



Clinical trial results:

A 12-Week Study to Assess the Efficacy and Safety of AF 219 in Subjects With Refractory Chronic Cough

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005064-42 |
| Trial protocol | GB |
| Global end of trial date | 04 November 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v3 (current) |
| This version publication date | 19 January 2019 |
| First version publication date | 12 November 2017 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 7264-012 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02612610 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | MK-7264-012: Merck Protocol Number |

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, ClinicalTrialsDisclosure@merck.com, 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 | 04 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study is designed to evaluate the efficacy of three dose regimens of gefapixant ([MK-7264] 7.5 mg, 20 mg, and 50 mg) relative to placebo in reducing awake objective cough frequency. The primary hypothesis for this trial is that at least one dose regimen of gefapixant is superior to placebo with respect to the mean change from baseline in awake cough frequency (on the log scale).

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 | 15 December 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 88 |
| Country: Number of subjects enrolled | United States: 165 |
| Worldwide total number of subjects | 253 |
| EEA total number of subjects | 88 |

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) | 152 |
| From 65 to 84 years | 101 |

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 367 screened, 253 were randomised to treatment with placebo or 7.5 mg, 20 mg, or 50 mg gefapixant. One participant randomised to receive 7.5 mg gefapixant was discontinued before receiving treatment.

Period 1

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

Arms

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

Arm description:

Participants received one matching placebo tablet administered by mouth twice daily for 12 weeks.

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

Dosage and administration details:

Dose-matched placebo tablet to gefapixant administered twice daily.

| | |
|------------------|-------------------|
| Arm title | Gefapixant 7.5 mg |
|------------------|-------------------|

Arm description:

Participants received one 7.5 mg gefapixant tablet administered by mouth twice daily for 12 weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | MK-7264, AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant administered as one 7.5 mg tablet twice daily.

| | |
|------------------|------------------|
| Arm title | Gefapixant 20 mg |
|------------------|------------------|

Arm description:

Participants received one 20 mg gefapixant tablet administered by mouth twice daily for 12 weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | MK-7264, AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant administered as one 20 mg tablet twice daily.

| | |
|---|------------------|
| Arm title | Gefapixant 50 mg |
| Arm description: | |
| Participants received one 50 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Gefapixant |
| Investigational medicinal product code | |
| Other name | MK-7264, AF-219 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gefapixant administered as one 50 mg tablet twice daily.

| Number of subjects in period 1 | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg |
|---------------------------------------|---------|-------------------|------------------|
| Started | 63 | 64 | 63 |
| Treated | 63 | 63 | 63 |
| Completed | 58 | 56 | 58 |
| Not completed | 5 | 8 | 5 |
| Consent withdrawn by subject | 1 | 1 | - |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 2 | 2 | 3 |
| Cough Improvement | - | - | 1 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | 1 | 2 | - |
| Noncompliance | 1 | - | - |
| Protocol deviation | - | 1 | 1 |

| Number of subjects in period 1 | Gefapixant 50 mg |
|---------------------------------------|------------------|
| Started | 63 |
| Treated | 63 |
| Completed | 50 |
| Not completed | 13 |
| Consent withdrawn by subject | 2 |
| Physician decision | - |
| Adverse event, non-fatal | 10 |
| Cough Improvement | - |
| Lost to follow-up | - |

| | |
|--------------------|---|
| Lack of efficacy | 1 |
| Noncompliance | - |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|--|-------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received one matching placebo tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 7.5 mg |
| Reporting group description: | |
| Participants received one 7.5 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 20 mg |
| Reporting group description: | |
| Participants received one 20 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 50 mg |
| Reporting group description: | |
| Participants received one 50 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |

| Reporting group values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg |
|------------------------------------|---------|-------------------|------------------|
| Number of subjects | 63 | 64 | 63 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|--------|---------|--------|
| Age Continuous Units: years | | | |
| arithmetic mean | 60.0 | 59.9 | 61.8 |
| standard deviation | ± 10.9 | ± 10.46 | ± 9.13 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 47 | 48 | 48 |
| Male | 16 | 16 | 15 |

| Reporting group values | Gefapixant 50 mg | Total | |
|------------------------------------|------------------|-------|--|
| Number of subjects | 63 | 253 | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|--------|-----|--|
| Age Continuous Units: years | | | |
| arithmetic mean | 59.3 | | |
| standard deviation | ± 9.19 | - | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 50 | 193 | |
| Male | 13 | 60 | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Placebo |
| Reporting group description: Participants received one matching placebo tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 7.5 mg |
| Reporting group description: Participants received one 7.5 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 20 mg |
| Reporting group description: Participants received one 20 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |
| Reporting group title | Gefapixant 50 mg |
| Reporting group description: Participants received one 50 mg gefapixant tablet administered by mouth twice daily for 12 weeks. | |

Primary: Change from Baseline in Awake Objective Cough Frequency after 12 Weeks of Treatment (Day 84)

| | |
|---|--|
| End point title | Change from Baseline in Awake Objective Cough Frequency after 12 Weeks of Treatment (Day 84) |
| End point description: Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period while the participant was awake divided by the total duration for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline ([BL], Study Day -1) and at Week 12 (Day 84) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. Least-squares (LS) mean change from BL (in log scale) with associated standard error (SE) reported for each treatment group. Change from BL in Awake Objective Cough Frequency = (Post-Treatment Awake Cough Frequency minus BL Awake Cough Frequency). All randomized participants who had taken at least 1 dose of study medication and provided at least 1 BL and ≥ 1 post BL endpoint observation during the treatment period were analysed. | |
| End point type | Primary |
| End point timeframe: Baseline Visit (Day -1), Day 84 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.40 (\pm 0.11) | -0.64 (\pm 0.11) | -0.65 (\pm 0.11) | -0.86 (\pm 0.11) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 84 Awake Cough Freq: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Estimated treatment differences (gefapixant vs. placebo [PBO]) and corresponding 95% confidence intervals (CIs) were estimated using a mixed effect repeated measures (MMRM) model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0971 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 0.05 |

Statistical analysis title

Day 84 Awake Cough Freq: 20 mg gefapixant v PBO

Statistical analysis description:

Estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0928 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 0.04 |

Statistical analysis title

Day 84 Awake Cough Freq: 50 mg gefapixant v PBO

Statistical analysis description:

Estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
|-------------------|----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0027 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | -0.16 |

Secondary: Change from Baseline in 24-Hour Objective Cough Frequency after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Change from Baseline in 24-Hour Objective Cough Frequency after 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 4 (Day 28) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in 24-Hour Objective Cough Frequency = (Post-Treatment 24-Hour Cough Frequency minus Baseline 24-Hour Cough Frequency).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 28

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.41 (± 0.10) | -0.59 (± 0.10) | -0.46 (± 0.10) | -0.93 (± 0.10) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 28 Awake Cough Freq: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1914 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | 0.09 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Awake Cough Freq: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7099 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0.23 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Awake Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0003 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.52 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | -0.24 |

Secondary: Change from Baseline in 24-Hour Objective Cough Frequency after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|---|
| End point title | Change from Baseline in 24-Hour Objective Cough Frequency after 8 Weeks of Treatment (Day 56) |
|-----------------|---|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 8 (Day 56) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in 24-Hour Objective Cough Frequency = (Post-Treatment 24-Hour Cough Frequency minus Baseline 24-Hour Cough Frequency).

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.31 (± 0.11) | -0.71 (± 0.11) | -0.59 (± 0.11) | -0.93 (± 0.11) |

Statistical analyses

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|----------------------------|--|
| Statistical analysis title | Day 56 24-hour Cough Freq: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0099 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.71 |
| upper limit | -0.1 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56 24-hour Cough Freq: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0695 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.58 |
| upper limit | 0.02 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56 24-hour Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0001 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | -0.31 |

Secondary: Change from Baseline in 24-Hour Objective Cough Frequency after 12

Weeks of Treatment (Day 84)

| | |
|-----------------|--|
| End point title | Change from Baseline in 24-Hour Objective Cough Frequency after 12 Weeks of Treatment (Day 84) |
|-----------------|--|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 12 (Day 84) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in 24-Hour Objective Cough Frequency = (Post-Treatment 24-Hour Cough Frequency minus Baseline 24-Hour Cough Frequency).

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 84

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.39 (± 0.10) | -0.62 (± 0.10) | -0.64 (± 0.10) | -0.86 (± 0.11) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 84 24-hour Cough Freq: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0991 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | 0.04 |

| | |
|--|---|
| Statistical analysis title | Day 84 24-hour Cough Freq: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0811 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.03 |

| | |
|--|---|
| Statistical analysis title | Day 84 24-hour Cough Freq: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0014 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.76 |
| upper limit | -0.19 |

Secondary: Change from Baseline in Awake Objective Cough Frequency after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Change from Baseline in Awake Objective Cough Frequency after 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period while the participant was awake divided by the total duration for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 4 (Day 28) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log

scale) with associated SE reported for each treatment group. Change from Baseline in Awake Objective Cough Frequency = (Post-Treatment Awake Cough Frequency minus Baseline Awake Cough Frequency).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Study Day -1), Day 28, | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.41 (± 0.10) | -0.62 (± 0.10) | -0.48 (± 0.10) | -0.90 (± 0.11) |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28 Awake Cough Freq: 7.5 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1468 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 0.07 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Awake Cough Freq: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
|-------------------|----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5874 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.36 |
| upper limit | 0.2 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Awake Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0008 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.78 |
| upper limit | -0.21 |

Secondary: Change from Baseline in Awake Objective Cough Frequency after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|---|
| End point title | Change from Baseline in Awake Objective Cough Frequency after 8 Weeks of Treatment (Day 56) |
|-----------------|---|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period while the participant was awake divided by the total duration for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 8 (Day 56) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in Awake Objective Cough Frequency = (Post-Treatment Awake Cough Frequency minus Baseline Awake Cough Frequency).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.31 (± 0.11) | -0.70 (± 0.12) | -0.63 (± 0.11) | -0.90 (± 0.12) |

Statistical analyses

| Statistical analysis title | Day 56 Awake Cough Freq: 7.5 mg gefapixant v PBO |
|---|--|
| Statistical analysis description: Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0177 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | Mixed Effect Repeated Measures model |
| Point estimate | -0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | -0.07 |

| Statistical analysis title | Day 56 Awake Cough Freq: 20 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0498 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.32 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 0 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56 Awake Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0004 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | -0.27 |

Secondary: Change from Baseline in Awake Objective Cough Frequency at the Follow-up Visit (Day 98)

| | |
|-----------------|---|
| End point title | Change from Baseline in Awake Objective Cough Frequency at the Follow-up Visit (Day 98) |
|-----------------|---|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period (in general, 24-hr interval) while the participant was awake divided by the total duration (in hours) for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at the Follow-up visit (Day 98) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. Change from Baseline in Awake Objective Cough Frequency = (Post-Treatment Awake Cough Frequency minus Baseline Awake Cough Frequency).

All randomised participants who had taken at least 1 dose of study medication and provided baseline and follow-up visit (Day 98) data during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 98

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|--------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 55 | 56 | 51 |
| Units: coughs/hour | | | | |
| arithmetic mean (standard deviation) | -6.4 (± 22.72) | -9.3 (± 47.72) | -7.4 (± 29.24) | -16.2 (± 39.00) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cough Severity Visual Analogue Scale (VAS) after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|--|
| End point title | Change from Baseline in Cough Severity Visual Analogue Scale (VAS) after 4 Weeks of Treatment (Day 28) |
|-----------------|--|

End point description:

Cough VAS was scored from 0 to 100 using a 100 mm visual analogue scale. Participants were asked to mark on a 100 mm scale between 0 (no cough) and 100 (the worst cough severity). Cough VAS was evaluated at Baseline (Study Day -1) and at Week 4 (Day 28). Baseline cough VAS was defined as the cough VAS at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 28

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -15.2 (± 3.02) | -21.6 (± 3.05) | -18.1 (± 3.04) | -25. (± 3.09) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 28 Cough Severity VAS: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1318 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.8 |
| upper limit | 1.9 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Cough Severity VAS: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4917 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.3 |
| upper limit | 5.4 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Cough Severity VAS: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0228 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -9.8 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.2 |
| upper limit | -1.4 |

Secondary: Change from Baseline in Cough Severity VAS after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|--|
| End point title | Change from Baseline in Cough Severity VAS after 8 Weeks of Treatment (Day 56) |
|-----------------|--|

End point description:

Cough VAS was scored from 0 to 100 using a 100 mm visual analogue scale. Participants were asked to mark on a 100 mm scale between 0 (no cough) and 100 (the worst cough severity). Cough VAS was evaluated at Baseline (Study Day -1) and at Week 8 (Day 56). Baseline cough VAS was defined as the cough VAS at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -16.1 (± 3.18) | -18.8 (± 3.19) | -19.4 (± 3.18) | -26.9 (± 3.33) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 56 Cough Severity VAS: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.554 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.5 |
| upper limit | 6.2 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56 Cough Severity VAS: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4702 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12 |
| upper limit | 5.6 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56 Cough Severity VAS: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0197 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -10.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.8 |
| upper limit | -1.7 |

Secondary: Change from Baseline in Cough Severity VAS after 12 Weeks of

Treatment (Day 84)

| | |
|-----------------|---|
| End point title | Change from Baseline in Cough Severity VAS after 12 Weeks of Treatment (Day 84) |
|-----------------|---|

End point description:

Cough VAS was scored from 0 to 100 using a 100 mm visual analogue scale. Participants were asked to mark on a 100 mm scale between 0 (no cough) and 100 (the worst cough severity). Cough VAS was evaluated at Baseline (Study Day -1) and at Week 12 (Day 84). Baseline cough VAS was defined as the cough VAS at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 84

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -16.7 (± 3.04) | -21.1 (± 3.08) | -23.1 (± 3.05) | -27.9 (± 3.16) |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Day 84 Cough Severity VAS: 7.5 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.302 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.9 |
| upper limit | 4 |

| | |
|----------------------------|---|
| Statistical analysis title | Day 84 Cough Severity VAS: 20 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were

estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1365 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -6.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.8 |
| upper limit | 2 |

| | |
|---|---|
| Statistical analysis title | Day 84 Cough Severity VAS: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0108 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -11.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.7 |
| upper limit | -2.6 |

Secondary: Change from Baseline in Cough Severity VAS At Day 85/Early Termination

| | |
|--|--|
| End point title | Change from Baseline in Cough Severity VAS At Day 85/Early Termination |
| End point description: | |
| Cough VAS was scored from 0 to 100 using a 100 mm visual analogue scale. Participants were asked to mark on a 100 mm scale between 0 (no cough) and 100 (the worst cough severity). Cough VAS was evaluated at Baseline (Study Day -1) and at Day 85/Early Termination. Baseline cough VAS was defined as the cough VAS at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group. | |
| All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed. | |
| End point type | Secondary |

End point timeframe:

Baseline (Study Day -1), Day 85

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: unit on a scale | | | | |
| least squares mean (standard error) | -15.2 (\pm 3.00) | -19.2 (\pm 3.04) | -23.4 (\pm 3.03) | -31.1 (\pm 3.09) |

Statistical analyses

| Statistical analysis title | Day 85 Cough Severity VAS: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3509 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.3 |
| upper limit | 4.4 |

| Statistical analysis title | Day 85 Cough Severity VAS: 20 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0519 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -8.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.6 |
| upper limit | 0.1 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 85 Cough Severity VAS: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0003 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -15.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.3 |
| upper limit | -7.5 |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period (in general, 24-hr interval) while the participant was awake divided by the total duration (in hours) for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 4 (Day 28) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in Awake Objective Cough Frequency were reported for each treatment group at Day 28.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 28 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 28

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 55 | 59 | 55 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| ≥70% Change | 15.0 | 25.5 | 16.9 | 34.5 |
| ≥50% Change | 23.3 | 38.2 | 30.5 | 47.3 |
| ≥30% Change | 46.7 | 63.6 | 50.8 | 60.0 |

Statistical analyses

| Statistical analysis title | Day 28: ≥70% Change: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1387 |
| Method | Cochran-Mantel-Haenszel |

| Statistical analysis title | Day 28: ≥70% Change: 20 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7238 |
| Method | Cochran-Mantel-Haenszel |

| Statistical analysis title | Day 28: ≥70% Change: 50 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0144 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0922 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3812 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0088 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 28: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0653 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 28: $\geq 30\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6443 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 28: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1511 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|--|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 8 Weeks of |
|-----------------|--|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period (in general, 24-hr interval) while the participant was awake divided by the total duration (in hours) for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 8 (Day 56) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in Awake Objective Cough Frequency were reported for each treatment group at Day 56.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 56 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 59 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 10.5 | 32.1 | 22.0 | 31.4 |
| $\geq 50\%$ Change | 26.3 | 46.4 | 39.0 | 54.9 |
| $\geq 30\%$ Change | 47.4 | 64.3 | 55.9 | 72.5 |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Day 56: $\geq 70\%$ Change: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0045 |
| Method | Cochran-Mantel-Haenszel |

| | |
|----------------------------|--|
| Statistical analysis title | Day 56: $\geq 70\%$ Change: 20 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless

stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0947 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 56: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.008 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0283 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
|-------------------|----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1493 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0026 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0652 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 56: $\geq 30\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3601 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 56: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0086 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 12 Weeks of Treatment (Day 84)

| | |
|-----------------|--|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency after 12 Weeks of Treatment (Day 84) |
|-----------------|--|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period (in general, 24-hr interval) while the participant was awake divided by the total duration (in hours) for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 12 (Day 84) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in Awake Objective Cough Frequency were reported for each treatment group at Day 84.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 84 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 84

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 56 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 15.8 | 21.4 | 23.2 | 31.4 |
| $\geq 50\%$ Change | 24.6 | 44.6 | 32.1 | 51.0 |
| $\geq 30\%$ Change | 43.9 | 64.3 | 48.2 | 80.4 |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3893 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2803 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0427 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0209 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3401 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0031 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0283 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 20 mg gefapixant v placebo |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6233 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency at the Follow-up Visit (Day 98)

| | |
|-----------------|---|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in Awake Objective Cough Frequency at the Follow-up Visit (Day 98) |
|-----------------|---|

End point description:

Awake Objective Cough Frequency (per hour) was defined as the total number of cough events during the monitoring period (in general, 24-hr interval) while the participant was awake divided by the total duration (in hours) for the monitoring period that the participant was awake. 24 hour sound recordings were made at Baseline (Study Day -1) and at the Follow-up visit (Day 98) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in Awake Objective Cough Frequency were reported for each treatment group at Day 98.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and

≥1 Day 98 endpoint observation during the treatment period were analysed.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Study Day -1), Day 98 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 55 | 56 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| ≥70% Change | 13.8 | 18.2 | 14.3 | 23.5 |
| ≥50% Change | 25.9 | 32.7 | 25.0 | 39.2 |
| ≥30% Change | 51.7 | 56.4 | 50.0 | 58.8 |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Day 98: ≥70% Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4925 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 98: ≥70% Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9007 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 98: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1602 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.344 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9876 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0993 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5968 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8726 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4092 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 4 (Day 28) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in 24-hr Objective Cough Frequency were reported for each treatment group at Day 28.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 28 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 28

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 55 | 59 | 55 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 13.3 | 25.5 | 15.3 | 34.5 |
| $\geq 50\%$ Change | 21.7 | 34.5 | 30.5 | 50.9 |
| $\geq 30\%$ Change | 51.7 | 58.2 | 45.8 | 67.3 |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Day 28: $\geq 70\%$ Change: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0781 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 28: $\geq 70\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7098 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 28: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0068 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 28: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1284 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant

treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.267 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Day 28: $\geq 50\%$ Change: 50 mg gefapixant v PBO

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0013 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Day 28: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4343 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Day 28: $\geq 30\%$ Change: 20 mg gefapixant v placebo

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
|-------------------|----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5384 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28: $\geq 30\%$ Change: 50 mg gefapixant v placebo |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0822 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|---|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 8 Weeks of Treatment (Day 56) |
|-----------------|---|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 8 (Day 56) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in 24-hr Objective Cough Frequency were reported for each treatment group at Day 56.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 56 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 59 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 7.0 | 32.1 | 22.0 | 37.3 |
| $\geq 50\%$ Change | 28.1 | 50.0 | 32.2 | 52.9 |

| | | | | |
|-------------|------|------|------|------|
| ≥30% Change | 45.6 | 62.5 | 54.2 | 78.4 |
|-------------|------|------|------|------|

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Day 56: ≥70% Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0006 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 56: ≥70% Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0223 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 56: ≥70% Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0001 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0165 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6255 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 56: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0085 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 56: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant

treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0722 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Day 56: $\geq 30\%$ Change: 20 mg gefapixant v placebo

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3577 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Day 56: $\geq 30\%$ Change: 50 mg gefapixant v PBO

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0006 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 12 Weeks of Treatment (Day 84)

| | |
|-----------------|--|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency after 12 Weeks of Treatment (Day 84) |
|-----------------|--|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 12 (Day 84) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in 24-hr Objective Cough Frequency were reported for

each treatment group at Day 84.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 84 endpoint observation during the treatment period were analysed.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Study Day -1), Day 84 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 56 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 14.0 | 19.6 | 25.0 | 31.4 |
| $\geq 50\%$ Change | 24.6 | 44.6 | 32.1 | 54.9 |
| $\geq 30\%$ Change | 42.1 | 62.5 | 50.0 | 78.4 |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3845 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1177 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0236 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0192 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3301 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 84: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0008 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0285 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3856 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 84: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant

treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency at the Follow-up Visit (Day 98)

| | |
|-----------------|---|
| End point title | Percentage of Participants with $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ Change in 24-Hour Objective Cough Frequency at the Follow-up Visit (Day 98) |
|-----------------|---|

End point description:

24-hr Objective Cough Frequency was defined as the total number of cough events during the monitoring period divided by the total duration in hours for the monitoring period (generally 24 hours). 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 14 (Day 98) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. The percentages of participants that met responder criteria for $\geq 70\%$, $\geq 50\%$, and $\geq 30\%$ change (reduction) from baseline levels in 24-hr Objective Cough Frequency were reported for each treatment group at Day 98.

All randomised participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 Day 98 endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 98

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 55 | 56 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| $\geq 70\%$ Change | 12.1 | 20.0 | 16.1 | 21.6 |
| $\geq 50\%$ Change | 25.9 | 34.5 | 25.0 | 39.2 |
| $\geq 30\%$ Change | 46.6 | 52.7 | 46.4 | 54.9 |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Day 98: $\geq 70\%$ Change: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a generalized linear mixed model (GLMM) with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified Cochran Mantel Haenszel (CMH) test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2441 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 70\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5055 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 70\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1602 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2721 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9763 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 98: $\geq 50\%$ Change: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0993 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4575 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9706 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--|
| Statistical analysis title | Day 98: $\geq 30\%$ Change: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Cough frequency responder endpoints were analyzed by a GLMM with treatment, visit, and treatment by visit interaction, and country as fixed effects. Comparison of response rates between each gefapixant treatment group and placebo was conducted using the stratified CMH test (stratified by country, unless stated otherwise). Missing data was categorised as discontinued or missing | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3258 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Change from Baseline in Sleep Objective Cough Frequency After 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Change from Baseline in Sleep Objective Cough Frequency After 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

Sleep Objective Cough Frequency was defined as the total number of cough events during the monitoring period while the participant was asleep divided by the total duration in hours for the monitoring period that the participant was asleep. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 4 (Day 28) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in Sleep Objective Cough Frequency = (Post-Treatment Objective Sleep Cough Frequency minus Baseline Sleep Cough Frequency).

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 28

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.37 (± 0.19) | -0.37 (± 0.20) | -0.38 (± 0.19) | -0.49 (± 0.20) |

Statistical analyses

| Statistical analysis title | Day 28 Sleep Cough Freq: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: | |
| Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9858 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.54 |

| Statistical analysis title | Day 28 Sleep Cough Freq: 20 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: | |
| Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9813 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.01 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.52 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 28 Sleep Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Gefapixant 50 mg v Placebo |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6746 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.65 |
| upper limit | 0.42 |

Secondary: Change from Baseline in Sleep Objective Cough Frequency After 8 Weeks of Treatment (Day 56)

| | |
|-----------------|---|
| End point title | Change from Baseline in Sleep Objective Cough Frequency After 8 Weeks of Treatment (Day 56) |
|-----------------|---|

End point description:

Sleep Objective Cough Frequency was defined as the total number of cough events during the monitoring period while the participant was asleep divided by the total duration in hours for the monitoring period that the participant was asleep. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 8 (Day 56) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in Sleep Objective Cough Frequency = (Post-Treatment Objective Sleep Cough Frequency minus Baseline Sleep Cough Frequency).

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.40 (\pm 0.20) | -0.72 (\pm 0.20) | -0.40 (\pm 0.20) | -0.80 (\pm 0.21) |

Statistical analyses

| Statistical analysis title | Day 56 Sleep Cough Freq: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: | |
| Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2583 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 0.24 |

| Statistical analysis title | Day 56 Sleep Cough Freq: 20 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: | |
| Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9826 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.56 |

| | |
|---|---|
| Statistical analysis title | Day 56 Sleep Cough Freq: 50 mg gefapixant v PBO |
| Statistical analysis description: Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1672 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.98 |
| upper limit | 0.17 |

Secondary: Change from Baseline in Sleep Objective Cough Frequency After 12 Weeks of Treatment (Day 84)

| | |
|-----------------|--|
| End point title | Change from Baseline in Sleep Objective Cough Frequency After 12 Weeks of Treatment (Day 84) |
|-----------------|--|

End point description:

Sleep Objective Cough Frequency was defined as the total number of cough events during the monitoring period while the participant was asleep divided by the total duration in hours for the monitoring period that the participant was asleep. 24 hour sound recordings were made at Baseline (Study Day -1) and at Week 12 (Day 84) using a digital recording device. An independent cough monitoring center documented the time of each cough event over the 24 hour period, as well as the time when the participant went to sleep and the time the participant woke. LS mean change from baseline (in log scale) with associated SE reported for each treatment group. Change from Baseline in Sleep Objective Cough Frequency = (Post-Treatment Objective Sleep Cough Frequency minus Baseline Sleep Cough Frequency)

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and ≥ 1 post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline (Study Day -1), Day 84

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: log coughs/hour | | | | |
| least squares mean (standard error) | -0.72 (\pm 0.19) | -0.58 (\pm 0.20) | -0.65 (\pm 0.19) | -0.44 (\pm 0.20) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Day 84 Sleep Cough Freq: 7.5 mg gefapixant v PBO |
| Statistical analysis description: Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6102 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.68 |

| | |
|---|---|
| Statistical analysis title | Day 84 Sleep Cough Freq: 20 mg gefapixant v PBO |
| Statistical analysis description: Day 84 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7782 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.61 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Day 84 Sleep Cough Freq: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Day 84 estimated treatment differences (gefaxipant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value (on log scale) as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3167 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 0.83 |

Secondary: Change from Baseline in Weekly Mean Daily Cough Severity Diary (CSD) Total Score at Week 1

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean Daily Cough Severity Diary (CSD) Total Score at Week 1 |
|-----------------|--|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 1

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.0 (± 0.15) | -0.7 (± 0.15) | -0.7 (± 0.15) | -1.10 (± 0.15) |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 1 CSD Total Score: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1545 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.7 |

Statistical analysis title

Week 1 CSD Total Score: 20 mg gefapixant v PBO

Statistical analysis description:

Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2013 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.7 |

Statistical analysis title

Week 1 CSD Total Score: 50 mg gefapixant v PBO

Statistical analysis description:

Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
|-------------------|----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9962 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.4 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 2

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 2 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.0 (± 0.18) | -0.9 (± 0.19) | -1.0 (± 0.19) | -1.5 (± 0.19) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Week 2 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7328 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.6 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 2 CSD Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7635 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.6 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 2 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0951 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 3

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 3 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 3

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.0 (± 0.20) | -1.2 (± 0.20) | -1.3 (± 0.20) | -1.5 (± 0.20) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Week 3 CSD Total Score: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5797 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 3 CSD Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2499 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.2 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 3 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0612 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 4

| | |
|--|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 4 |
| End point description: | |
| <p>The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).</p> <p>All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.2 (± 0.20) | -1.4 (± 0.20) | -1.5 (± 0.20) | -1.7 (± 0.20) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Week 4 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| <p>Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.</p> | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5358 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.4 |

| | |
|---|--|
| Statistical analysis title | Week 4 CSD Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| <p>Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country,</p> | |

treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3129 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.3 |

Statistical analysis title

Week 4 CSD Total Score: 50 mg gefapixant v PBO

Statistical analysis description:

Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1046 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 5

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 5 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 5

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.1 (\pm 0.20) | -1.3 (\pm 0.20) | -1.5 (\pm 0.20) | -1.8 (\pm 0.21) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Week 5 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5796 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.4 |

| | |
|--|--|
| Statistical analysis title | Week 5 CSD Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.143 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 5 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0221 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | -0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 6

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 6 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 6 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.0 (\pm 0.21) | -1.4 (\pm 0.21) | -1.5 (\pm 0.21) | -1.7 (\pm 0.21) |

Statistical analyses

| Statistical analysis title | Week 6 CSD Total Score: 7.5 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: | |
| Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1562 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.2 |

| Statistical analysis title | Week 6 CSD Total Score: 20 mg gefapixant v PBO |
|---|--|
| Statistical analysis description: | |
| Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.071 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0 |

| | |
|--|--|
| Statistical analysis title | Week 6 CSD Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0274 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 7

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 7 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 7 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.2 (± 0.21) | -1.4 (± 0.22) | -1.5 (± 0.22) | -1.7 (± 0.22) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Week 7 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4464 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.4 |

| | |
|--|--|
| Statistical analysis title | Week 7 CSD Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.332 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.3 |

| | |
|--|--|
| Statistical analysis title | Week 7 CSD Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0792 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 8

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 8 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 8 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.3 (± 0.22) | -1.5 (± 0.22) | -1.6 (± 0.22) | -1.7 (± 0.23) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Week 8 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4716 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 8 CSD Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4371 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 8 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1907 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.2 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 9

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 9 |
|-----------------|---|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 9

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.3 (± 0.21) | -1.6 (± 0.22) | -1.7 (± 0.22) | -1.8 (± 0.22) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Week 9 CSD Total Score: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2772 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.3 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 9 CSD Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1132 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 9 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0737 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 10

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 10 |
|-----------------|--|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 10

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.2 (± 0.22) | -1.4 (± 0.22) | -1.6 (± 0.22) | -1.9 (± 0.22) |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 10 CSD Total Score: 7.5 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6266 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.5 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 10 CSD Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country,

treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1769 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.2 |

Statistical analysis title

Week 10 CSD Total Score: 50 mg gefapixant v PBO

Statistical analysis description:

Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0313 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | -0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 11

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 11 |
|-----------------|--|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 11

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.1 (\pm 0.22) | -1.5 (\pm 0.22) | -1.7 (\pm 0.22) | -1.9 (\pm 0.23) |

Statistical analyses

| Statistical analysis title | Week 10 CSD Total Score: 7.5 mg gefapixant v PBO |
|---|--|
| Statistical analysis description: Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2058 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.2 |

| Statistical analysis title | Week 10 CSD Total Score: 20 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0665 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 10 CSD Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0155 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | -0.1 |

Secondary: Change from Baseline in Weekly Mean Daily CSD Total Score at Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean Daily CSD Total Score at Week 12 |
|-----------------|--|

End point description:

The daily CSD instrument has a total of 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD is the sum of these 7 item scores (Min=0, Max=70). Mean total daily score (the sum of 7 item scores divided by 7) was derived for each day. Weekly mean total daily score was defined as the average of the mean total daily scores for each week. LS mean change from baseline with associated SE reported for each treatment group. Baseline was defined as the average CSD scores collected during the week prior to Day 1 (Study Day -7 to Day -1).

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.2 (\pm 0.22) | -1.5 (\pm 0.22) | -1.7 (\pm 0.22) | -1.9 (\pm 0.23) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Week 12 CSD Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2458 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.3 |

| | |
|--|---|
| Statistical analysis title | Week 12 CSD Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0662 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0 |

| | |
|---|---|
| Statistical analysis title | Week 12 CSD Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0197 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | -0.1 |

Secondary: Change from Baseline in Weekly Mean Daily Cough Score (DCS) at Week 1

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean Daily Cough Score (DCS) at Week 1 |
|-----------------|---|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 1 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.1 (± 0.18) | -0.7 (± 0.18) | -0.8 (± 0.19) | -1.1 (± 0.19) |

Statistical analyses

| Statistical analysis title | Week 1 DCS Total Score: 7.5 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1921 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.8 |

| Statistical analysis title | Week 1 DCS Total Score: 20 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2428 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.8 |

| Statistical analysis title | Week 1 DCS Total Score: 50 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: Week 1 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7383 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.4 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 2

| | |
|---|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 2 |
| End point description: | |
| <p>The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.</p> <p>All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.4 (± 0.22) | -1.1 (± 0.23) | -1.1 (± 0.23) | -1.7 (± 0.23) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Week 2 DCS Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| <p>Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.</p> | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4033 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.9 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 2 DCS Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4599 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.9 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 2 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 2 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2837 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.3 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 3

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 3 |
|-----------------|---|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 3

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.4 (± 0.24) | -1.3 (± 0.24) | -1.6 (± 0.25) | -1.7 (± 0.25) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Week 3 DCS Total Score: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8084 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.8 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 3 DCS Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6108 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.5 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 3 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 3 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.422 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.4 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 4

| | |
|---|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 4 |
| End point description: | |
| The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group. | |
| All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.5 (\pm 0.24) | -1.6 (\pm 0.24) | -1.8 (\pm 0.24) | -1.9 (\pm 0.24) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Week 4 DCS Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8457 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.6 |

| | |
|---|--|
| Statistical analysis title | Week 4 DCS Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4044 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 4 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 4 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3031 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.3 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 5

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 5 |
|-----------------|---|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 5

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.4 (± 0.23) | -1.4 (± 0.24) | -1.9 (± 0.24) | -2.1 (± 0.24) |

Statistical analyses

| Statistical analysis title | Week 5 DCS Total Score: 7.5 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: | |
| Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9126 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.6 |

| Statistical analysis title | Week 5 DCS Total Score: 20 mg gefapixant v PBO |
|---|--|
| Statistical analysis description: | |
| Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1136 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 5 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 5 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0352 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 6

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 6 |
|-----------------|---|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 6

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.2 (\pm 0.24) | -1.7 (\pm 0.24) | -1.9 (\pm 0.24) | -1.8 (\pm 0.24) |

Statistical analyses

| Statistical analysis title | Week 6 DCS Total Score: 7.5 mg gefapixant v PBO |
|---|---|
| Statistical analysis description: | |
| Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1718 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.2 |

| Statistical analysis title | Week 6 DCS Total Score: 20 mg gefapixant v PBO |
|---|--|
| Statistical analysis description: | |
| Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0651 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0 |

| | |
|--|--|
| Statistical analysis title | Week 6 DCS Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: Week 6 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0848 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 7

| | |
|--|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 7 |
| End point description: The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group. All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 7 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.5 (± 0.25) | -1.7 (± 0.25) | -1.9 (± 0.25) | -1.9 (± 0.25) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Week 7 DCS Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6715 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.5 |

| | |
|---|--|
| Statistical analysis title | Week 7 DCS Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3514 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

| | |
|---|--|
| Statistical analysis title | Week 7 DCS Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 7 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2809 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.3 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 8

| | |
|---|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 8 |
| End point description: | |
| <p>The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.</p> <p>All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 8 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.7 (± 0.25) | -1.8 (± 0.25) | -1.9 (± 0.25) | -1.9 (± 0.26) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Week 8 DCS Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| <p>Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.</p> | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6022 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.5 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 8 DCS Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4456 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 8 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 8 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4629 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 9

| | |
|-----------------|---|
| End point title | Change from Baseline in Weekly Mean DCS at Week 9 |
|-----------------|---|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 9

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.6 (± 0.25) | -1.9 (± 0.25) | -2.2 (± 0.25) | -2.0 (± 0.26) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Week 9 DCS Total Score: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3749 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 9 DCS Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0854 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0.1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Week 9 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Week 9 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2672 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 0.3 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 10

| | |
|---|--|
| End point title | Change from Baseline in Weekly Mean DCS at Week 10 |
| End point description: | |
| The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group. | |
| All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 10 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.5 (± 0.25) | -1.6 (± 0.25) | -2.1 (± 0.25) | -2.1 (± 0.26) |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Week 10 DCS Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7255 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.6 |

| | |
|--|---|
| Statistical analysis title | Week 10 DCS Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0918 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0.1 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 10 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Week 10 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1263 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 0.2 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 11

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean DCS at Week 11 |
|-----------------|--|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 11 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.5 (± 0.25) | -1.8 (± 0.25) | -2.1 (± 0.25) | -2.2 (± 0.26) |

Statistical analyses

| Statistical analysis title | Week 11 DCS Total Score: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: | |
| Week 11 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4058 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

| Statistical analysis title | Week 11 DCS Total Score: 20 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: | |
| Week 11 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0828 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0.1 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Week 11 DCS Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

Week 11 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0575 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0 |

Secondary: Change from Baseline in Weekly Mean DCS at Week 12

| | |
|-----------------|--|
| End point title | Change from Baseline in Weekly Mean DCS at Week 12 |
|-----------------|--|

End point description:

The DCS has a score ranging from 0 (best) to 10 (worst). Weekly mean daily score was defined as the average of the daily scores for each week. Baseline was defined as the average DCS score collected during the week prior to Day 1 (Day -7 to Day -1). Participants rated the severity of their cough using the DCS each day. LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken at least 1 dose of study medication and provided at least 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Week 12

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.5 (\pm 0.26) | -1.8 (\pm 0.26) | -2.2 (\pm 0.26) | -2.2 (\pm 0.27) |

Statistical analyses

| Statistical analysis title | Week 12 DCS Total Score: 7.5 mg gefapixant v PBO |
|--|--|
| Statistical analysis description: | |
| Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4163 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 0.4 |

| Statistical analysis title | Week 12 DCS Total Score: 20 mg gefapixant v PBO |
|--|---|
| Statistical analysis description: | |
| Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0882 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 0.1 |

| | |
|--|---|
| Statistical analysis title | Week 12 DCS Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Week 12 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0961 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|---|
| End point title | Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score after 4 Weeks of Treatment (Day 28) |
|-----------------|---|

End point description:

The LCQ instrument is designed to assess the impact of cough on various aspects of a participant's life over the preceding 2 weeks. It consists of 19 items which are divided over 3 domains: Physical (items 1, 2, 3, 9, 10, 11, 14 and 15), Psychological (4, 5, 6, 12, 13, 16, and 17), and Social (7, 8, 18, 19). A 7-point Likert scale is used to rate each item. For each domain, the domain score (range 1-7) is the sum of the individual item scores within the domain divided by the number of items in the domain. The total score is the sum of the three domain scores and ranges from 3-21; a higher score corresponds to a better health status. Baseline LCQ was defined as the LCQ collected at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 28 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|-------------------|-------------------|-------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 2.1 (\pm 0.40) | 2.9 (\pm 0.40) | 2.3 (\pm 0.40) | 4.2 (\pm 0.4) |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Day 28 LCQ Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.163 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 1.9 |

| | |
|--|--|
| Statistical analysis title | Day 28 LCQ Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7601 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1.3 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 28 LCQ Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Day 28 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0004 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 3.2 |

Secondary: Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|---|
| End point title | Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score after 8 Weeks of Treatment (Day 56) |
|-----------------|---|

End point description:

The LCQ instrument is designed to assess the impact of cough on various aspects of a participant's life over the preceding 2 weeks. It consists of 19 items which are divided over 3 domains: Physical (items 1, 2, 3, 9, 10, 11, 14 and 15), Psychological (4, 5, 6, 12, 13, 16, and 17), and Social (7, 8, 18, 19). A 7-point Likert scale is used to rate each item. For each domain, the domain score (range 1-7) is the sum of the individual item scores within the domain divided by the number of items in the domain. The total score is the sum of the three domain scores and ranges from 3-21; a higher score corresponds to a better health status. Baseline LCQ was defined as the LCQ collected at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Day 56

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|------------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 2.0 (\pm 0.4) | 3.1 (\pm 0.4) | 3.0 (\pm 0.4) | 3.5 (\pm 0.5) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Day 56 LCQ Total Score: 7.5 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0941 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 2.3 |

| | |
|---|--|
| Statistical analysis title | Day 56 LCQ Total Score: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1321 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 2.2 |

| | |
|---|--|
| Statistical analysis title | Day 56 LCQ Total Score: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| Day 56 estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate. | |
| Comparison groups | Placebo v Gefapixant 50 mg |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0192 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 2.7 |

Secondary: Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score At Day 85/Early Termination

| | |
|-----------------|---|
| End point title | Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score At Day 85/Early Termination |
|-----------------|---|

End point description:

The LCQ instrument is designed to assess the impact of cough on various aspects of a participant's life over the preceding 2 weeks. It consists of 19 items which are divided over 3 domains: Physical (items 1, 2, 3, 9, 10, 11, 14 and 15), Psychological (4, 5, 6, 12, 13, 16, and 17), and Social (7, 8, 18, 19). A 7-point Likert scale is used to rate each item. For each domain, the domain score (range 1-7) is the sum of the individual item scores within the domain divided by the number of items in the domain. The total score is the sum of the three domain scores and ranges from 3-21; a higher score corresponds to a better health status. Baseline LCQ was defined as the LCQ collected at Baseline (Study Day -1). LS mean change from baseline with associated SE reported for each treatment group.

All randomized participants who had taken ≥ 1 dose of study medication and provided ≥ 1 baseline and at least one post baseline endpoint observation during the treatment period were analysed.

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

End point timeframe:

Baseline, Day 85/Early Termination

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-------------------------------------|------------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 61 | 59 | 59 | 57 |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 2.1 (\pm 0.4) | 3.3 (\pm 0.4) | 3.2 (\pm 0.4) | 4.0 (\pm 0.5) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Day 85 LCQ Total Score: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0626 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 2.4 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 85 LCQ Total Score: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0967 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 2.3 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Day 85 LCQ Total Score: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

Day 85/Early Termination estimated treatment differences (gefapixant vs. placebo) and corresponding 95% CIs were estimated using a MMRM model, which included fixed effects for treatment group, visit, country, treatment-by-visit interaction, and Baseline value as a covariate.

| | |
|---|--------------------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0028 |
| Method | Mixed Effect Repeated Measures model |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 3.1 |

Secondary: Percentage of Participants Reporting "Very Much Improved" or "Much Improved" According to the Patient's Global Impression of Change (PGIC) after 4 Weeks of Treatment (Day 28)

| | |
|-----------------|--|
| End point title | Percentage of Participants Reporting "Very Much Improved" or "Much Improved" According to the Patient's Global Impression of Change (PGIC) after 4 Weeks of Treatment (Day 28) |
|-----------------|--|

End point description:

The self-reported measure Patient's Global Impression of Change (PGIC) reflects a participant's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. Participants rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The counts and percentages of ordered responses to the participant's global perception of change were computed for each treatment group on Day 28 and the percentage of participants with improvements (either "very much improved" or "much improved" on the PGIC scale) was reported for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and 1 Day 28 PGIC observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 28 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 59 | 56 |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.0 | 37.9 | 35.6 | 46.4 |

Statistical analyses

| | |
|-----------------------------------|--------------------------------------|
| Statistical analysis title | Day 28 PGIC: 7.5 mg gefapixant v PBO |
|-----------------------------------|--------------------------------------|

Statistical analysis description:

The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test.

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3182 |
| Method | Cochran-Mantel-Haenszel |

| | |
|--|-------------------------------------|
| Statistical analysis title | Day 28 PGIC: 20 mg gefapixant v PBO |
| Statistical analysis description: | |
| The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5021 |
| Method | Cochran-Mantel-Haenszel |

| | |
|--|-------------------------------------|
| Statistical analysis title | Day 28 PGIC: 50 mg gefapixant v PBO |
| Statistical analysis description: | |
| The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0665 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants Reporting "Very Much Improved" or "Much Improved" According to the PGIC after 8 Weeks of Treatment (Day 56)

| | |
|-----------------|--|
| End point title | Percentage of Participants Reporting "Very Much Improved" or "Much Improved" According to the PGIC after 8 Weeks of Treatment (Day 56) |
|-----------------|--|

End point description:

The self-reported measure Patient's Global Impression of Change (PGIC) reflects a participant's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. Participants rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The counts and percentages of ordered responses to the participant's global perception of change were computed for each treatment group on Day 28 and the percentage of participants with improvements (either "very much improved" or "much improved" on the PGIC scale) was reported for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and 1 Day 56 PGIC observation during the treatment period were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 56 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 58 | 59 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | 29.3 | 44.8 | 44.1 | 60.8 |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Day 56 PGIC: 7.5 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0872 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|-------------------------------------|
| Statistical analysis title | Day 56 PGIC: 20 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0994 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|-------------------------------------|
| Statistical analysis title | Day 56 PGIC: 50 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0009 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants Reporting "Very Much Improved" or "Much

Improved" According to the PGIC at Day 85/Early Termination

| | |
|-----------------|--|
| End point title | Percentage of Participants Reporting "Very Much Improved" or "Much Improved" According to the PGIC at Day 85/Early Termination |
|-----------------|--|

End point description:

The self-reported measure Patient's Global Impression of Change (PGIC) reflects a participant's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. Participants rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The counts and percentages of ordered responses to the participant's global perception of change were computed for each treatment group on Day 28 and the percentage of participants with improvements (either "very much improved" or "much improved" on the PGIC scale) was reported for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and 1 Day 85 PGIC observation during the treatment period were analysed.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 85/Early Termination | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 59 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | 28.3 | 53.4 | 49.2 | 64.9 |

Statistical analyses

| | |
|----------------------------|--------------------------------------|
| Statistical analysis title | Day 85 PGIC: 7.5 mg gefapixant v PBO |
|----------------------------|--------------------------------------|

Statistical analysis description:

The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test.

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0037 |
| Method | Cochran-Mantel-Haenszel |

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | Day 85 PGIC: 20 mg gefapixant v PBO |
|----------------------------|-------------------------------------|

Statistical analysis description:

The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
|-------------------|----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0166 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|--------------------------------|
| Statistical analysis title | Day 85: 50 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percentage of Participants Rated as "Very Much Improved" or "Much Improved" by Clinicians according to the Clinician's Global Impression of Change (CGIC) at Day 85/Early Termination

| | |
|-----------------|---|
| End point title | Percentage of Participants Rated as "Very Much Improved" or "Much Improved" by Clinicians according to the Clinician's Global Impression of Change (CGIC) at Day 85/Early Termination |
|-----------------|---|

End point description:

The Clinician's Global Impression of Change (CGIC) reflects a clinician's belief about the efficacy of treatment. CGIC is a 7-point scale depicting a clinician's rating of a participant's overall improvement. Clinicians rated the participant's change at Week 12 (Day 85) as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The counts and percentages of ordered responses to the clinician's global perception of change were computed for each treatment group, and the percentage of participants rated by clinicians as having improvement (either "very much improved" or "much improved" on the CGIC scale) was reported for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and provided at least 1 baseline and 1 Day 85 CGIC observation during the treatment period were analysed.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: Day 85/Early Termination | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 59 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | 35.0 | 53.4 | 50.8 | 64.9 |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Day 85 CGIC: 7.5 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0396 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|-------------------------------------|
| Statistical analysis title | Day 85 CGIC: 20 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0751 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|-------------------------------------|
| Statistical analysis title | Day 85 CGIC: 50 mg gefapixant v PBO |
| Statistical analysis description: The distribution of responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication For At Least One Year

| | |
|-----------------|---|
| End point title | Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication For At Least One Year |
|-----------------|---|

End point description:

At the end of the treatment period (Day 85), participants were asked "How likely would you be to take this medication?" This question was asked in reference to the time frame of "At least one year". The counts and percentages of ordered categorical responses to this question were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and had available Acceptability Questionnaire data at Day 85 were analysed.

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

End point timeframe:

Day 85/Early Termination

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 58 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Extremely unlikely | 3.3 | 6.9 | 5.2 | 1.8 |
| Unlikely | 3.3 | 1.7 | 3.4 | 12.3 |
| Neither likely or unlikely | 5.0 | 5.2 | 12.1 | 1.8 |
| Likely | 30.0 | 15.5 | 13.8 | 29.8 |
| Extremely likely | 58.3 | 70.7 | 65.5 | 54.4 |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | 1 Year Acceptability: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

The distribution of "Extremely likely" responses was compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for the gefapixant vs. placebo using CMH test.

| | |
|-------------------|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
|-------------------|-----------------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 118 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|--|
| Analysis type | |
|---------------|--|

| | |
|---------|----------|
| P-value | = 0.8464 |
|---------|----------|

| | |
|--------|-------------------------|
| Method | Cochran-Mantel-Haenszel |
|--------|-------------------------|

| | |
|-----------------------------------|--|
| Statistical analysis title | 1 Year Acceptability: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "Extremely likely" responses was compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
|-------------------|----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4364 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | 1 Year Acceptability: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "Extremely likely" responses was compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7687 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication For At Least Six Months

| | |
|-----------------|---|
| End point title | Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication For At Least Six Months |
|-----------------|---|

End point description:

At the end of the treatment period (Day 85), participants were asked "How likely would you be to take this medication?" This question was asked in reference to the time frame of "At least six months". The counts and percentages of ordered categorical responses to this question were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and had available Acceptability Questionnaire data at Day 85 were analysed.

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

End point timeframe:

Day 85/Early Termination

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 57 | 58 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Extremely unlikely | 3.3 | 5.3 | 5.2 | 1.8 |
| Unlikely | 1.7 | 3.5 | 3.4 | 10.5 |
| Neither likely or unlikely | 6.7 | 3.5 | 6.9 | 3.5 |
| Likely | 21.7 | 14.0 | 17.2 | 29.8 |
| Extremely likely | 66.7 | 73.7 | 67.2 | 54.4 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | 6 Month Acceptability: 7.5 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9966 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | 6 Month Acceptability: 50 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2155 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | 6 Month Acceptability: 20 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6372 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Acceptability Questionnaire: Percentage of Participants That Were Likely

to Take Study Medication For At Least Four Weeks

| | |
|-----------------|---|
| End point title | Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication For At Least Four Weeks |
|-----------------|---|

End point description:

At the end of the treatment period (Day 85), participants were asked "How likely would you be to take this medication?" This question was asked in reference to the time frame of "At least four weeks". The counts and percentages of ordered categorical responses to this question were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and had available Acceptability Questionnaire data at Day 85 were analysed.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 85/Early Termination | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 58 | 58 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Extremely unlikely | 3.3 | 5.2 | 5.2 | 0.0 |
| Unlikely | 1.7 | 1.7 | 1.7 | 5.3 |
| Neither likely or unlikely | 3.3 | 1.7 | 6.9 | 8.8 |
| Likely | 18.3 | 19.0 | 15.5 | 26.3 |
| Extremely likely | 73.3 | 72.4 | 70.7 | 59.6 |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | 4 Week Acceptability: 7.5 mg gefapixant v PBO |
|----------------------------|---|

Statistical analysis description:

The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7559 |
| Method | Cochran-Mantel-Haenszel |

| | |
|----------------------------|--|
| Statistical analysis title | 4 Week Acceptability: 50 mg gefapixant v PBO |
|----------------------------|--|

Statistical analysis description:

The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|-------------------|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
|-------------------|----------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.279 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | 4 Week Acceptability: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 118 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.5091 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication Twice Daily

| | |
|-----------------|---|
| End point title | Acceptability Questionnaire: Percentage of Participants That Were Likely to Take Study Medication Twice Daily |
|-----------------|---|

End point description:

At the end of the treatment period (Day 85), participants were asked "How likely would you be to take this medication?" This question was asked in reference to the time frame of "Twice daily". The counts and percentages of ordered categorical responses to this question were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication and had available Acceptability Questionnaire data at Day 85 were analysed.

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

End point timeframe:

Day 85/Early Termination

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 57 | 57 | 56 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Extremely unlikely | 3.3 | 7.0 | 5.3 | 1.8 |
| Unlikely | 0.0 | 0.0 | 3.5 | 5.4 |
| Neither likely or unlikely | 3.3 | 5.3 | 3.5 | 8.9 |
| Likely | 20.0 | 15.8 | 22.8 | 30.4 |
| Extremely likely | 73.3 | 71.9 | 64.9 | 53.6 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Twice Daily Acceptability: 7.5 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.3887 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Twice Daily Acceptability: 20 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2333 |
| Method | Cochran-Mantel-Haenszel |

| | |
|---|---|
| Statistical analysis title | Twice Daily Acceptability: 50 mg gefapixant v PBO |
| Statistical analysis description: The distribution of "Extremely likely" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test. | |
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0534 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Taste Questionnaire: Percentage of Participants That Experienced Taste

Effect After Taking Medication by Frequency after 12 Weeks of Treatment (Day 84)

| | |
|-----------------|---|
| End point title | Taste Questionnaire: Percentage of Participants That Experienced Taste Effect After Taking Medication by Frequency after 12 Weeks of Treatment (Day 84) |
|-----------------|---|

End point description:

The tolerance to taste-related adverse events (AEs) was evaluated at the end of the study (Day 84) and a structured taste questionnaire was administered to participants experiencing a taste-related AE. Participants were asked to indicate the frequency that they experienced the taste effect by answering the question "How frequently do you experience the taste effect after taking each dose of medication?" The counts and percentages of categorical frequency responses to the individual items were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication, who had experienced a taste-related AE, and who had Day 84 taste questionnaire data available were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 84 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 57 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| No Taste Effect Noted | 96.5 | 96.4 | 61.4 | 35.3 |
| Never | 1.8 | 0.0 | 0.0 | 0.0 |
| Occasionally | 1.8 | 1.8 | 8.8 | 0.0 |
| Often | 0.0 | 1.8 | 7.0 | 3.9 |
| Almost Always | 0.0 | 0.0 | 7.0 | 9.8 |
| Always | 0.0 | 0.0 | 15.8 | 51.0 |
| No Taste Effect Noted + Never | 98.2 | 96.4 | 61.4 | 35.3 |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Taste Effect Frequency: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Never" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6115 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Taste Effect Frequency: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Never" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Statistical analysis title

Taste Effect Frequency: 50 mg gefapixant v PBO

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Never" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Taste Questionnaire: Percentage of Participants That Found Taste Effect of Study Medication Bothersome after 12 Weeks of Treatment (Day 84)

| | |
|-----------------|---|
| End point title | Taste Questionnaire: Percentage of Participants That Found Taste Effect of Study Medication Bothersome after 12 Weeks of Treatment (Day 84) |
|-----------------|---|

End point description:

The tolerance to taste-related adverse events (AEs) was evaluated at the end of the study (Day 84) and a structured taste questionnaire was administered to participants experiencing a taste-related AE to determine what degree the participant found the taste effect bothersome by answering the question "How bothersome is the taste effect of the medication? The counts and percentages of categorical responses to the individual items were computed for each treatment group.

All randomised participants who had taken at least 1 dose of study medication, who had experienced a taste-related AE, and who had Day 84 taste questionnaire data available were analysed.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 84 | |

| End point values | Placebo | Gefapixant 7.5 mg | Gefapixant 20 mg | Gefapixant 50 mg |
|-----------------------------------|-----------------|-------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 56 | 57 | 51 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| No Taste Effect Noted | 96.5 | 96.4 | 61.4 | 35.3 |

| | | | | |
|------------------------------------|-------|-------|------|------|
| Not At All | 3.5 | 3.6 | 7.0 | 5.9 |
| A Little | 0.0 | 0.0 | 8.8 | 3.9 |
| Somewhat | 0.0 | 0.0 | 17.5 | 13.7 |
| Very | 0.0 | 0.0 | 5.3 | 29.4 |
| Extremely | 0.0 | 0.0 | 0.0 | 11.8 |
| No Taste Effect Noted + Not At All | 100.0 | 100.0 | 68.4 | 41.2 |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Taste Effect Frequency: 7.5 mg gefapixant v PBO |
|-----------------------------------|---|

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Not at All" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|-----------------------------|
| Comparison groups | Placebo v Gefapixant 7.5 mg |
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0 [1] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[1] - A p-value of zero was calculated if all participants (100%) had "No Taste Effect Noted" or "Not at All" responses in both comparison groups.

| | |
|-----------------------------------|--|
| Statistical analysis title | Taste Effect Frequency: 20 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Not at All" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 20 mg |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

| | |
|-----------------------------------|--|
| Statistical analysis title | Taste Effect Frequency: 50 mg gefapixant v PBO |
|-----------------------------------|--|

Statistical analysis description:

The distribution of "No Taste Effect Noted" or "Not at All" responses were compared between each of the gefapixant treatment groups and placebo using the stratified CMH test (stratified by country). P-values calculated for gefapixant vs. placebo using CMH test.

| | |
|---|----------------------------|
| Comparison groups | Placebo v Gefapixant 50 mg |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to ~14 weeks (Day 99)

Adverse event reporting additional description:

All randomised participants who received at least 1 dose of study drug. One participant randomised to receive 7.5 mg gefapixant was discontinued before receiving treatment.

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Participants received one matching placebo tablet administered by mouth twice daily for 12 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | Gefapixant 20 mg |
|-----------------------|------------------|

Reporting group description:

Participants received one 20 mg gefapixant tablet administered by mouth twice daily for 12 weeks.

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

Reporting group description:

Participants received one 7.5 mg gefapixant tablet administered by mouth twice daily for 12 weeks.

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

Reporting group description:

Participants received one 50 mg gefapixant tablet administered by mouth twice daily for 12 weeks.

| Serious adverse events | Placebo | Gefapixant 20 mg | Gefapixant 7.5 mg |
|---|----------------|------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 63 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Frostbite | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 63 (0.00%) | 0 / 63 (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 | Gefapixant 50 mg | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|---|----------------|--|--|
| Injury, poisoning and procedural complications | | | |
| Frostbite | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo | Gefapixant 20 mg | Gefapixant 7.5 mg |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 63 (33.33%) | 45 / 63 (71.43%) | 26 / 63 (41.27%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 63 (3.17%) | 5 / 63 (7.94%) |
| occurrences (all) | 0 | 2 | 5 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 3 / 63 (4.76%) | 0 / 63 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 21 / 63 (33.33%) | 6 / 63 (9.52%) |
| occurrences (all) | 4 | 26 | 7 |
| Headache | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 12 / 63 (19.05%) | 4 / 63 (6.35%) |
| occurrences (all) | 4 | 16 | 4 |
| Hypogeusia | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 11 / 63 (17.46%) | 0 / 63 (0.00%) |
| occurrences (all) | 1 | 12 | 0 |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 63 (9.52%) | 3 / 63 (4.76%) | 2 / 63 (3.17%) |
| occurrences (all) | 7 | 3 | 2 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 4 / 63 (6.35%) | 2 / 63 (3.17%) |
| occurrences (all) | 4 | 4 | 2 |
| Nausea | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | 4 / 63 (6.35%) 4 | 0 / 63 (0.00%) 0 |
| Paraesthesia oral subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 8 | 5 / 63 (7.94%) 5 | 4 / 63 (6.35%) 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 5 / 63 (7.94%) 5 | 2 / 63 (3.17%) 3 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 0 / 63 (0.00%) 0 | 1 / 63 (1.59%) 1 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 3 | 4 / 63 (6.35%) 4 | 0 / 63 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 9 / 63 (14.29%) 9 | 5 / 63 (7.94%) 5 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 5 / 63 (7.94%) 6 | 3 / 63 (4.76%) 3 |

| | | | |
|--|------------------------|--|--|
| Non-serious adverse events | Gefapixant 50 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 63 (82.54%) | | |
| Investigations | | | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Ageusia subjects affected / exposed occurrences (all) | 13 / 63 (20.63%) 14 | | |
| Dysgeusia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 30 / 63 (47.62%) | | |
| occurrences (all) | 39 | | |
| Headache | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 4 | | |
| Hypogeusia | | | |
| subjects affected / exposed | 15 / 63 (23.81%) | | |
| occurrences (all) | 18 | | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | | |
| occurrences (all) | 3 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | | |
| occurrences (all) | 5 | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 63 (9.52%) | | |
| occurrences (all) | 6 | | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 4 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | | |
| occurrences (all) | 5 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 4 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 63 (9.52%) | | |
| occurrences (all) | 6 | | |
| Urinary tract infection | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 63 (3.17%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 22 December 2015 | Amendment 1 (AM1) included revisions to inclusion and exclusion criteria, revisions to Subject Discontinuation criteria, and addition of Interactive Web Response System (IWRS) as a randomization method. AM1 also revised the selection and timing of dose for each subject, revised the primary endpoint to specify "after 4 weeks (Day 28)", and removed the safety assessment for renal/urological AEs. |
| 11 March 2016 | AM2 included revisions to inclusion and exclusion criteria and to the Prohibited Concomitant Therapy section, and updated the Independent Data Monitoring Committee section of the protocol. |
| 04 November 2016 | AM3 removed the Week 4 timepoint from the primary objective and primary endpoint, and moved this timepoint to the Secondary Objectives/Endpoints. AM3 also revised the Secondary Objectives and divided the Secondary Endpoints into "key" and "other" categories. The statistical sections were also updated to reflect the changes made to the primary endpoint and primary analysis. This protocol amendment aligned key aspects of the statistical section of the study protocol with the statistical analysis plan. These revisions to the protocol, which provided additional detail and specificity of the planned analyses in order to facilitate the validity of the conclusions from the trial, were finalized after Last Subject Last Visit (LSLV) but prior to database lock, as was the statistical analysis plan. These changes did not result in any changes to the conduct of the trial. AM3 was approved on 15 December 2016, but due to system limitations, the Global End of Trial Date (LSLV) was imputed as the Amendment Date. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported