability of gefapixant. The primary hypothesis is that at least one gefapixant dose is superior to placebo in reducing coughs per hour (over 24 hours) at Week 12.

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 | 14 March 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 49 |
| Country: Number of subjects enrolled | Canada: 44 |
| Country: Number of subjects enrolled | Czechia: 53 |
| Country: Number of subjects enrolled | Denmark: 42 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Hungary: 14 |
| Country: Number of subjects enrolled | Israel: 41 |
| Country: Number of subjects enrolled | Japan: 34 |
| Country: Number of subjects enrolled | Korea, Republic of: 54 |
| Country: Number of subjects enrolled | Peru: 46 |
| Country: Number of subjects enrolled | Poland: 53 |
| Country: Number of subjects enrolled | Spain: 46 |
| Country: Number of subjects enrolled | Taiwan: 15 |
| Country: Number of subjects enrolled | Turkey: 22 |
| Country: Number of subjects enrolled | Ukraine: 12 |
| Country: Number of subjects enrolled | United Kingdom: 65 |
| Country: Number of subjects enrolled | United States: 123 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 732 |
| EEA total number of subjects | 227 |

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) | 447 |
| From 65 to 84 years | 283 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 732 participants randomized to the 52-week treatment period, 730 participants received at least 1 dose of study intervention. After the main study, 41 participants continued in an optional Off-Treatment (Off-Tx) Durability observational study period (no treatment).

Period 1

| | |
|------------------------------|--|
| Period 1 title | 52-Week Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Assessor, Subject |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.

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

Dosage and administration details:

Participants receive dose-matched placebo tablets orally BID during the 12-week main study period and during the 40-week extension period.

| | |
|------------------|----------------------|
| Arm title | Gefapixant 15 mg BID |
|------------------|----------------------|

Arm description:

Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.

| | |
|--|--------------|
| 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:

Participants receive placebo to gefapixant 45 mg tablet orally BID during the 12-week main study period and during the 40-week extension period.

| | |
|--|------------|
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | MK-7264 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant 15 mg tablet administered orally BID during the 12-week main study period and during the 40-week extension period.

| | |
|---|----------------------|
| Arm title | Gefapixant 45 mg BID |
| Arm description: | |
| Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | MK-7264 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Gefapixant 45 mg tablet administered orally BID during the 12-week main study period and during the 40-week extension period. | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Participants receive placebo to gefapixant 15 mg tablet orally BID during the 12-week main study period and during the 40-week extension period. | |

| Number of subjects in period 1 | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID |
|--------------------------------|---------|----------------------|----------------------|
| Started | 244 | 244 | 244 |
| Treated | 243 | 244 | 243 |
| Completed | 199 | 200 | 184 |
| Not completed | 45 | 44 | 60 |
| Adverse event, serious fatal | 2 | 1 | - |
| Site Closure | 1 | - | - |
| Physician decision | 2 | 3 | 3 |
| Consent withdrawn by subject | 37 | 39 | 55 |
| Screen Failure | 1 | - | 1 |
| Lost to follow-up | 2 | 1 | 1 |

| | |
|------------------------------|--|
| Period 2 | |
| Period 2 title | 12-Week Off-Treatment Durability Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Assessor, Subject |
| Arms | |
| Are arms mutually exclusive? | Yes |

| | |
|--|------------------------------|
| Arm title | Placebo: Off Tx |
| Arm description: Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Gefapixant 15 mg BID: Off Tx |
| Arm description: Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Gefapixant 45 mg BID: Off Tx |
| Arm description: Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2^[1] | Placebo: Off Tx | Gefapixant 15 mg BID: Off Tx | Gefapixant 45 mg BID: Off Tx |
|---|-----------------|------------------------------|------------------------------|
| Started | 10 | 18 | 13 |
| Completed | 10 | 18 | 13 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all participants continued in the optional Off-Treatment Period.

Baseline characteristics

Reporting groups

| | |
|---|----------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period. | |
| Reporting group title | Gefapixant 15 mg BID |
| Reporting group description: | |
| Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period. | |
| Reporting group title | Gefapixant 45 mg BID |
| Reporting group description: | |
| Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period. | |

| Reporting group values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID |
|--|---------|----------------------|----------------------|
| Number of subjects | 244 | 244 | 244 |
| Age categorical | | | |
| Units: Participants | | | |
| Adults (18-64 years) | 147 | 152 | 148 |
| From 65-84 years | 97 | 91 | 95 |
| 85 years and over | 0 | 1 | 1 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 57.9 | 59.6 | 59.5 |
| standard deviation | ± 13.1 | ± 11.7 | ± 13.1 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 182 | 181 | 181 |
| Male | 62 | 63 | 63 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 6 | 8 |
| Asian | 35 | 35 | 34 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 4 | 3 | 4 |
| White | 190 | 195 | 187 |
| More than one race | 8 | 5 | 11 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 33 | 35 | 33 |
| Not Hispanic or Latino | 204 | 205 | 208 |
| Unknown or Not Reported | 7 | 4 | 3 |
| Geographic Region | | | |
| Geographic region of enrollment with 5 categories: Asia-Pacific, Europe, North America, Others, and Missing. | | | |
| Units: Subjects | | | |

| | | | |
|--|---------|---------|---------|
| Asia Pacific | 35 | 34 | 34 |
| Europe | 121 | 123 | 122 |
| North America | 56 | 55 | 56 |
| Others | 31 | 32 | 32 |
| Missing | 1 | 0 | 0 |
| Baseline 24-hour Coughs per Hour | | | |
| 24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours (denominator could be different if the recording period was actually <24 hours but ≥20 hours). Baseline assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. All participants with 24-hour Coughs per Hour data available at baseline were analyzed (n=232, 235, 237). | | | |
| Units: coughs/hour | | | |
| arithmetic mean | 38.07 | 26.79 | 28.53 |
| standard deviation | ± 79.42 | ± 21.13 | ± 37.14 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 732 | | |
| Age categorical | | | |
| Units: Participants | | | |
| Adults (18-64 years) | 447 | | |
| From 65-84 years | 283 | | |
| 85 years and over | 2 | | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 544 | | |
| Male | 188 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 21 | | |
| Asian | 104 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 11 | | |
| White | 572 | | |
| More than one race | 24 | | |
| Unknown or Not Reported | 0 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 101 | | |
| Not Hispanic or Latino | 617 | | |
| Unknown or Not Reported | 14 | | |
| Geographic Region | | | |
| Geographic region of enrollment with 5 categories: Asia-Pacific, Europe, North America, Others, and Missing. | | | |
| Units: Subjects | | | |
| Asia Pacific | 103 | | |
| Europe | 366 | | |
| North America | 167 | | |

| | | | |
|---------|----|--|--|
| Others | 95 | | |
| Missing | 1 | | |

| | | | |
|--|---|--|--|
| Baseline 24-hour Coughs per Hour | | | |
| <p>24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours (denominator could be different if the recording period was actually <24 hours but ≥20 hours). Baseline assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. All participants with 24-hour Coughs per Hour data available at baseline were analyzed (n=232, 235, 237).</p> | | | |
| Units: coughs/hour | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period. | |
| Reporting group title | Gefapixant 15 mg BID |
| Reporting group description: Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period. | |
| Reporting group title | Gefapixant 45 mg BID |
| Reporting group description: Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period. | |
| Reporting group title | Placebo: Off Tx |
| Reporting group description: Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |
| Reporting group title | Gefapixant 15 mg BID: Off Tx |
| Reporting group description: Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |
| Reporting group title | Gefapixant 45 mg BID: Off Tx |
| Reporting group description: Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment). | |

Primary: Model-Based Geometric Mean Ratio (GMR) of 24-hour Objective Coughs Per Hour (Week 12/Baseline)

| | |
|--|--|
| End point title | Model-Based Geometric Mean Ratio (GMR) of 24-hour Objective Coughs Per Hour (Week 12/Baseline) |
| End point description: 24-hour objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) divided by 24 hours. Assessment was based on 24-hour sound recordings using a digital recording device which recorded sounds from the lungs and trachea through a chest contact sensor, as well as ambient sounds through a lapel microphone. A longitudinal analysis of covariance (ANCOVA) model was applied to log-transformed cough counts to determine geometric mean (GM) 24-hour objective coughs per hour at baseline and Week 12 on the original scale. The GMR corresponding to the Week 12 GM 24-hour objective coughs per hour divided by the Baseline GM 24-hour objective coughs per hour was reported for all treatment study arms. All randomized participants in the analysis model who had taken at least 1 dose of study intervention and provided at least 1 baseline and at least 1 Week 12 24-hour cough observation during the treatment period were analyzed. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 | |

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|--|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 227 | 217 | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | 0.47 (0.41 to 0.54) | 0.48 (0.41 to 0.55) | 0.38 (0.33 to 0.44) | |

Statistical analyses

| Statistical analysis title | 24-Hour Coughs/Hour ERR: PBO vs Gefapixant 45 mg |
|--|--|
| Statistical analysis description: | |
| Estimated relative reduction (ERR) relative to Placebo (PBO) (i.e. estimated percent change difference) was calculated by $100(e^{DIFF} - 1)$, where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data. | |
| Comparison groups | Placebo v Gefapixant 45 mg BID |
| Number of subjects included in analysis | 439 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.041 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Estimated Percent Change Difference |
| Point estimate | -18.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.92 |
| upper limit | -0.86 |

Notes:

[1] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

| Statistical analysis title | 24-Hour Coughs/Hour ERR: PBO vs Gefapixant 15 mg |
|--|--|
| Statistical analysis description: | |
| Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by $100(e^{DIFF} - 1)$, where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data. | |
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 449 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.874 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Estimated Percent Change Difference |
| Point estimate | 1.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.13 |
| upper limit | 22.99 |

Notes:

[2] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Primary: Number of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up

| | |
|-----------------|---|
| End point title | Number of Participants Experiencing At Least One Adverse Event (AE) During Treatment and Follow-up ^[3] |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants with at least one AE during either the 52-week treatment period or 2-week telephone follow-up was reported for all treatment study arms.

All randomized participants who received at least 1 dose of study intervention during the 52-week treatment period were analyzed. Per protocol, participants who continued in the optional Off-Treatment observational period were not included in the primary safety analysis.

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

End point timeframe:

Up to approximately 54 weeks

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 planned for this endpoint.

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 243 | 244 | 243 | |
| Units: Participants | 184 | 186 | 208 | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Discontinued Treatment Due to AEs

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Treatment Due to AEs ^[4] |
|-----------------|---|

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants with at least one AE during either the 52-week treatment period or 2-week telephone follow-up was reported for all treatment study arms.

All randomized participants who received at least 1 dose of study intervention during the 52-week treatment period were analyzed. Per protocol, participants who continued in the optional Off-Treatment observational period were not included in the primary safety analysis.

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

End point timeframe:

Up to approximately 52 weeks

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 planned for this endpoint.

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 243 | 244 | 243 | |
| Units: Participants | 14 | 15 | 51 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Model-Based Geometric Mean Ratio (GMR) of Awake Objective Coughs Per Hour (Week 12/Baseline)

| | |
|-----------------|--|
| End point title | Model-Based Geometric Mean Ratio (GMR) of Awake Objective Coughs Per Hour (Week 12/Baseline) |
|-----------------|--|

End point description:

Awake objective coughs per hour was defined as the total number of cough events during the monitoring period (24-hour interval) while the participant is awake divided by the total duration (in hours) for the monitoring period that the participant was awake. Assessment was based on 24-hour sound recordings using a digital recording device. A longitudinal ANCOVA model was applied to log-transformed cough counts to determine GM awake objective coughs per hour at baseline and Week 12 on the original scale. The GMR corresponding to the Week 12 GM awake objective coughs per hour divided by the Baseline GM awake objective coughs per hour was reported for all treatment study arms.

All randomized participants in the analysis model who had taken at least 1 dose of study intervention and provided at least 1 baseline and at least 1 Week 12 awake cough observation during the treatment period were analyzed.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|--|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 227 | 217 | |
| Units: ratio | | | | |
| geometric mean (confidence interval 95%) | 0.46 (0.40 to 0.53) | 0.47 (0.41 to 0.55) | 0.38 (0.33 to 0.44) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Awake Coughs/Hour ERR: PBO vs Gefapixant 45 mg |
|----------------------------|--|

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by $100(e^{DIFF} - 1)$, where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

| | |
|-------------------|--------------------------------|
| Comparison groups | Placebo v Gefapixant 45 mg BID |
|-------------------|--------------------------------|

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 439 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.056 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Estimated Percent Change Difference |
| Point estimate | -17.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.57 |
| upper limit | 0.5 |

Notes:

[5] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

| | |
|-----------------------------------|--|
| Statistical analysis title | Awake Coughs/Hour ERR: PBO vs Gefapixant 15 mg |
|-----------------------------------|--|

Statistical analysis description:

Estimated relative reduction (ERR) relative to Placebo (i.e. estimated percent change difference) was calculated by $100(e^{\text{DIFF}} - 1)$, where e = exponent of difference; and DIFF= treatment difference in change from baseline at Week 12 based on log transformed data.

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 449 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.77 ^[6] |
| Method | ANCOVA |
| Parameter estimate | Estimated Percent Change Difference |
| Point estimate | 2.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.33 |
| upper limit | 25.19 |

Notes:

[6] - Comparison based on a longitudinal ANCOVA model that included treatment, visit, treatment-by-visit interaction, gender, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates.

Secondary: Percentage of Participants (Model-Based) With a \leq -30% Change from Baseline in 24-hour Objective Coughs Per Hour at Week 12

| | |
|-----------------|--|
| End point title | Percentage of Participants (Model-Based) With a \leq -30% Change from Baseline in 24-hour Objective Coughs Per Hour at Week 12 |
|-----------------|--|

End point description:

24-hour coughs/hour defined as the total number of cough events during the 24-hour monitoring period divided by 24 hours. Assessment based on 24-hour sound recordings using a digital recording device. Percent change in 24-hour coughs/hour = (change from baseline in 24-hour coughs per hour/baseline 24-hour coughs per hour) \times 100%. Negative values indicate a decrease in cough rate, while positive values indicate an increase in cough rate. A participant considered a responder if percent change from baseline in 24-hour coughs/hour was \leq -30% (or a \geq 30% reduction from baseline); and considered a non-responder otherwise. Percentage of participants (logistic regression model-based) with a \leq -30% change from baseline in 24-hour coughs/hour at Week 12 reported for all treatment study arms.

All randomized participants in the analysis model who had taken \geq 1 dose of study intervention and had available 24-hour cough data at baseline and \geq 1 available post-baseline measurement were analyzed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 227 | 217 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 65.9 | 66.2 | 69.9 | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | 24-Hour Coughs/Hour OR: PBO vs Gefapixant 45 mg |
| Statistical analysis description: | |
| Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 45 mg BID |
| Number of subjects included in analysis | 439 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.416 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.86 |

| | |
|--|---|
| Statistical analysis title | 24-Hour Coughs/Hour OR: PBO vs Gefapixant 15 mg |
| Statistical analysis description: | |
| Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 449 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.948 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.55 |

Secondary: Percentage of Participants (Model-Based) With a ≤ -1.3 -point Change from Baseline in Mean Weekly Cough Severity Diary (CSD) Total Score at Week 12

| | |
|-----------------|--|
| End point title | Percentage of Participants (Model-Based) With a ≤ -1.3 -point Change from Baseline in Mean Weekly Cough Severity Diary (CSD) Total Score at Week 12 |
|-----------------|--|

End point description:

The CSD evaluates the frequency of cough, intensity of cough and disruption and has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score was the sum of these seven item scores (Min=0, Max=70). Mean weekly total score was defined as the average of mean total daily scores collected during the week prior to each visit. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Day -6 to Day 0). Participants were considered responders if the change from baseline in mean weekly CSD total score was ≤ -1.3 points (or a ≥ 1.3 point reduction from baseline); and considered non-responder otherwise. The percentage of participants with a ≤ -1.3 point change from baseline in CSD at Week 12 was reported for all treatment study arms.

All randomized participants who received ≥ 1 dose of study intervention, had available CSD data at baseline and ≥ 1 available post-baseline measurement were analyzed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 237 | 241 | 234 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 52.4 | 62.1 | 60.5 | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | CSD OR: PBO vs Gefapixant 45 mg |
|----------------------------|---------------------------------|

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.

| | |
|-------------------|--------------------------------|
| Comparison groups | Placebo v Gefapixant 45 mg BID |
|-------------------|--------------------------------|

| | |
|---|-----------------|
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 2.05 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | CSD OR: PBO vs Gefapixant 15 mg |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 478 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 2.18 |

Secondary: Percentage of Participants (Model-Based) With a ≤ -2.7 -point Change from Baseline in Mean Weekly CSD Total Score at Week 12

| | |
|-----------------|---|
| End point title | Percentage of Participants (Model-Based) With a ≤ -2.7 -point Change from Baseline in Mean Weekly CSD Total Score at Week 12 |
|-----------------|---|

End point description:

The CSD evaluates frequency of cough, intensity of cough and disruption and has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score was the sum of these seven item scores (Min=0, Max=70). Mean weekly total score was defined as the average of the mean total daily scores collected during the week prior to each visit. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Day -6 to Day 0). Participants were considered responders if the change from baseline in mean weekly CSD total score was ≤ -2.7 points (or a ≥ 2.7 point reduction from baseline); and considered non-responder otherwise. The percentage of participants with a ≤ -2.7 point change from baseline in CSD at Week 12 was reported for all treatment study arms.

All randomized participants who had taken ≥ 1 dose of study intervention and had available CSD data at baseline and ≥ 1 available post-baseline measurement were analyzed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 237 | 241 | 234 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 28.6 | 37.9 | 40.1 | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | CSD OR: PBO vs Gefapixant 45 mg |
| Statistical analysis description: | |
| Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 45 mg BID |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.11 |
| upper limit | 2.54 |

| | |
|--|---------------------------------|
| Statistical analysis title | CSD OR: PBO vs Gefapixant 15 mg |
| Statistical analysis description: | |
| Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline CSD score, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 478 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 2.3 |

Secondary: Percentage of Participants (Model-Based) With a \leq -30 millimeter (mm) Change from Baseline in Cough Severity Visual Analog Scale (VAS) Score at Week 12

| | |
|-----------------|--|
| End point title | Percentage of Participants (Model-Based) With a \leq -30 millimeter (mm) Change from Baseline in Cough Severity Visual Analog Scale (VAS) Score at Week 12 |
|-----------------|--|

End point description:

Cough severity was scored using the Cough Severity VAS, a single-item question asking the participant to rate the severity of their cough "today" using a 100 mm VAS (100-point scale) ranging from 0 ("No Cough") to 100 ("Extremely Severe Cough"). Mean weekly VAS score was derived as the average of VAS scores collected during the week prior to each visit. Baseline was defined as the average VAS scores collected during the week prior to Day 1 (Day -6 to Day 0). A participant was considered a responder if the change from baseline in mean weekly Cough Severity VAS score was \leq -30 mm (or a \geq 30 mm reduction from baseline); and considered non-responder otherwise. The percentage of participants with \leq -30 mm change from baseline in Cough Severity VAS at Week 12 was reported for all treatment study arms.

All randomized participants who had taken \geq 1 dose of study intervention and had available Cough Severity VAS data at baseline and \geq 1 available post-baseline measurement were analyzed.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 237 | 241 | 234 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 31.3 | 36.7 | 41.2 | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Cough Severity VAS OR: PBO vs Gefapixant 45 mg |
|----------------------------|--|

Statistical analysis description:

Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline VAS score, and the interaction of baseline (underlying continuous response) by visit as covariates.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Gefapixant 45 mg BID |
| Number of subjects included in analysis | 471 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 2.3 |

| | |
|---|--|
| Statistical analysis title | Cough Severity VAS OR: PBO vs Gefapixant 15 mg |
| Statistical analysis description: Comparison based on a logistic regression model that included treatment, visit, treatment-by-visit interaction, gender, region, baseline VAS score, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 478 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.86 |
| upper limit | 1.89 |

Secondary: Percentage of Participants (Model-Based) With a ≥ 1.3 -point Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score at Week 12

| | |
|-----------------|--|
| End point title | Percentage of Participants (Model-Based) With a ≥ 1.3 -point Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score at Week 12 |
|-----------------|--|

End point description:

The LCQ assesses the impact of chronic cough on health-related quality of life. It consists of 19 items which are divided over 3 domains: Physical, Psychological, and Social. A 7-point Likert scale is used to rate each item. For each domain, the domain score (range 1-7) is the sum of individual item score within the domain divided by the number of items in the domain. LCQ total score is the sum of the three domain scores and ranges from 3-21; with a higher score corresponding to a better health status. A participant was considered a responder if the change from baseline in LCQ total score was ≥ 1.3 -points (increase from baseline); and considered non-responder otherwise. The percentage of participants with a ≥ 1.3 -point change from baseline in LCQ total score at Week 12 was reported for all treatment study arms.

All randomized participants who had taken ≥ 1 dose of study intervention and had available LCQ data at baseline and ≥ 1 available post-baseline measurement were analyzed.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Gefapixant 15 mg BID | Gefapixant 45 mg BID | |
|-----------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 217 | 226 | 214 | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 61.3 | 68.8 | 67.3 | |

Statistical analyses

| | |
|--|---------------------------------|
| Statistical analysis title | LCQ OR: PBO vs Gefapixant 45 mg |
| Statistical analysis description: Comparison based on a logistic regression model that included visit, treatment-by-visit interaction, gender, region, baseline LCQ score, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 45 mg BID |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.98 |

| | |
|--|---------------------------------|
| Statistical analysis title | LCQ OR: PBO vs Gefapixant 15 mg |
| Statistical analysis description: Comparison based on a logistic regression model that included visit, treatment-by-visit interaction, gender, region, baseline LCQ score, and the interaction of baseline (underlying continuous response) by visit as covariates. | |
| Comparison groups | Placebo v Gefapixant 15 mg BID |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 2.12 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-Treatment Period (plus 2-week telephone follow-up): Up to Week 54; Off-Treatment (Off-Tx) Period: From Week 52 through Week 64 (approximately 12 weeks)

Adverse event reporting additional description:

All-Cause Mortality (ACM) reported for all randomized participants. Serious and Nonserious AEs reported for participants treated during 52-Week Treatment Period. AEs reported separately for treatment period and optional Off-Tx Period. Per protocol, only ACM, drug-related serious and nonserious AEs, and pregnancies monitored during Off-Tx Period.

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

Dictionary used

| | |
|--------------------|------------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0, 23.1 |

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Placebo: On Tx |
|-----------------------|----------------|

Reporting group description:

Participants received dose-matched placebo tablets twice daily (BID) during the 12-week main study period and 40-week extension period.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Gefapixant 15 mg BID: On Tx |
|-----------------------|-----------------------------|

Reporting group description:

Participants received a gefapixant 15 mg tablet and placebo tablet to match gefapixant 45 mg BID during the 12-week main study period and 40-week extension period.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Gefapixant 45 mg BID: On Tx |
|-----------------------|-----------------------------|

Reporting group description:

Participants received a gefapixant 45 mg tablet and placebo tablet to match gefapixant 15 mg BID during the 12-week main study period and 40-week extension period.

| | |
|-----------------------|-----------------|
| Reporting group title | Placebo: Off Tx |
|-----------------------|-----------------|

Reporting group description:

Participants previously treated with dose-matched placebo BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

| | |
|-----------------------|------------------------------|
| Reporting group title | Gefapixant 15 mg BID: Off Tx |
|-----------------------|------------------------------|

Reporting group description:

Participants previously treated with gefapixant 15 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

| | |
|-----------------------|------------------------------|
| Reporting group title | Gefapixant 45 mg BID: Off Tx |
|-----------------------|------------------------------|

Reporting group description:

Participants previously treated with gefapixant 45 mg BID for 52 weeks during the main study and extension study periods were observed for up to 3 months during an optional Off-Treatment Durability study period (participants received no treatment).

| Serious adverse events | Placebo: On Tx | Gefapixant 15 mg BID: On Tx | Gefapixant 45 mg BID: On Tx |
|---|------------------|-----------------------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 243 (5.76%) | 17 / 244 (6.97%) | 13 / 243 (5.35%) |
| number of deaths (all causes) | 2 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Malignant neoplasm of ampulla of Vater | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Temporal arteritis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| General disorders and administration site conditions | | | |
| Accidental death | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Cartilage injury | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cardiac disorders | | | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Cardiac amyloidosis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Lacunar infarction | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal wall cyst | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bursitis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Infections and infestations | | | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Papilloma viral infection | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Pneumonia staphylococcal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 1 / 244 (0.41%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 0 / 244 (0.00%) | 0 / 243 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 0 / 244 (0.00%) | 1 / 243 (0.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo: Off Tx | Gefapixant 15 mg BID: Off Tx | Gefapixant 45 mg BID: Off Tx |
|---|-----------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Invasive ductal breast carcinoma | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Malignant neoplasm of ampulla of Vater | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Temporal arteritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|----------------|----------------|
| Accidental death | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Death | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Injury, poisoning and procedural complications | | | |
| Cartilage injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Cardiac disorders | | | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Cardiac amyloidosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Lacunar infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Abdominal wall cyst | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Vomiting | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Infections and infestations | | | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Papilloma viral infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Tonsillitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (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 |

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

| Non-serious adverse events | Placebo: On Tx | Gefapixant 15 mg BID: On Tx | Gefapixant 45 mg BID: On Tx |
|---|--------------------|--------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 129 / 243 (53.09%) | 140 / 244 (57.38%) | 179 / 243 (73.66%) |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 243 (0.00%) | 3 / 244 (1.23%) | 33 / 243 (13.58%) |
| occurrences (all) | 0 | 5 | 37 |
| Dysgeusia | | | |
| subjects affected / exposed | 8 / 243 (3.29%) | 22 / 244 (9.02%) | 88 / 243 (36.21%) |
| occurrences (all) | 9 | 25 | 101 |
| Headache | | | |
| subjects affected / exposed | 31 / 243 (12.76%) | 34 / 244 (13.93%) | 29 / 243 (11.93%) |
| occurrences (all) | 55 | 57 | 51 |
| Hypogeusia | | | |
| subjects affected / exposed | 1 / 243 (0.41%) | 5 / 244 (2.05%) | 13 / 243 (5.35%) |
| occurrences (all) | 1 | 5 | 14 |
| Taste disorder | | | |
| subjects affected / exposed | 2 / 243 (0.82%) | 2 / 244 (0.82%) | 24 / 243 (9.88%) |
| occurrences (all) | 2 | 2 | 24 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-------------------------|-------------------------|-------------------------|
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 243 (5.76%) 19 | 15 / 244 (6.15%) 19 | 12 / 243 (4.94%) 23 |
| Dry mouth subjects affected / exposed occurrences (all) | 6 / 243 (2.47%) 7 | 7 / 244 (2.87%) 7 | 13 / 243 (5.35%) 13 |
| Nausea subjects affected / exposed occurrences (all) | 13 / 243 (5.35%) 22 | 8 / 244 (3.28%) 8 | 17 / 243 (7.00%) 20 |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 16 / 243 (6.58%) 21 | 9 / 244 (3.69%) 10 | 11 / 243 (4.53%) 18 |
| Cough subjects affected / exposed occurrences (all) | 10 / 243 (4.12%) 11 | 14 / 244 (5.74%) 14 | 16 / 243 (6.58%) 17 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 10 / 243 (4.12%) 14 | 13 / 244 (5.33%) 18 | 14 / 243 (5.76%) 14 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 8 / 243 (3.29%) 8 | 13 / 244 (5.33%) 18 | 9 / 243 (3.70%) 12 |
| Back pain subjects affected / exposed occurrences (all) | 19 / 243 (7.82%) 21 | 14 / 244 (5.74%) 17 | 20 / 243 (8.23%) 27 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 11 / 243 (4.53%) 12 | 20 / 244 (8.20%) 25 | 11 / 243 (4.53%) 17 |
| Localised infection subjects affected / exposed occurrences (all) | 1 / 243 (0.41%) 1 | 1 / 244 (0.41%) 1 | 1 / 243 (0.41%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 51 / 243 (20.99%) 75 | 47 / 244 (19.26%) 60 | 50 / 243 (20.58%) 63 |

| | | | |
|---|------------------------|------------------------|------------------------|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 243 (0.41%) 1 | 2 / 244 (0.82%) 2 | 0 / 243 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 9 / 243 (3.70%) 12 | 18 / 244 (7.38%) 20 | 13 / 243 (5.35%) 19 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 11 / 243 (4.53%) 14 | 14 / 244 (5.74%) 14 | 9 / 243 (3.70%) 13 |

| Non-serious adverse events | Placebo: Off Tx | Gefapixant 15 mg BID: Off Tx | Gefapixant 45 mg BID: Off Tx |
|---|---------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 0 / 10 (0.00%) | 1 / 18 (5.56%) | 1 / 13 (7.69%) |
| Nervous system disorders | | | |
| Ageusia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Hypogeusia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Taste disorder subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Nausea | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 18 (0.00%) 0 | 0 / 13 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 18 (5.56%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 18 (5.56%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 18 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 15 December 2017 | Major changes of Amendment (AM) 1 include revision of eligibility criteria and editorial clarifications. |
| 27 September 2018 | Major changes of Amendment AM 2 include a clarification of treatment of co-morbid conditions, and an update of the estimated glomerular filtration rate (eGFR). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported