



Clinical trial results:

A Multicenter, Randomized, Double-blind Phase 3 Study to Evaluate Tolerability and Pharmacokinetics of 500 µg Roflumilast Once Daily with an Up-titration Regimen in COPD, including an Open-label Down-titration Period Evaluating Tolerability and Pharmacokinetics of 250 µg Roflumilast Once Daily in Subjects not Tolerating 500 µg Roflumilast Once-daily

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2013-001788-21 |
| Trial protocol | GB SK DE HU RO GR BG |
| Global end of trial date | 21 October 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 16 October 2016 |
| First version publication date | 16 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | RO-2455-302-RD |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02165826 |
| WHO universal trial number (UTN) | U1111-1150-2477 |
| Other trial identifiers | NRES: 14/NW/0138, Philippines: PHRR150519-001004, REec: REec-2014-0965 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Takeda Development Center Americas, Inc. |
| Sponsor organisation address | One Takeda Parkway, Deerfield, United States, 60015 |
| Public contact | Director, Clinical Science, Takeda, +1 8778253327, clinicaltrialregistry@tpna.com |
| Scientific contact | Director, Clinical Science, Takeda, +1 8778253327, clinicaltrialregistry@tpna.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 21 October 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 September 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate discontinuation rates of roflumilast 500 µg once daily (OD) using an up-titration regimen with either 250 µg OD or 500 µg every other day (EOD) for the first 4 weeks of treatment followed by 500 µg OD for 8 weeks compared with continuous treatment of 500 µg OD during the entire 12-week main period, and to evaluate if participants who do not tolerate roflumilast 500 µg OD have a drug exposure with 250 µg roflumilast OD similar to that observed in other participants with the 500 µg OD dose.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 April 2014 |
| 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 | Bulgaria: 84 |
| Country: Number of subjects enrolled | Germany: 52 |
| Country: Number of subjects enrolled | Greece: 20 |
| Country: Number of subjects enrolled | Hungary: 235 |
| Country: Number of subjects enrolled | Korea, Republic of: 46 |
| Country: Number of subjects enrolled | Philippines: 30 |
| Country: Number of subjects enrolled | Poland: 199 |
| Country: Number of subjects enrolled | Romania: 144 |
| Country: Number of subjects enrolled | Russian Federation: 141 |
| Country: Number of subjects enrolled | Slovakia: 106 |
| Country: Number of subjects enrolled | South Africa: 61 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | Thailand: 17 |
| Country: Number of subjects enrolled | Ukraine: 168 |
| Country: Number of subjects enrolled | United Kingdom: 15 |

| | |
|------------------------------------|------|
| Worldwide total number of subjects | 1323 |
| EEA total number of subjects | 860 |

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) | 668 |
| From 65 to 84 years | 653 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 161 investigative sites in Bulgaria, Germany, Greece, Hungary, Korea, Philippines, Poland, Romania, Russia, Slovakia, South Africa, Spain, Thailand, Ukraine and the United Kingdom from 30 April 2014 to 21 October 2015.

Pre-assignment

Screening details:

Participants with a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) were enrolled equally in 1 of 3 treatment groups in the Main Treatment Period: roflumilast 250 µg then 500 µg once daily (OD), 500 µg every other day (EOD) then 500 µg OD and 500 µg OD. Participants who discontinued received 250 µg in the Down-Titration Period.

Pre-assignment period milestones

| | |
|------------------------------|------|
| Number of subjects started | 1323 |
| Number of subjects completed | 1321 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-------------------------------|
| Reason: Number of subjects | Did Not Receive Study Drug: 2 |
|----------------------------|-------------------------------|

Period 1

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

Arms

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

| | |
|------------------|--------------------------------------|
| Arm title | Roflumilast 250 µg OD then 500 µg OD |
|------------------|--------------------------------------|

Arm description:

Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Roflumilast tablets

| | |
|------------------|---------------------------------------|
| Arm title | Roflumilast 500 µg EOD then 500 µg OD |
|------------------|---------------------------------------|

Arm description:

Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

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

| | |
|--|---------------------------|
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Roflumilast tablets | |
| Investigational medicinal product name | Roflumilast Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Roflumilast placebo-matching tablets | |
| Arm title | Roflumilast 500 µg OD |
| Arm description: | |
| Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Roflumilast tablets | |

| Number of subjects in period 1^[1] | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | Roflumilast 500 µg OD |
|---|--------------------------------------|---------------------------------------|-----------------------|
| Started | 441 | 437 | 443 |
| Safety Analysis Set: Received Study Drug | 441 | 437 | 443 |
| Completed | 360 | 349 | 334 |
| Not completed | 81 | 88 | 109 |
| Pre-treatment Event/Adverse Event | 44 | 57 | 68 |
| Major/Significant Protocol Deviation | - | 1 | 3 |
| Voluntary Withdrawal | 23 | 23 | 21 |
| Reason Not Specified | 8 | 5 | 16 |
| Lost to follow-up | 4 | 2 | 1 |
| Lack of efficacy | 2 | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 2 participants were randomized but did not receive study treatment and are not included in the Baseline Period.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Down-Titration Period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Roflumilast 250 µg OD then 500 µg OD |

Arm description:

Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Roflumilast tablets

| | |
|------------------|---------------------------------------|
| Arm title | Roflumilast 500 µg EOD then 500 µg OD |
|------------------|---------------------------------------|

Arm description:

Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Roflumilast tablets

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

Dosage and administration details:

Roflumilast placebo-matching tablets

| | |
|------------------|-----------------------|
| Arm title | Roflumilast 500 µg OD |
|------------------|-----------------------|

Arm description:

Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Roflumilast |
| Investigational medicinal product code | |
| Other name | Daxas, Daliresp, Libertek |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| Number of subjects in period 2^[2] | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | Roflumilast 500 µg OD |
|---|--------------------------------------|---------------------------------------|-----------------------|
| Started | 27 | 39 | 38 |
| Safety Analysis Set: Received Study Drug | 27 | 39 | 38 |
| Completed | 20 | 28 | 31 |
| Not completed | 7 | 11 | 7 |
| Pre-treatment Event/Adverse Event | 4 | 10 | 3 |
| Voluntary Withdrawal | 2 | 1 | 2 |
| Reason Not Specified | 1 | - | 2 |

Notes:

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

Justification: Not all participants from the Main Treatment Period entered the Down-Titration Period.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Roflumilast 250 µg OD then 500 µg OD |
|-----------------------|--------------------------------------|

Reporting group description:

Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Roflumilast 500 µg EOD then 500 µg OD |
|-----------------------|---------------------------------------|

Reporting group description:

Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|-----------------------|
| Reporting group title | Roflumilast 500 µg OD |
|-----------------------|-----------------------|

Reporting group description:

Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period.

| Reporting group values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | Roflumilast 500 µg OD |
|---|--------------------------------------|---------------------------------------|-----------------------|
| Number of subjects | 441 | 437 | 443 |
| Age, Customized Units: participants | | | |
| 40-64 years | 242 | 202 | 224 |
| 65-84 years | 199 | 235 | 217 |
| 85 years and over | 0 | 0 | 2 |
| Age Continuous Units: years | | | |
| arithmetic mean | 64.2 | 65 | 64.6 |
| standard deviation | ± 7.81 | ± 8.21 | ± 8.36 |
| Gender, Male/Female Units: participants | | | |
| Female | 121 | 112 | 105 |
| Male | 320 | 325 | 338 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | 5 |
| Not Hispanic or Latino | 428 | 423 | 426 |
| Missing | 12 | 12 | 12 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 0 | 1 | 0 |
| Asian | 32 | 30 | 32 |
| Black or African American | 3 | 3 | 3 |
| Native Hawaiian/Other Pacific Islander | 1 | 4 | 3 |
| White | 405 | 399 | 405 |
| Smoking Classification Units: Subjects | | | |
| Current Smoker | 213 | 198 | 196 |

| | | | |
|---|----------|----------|----------|
| Ex-smoker | 228 | 239 | 247 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Bulgaria | 36 | 18 | 30 |
| Germany | 12 | 24 | 16 |
| Greece | 8 | 6 | 6 |
| Hungary | 82 | 74 | 79 |
| Korea, Republic Of | 22 | 11 | 13 |
| Philippines | 7 | 13 | 10 |
| Poland | 60 | 68 | 71 |
| Romania | 54 | 46 | 44 |
| Russia | 37 | 48 | 55 |
| Slovakia | 40 | 38 | 27 |
| South Africa | 17 | 18 | 26 |
| Spain | 2 | 2 | 1 |
| Thailand | 2 | 6 | 9 |
| Ukraine | 56 | 58 | 54 |
| United Kingdom | 6 | 7 | 2 |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 169.1 | 168.8 | 169.1 |
| standard deviation | ± 8.73 | ± 8.66 | ± 8.55 |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 75.59 | 74.31 | 75.68 |
| standard deviation | ± 18.627 | ± 17.808 | ± 16.949 |
| Body Mass Index (BMI) | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 26.36 | 25.98 | 26.44 |
| standard deviation | ± 5.957 | ± 5.614 | ± 5.888 |
| Number of Cigarette Pack-Years | | | |
| Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked | | | |
| Units: pack-years | | | |
| arithmetic mean | 38.1 | 40.2 | 37.6 |
| standard deviation | ± 17.49 | ± 19.22 | ± 17.7 |
| Pre-bronchodilator Forced Expiratory Volume in the First Second (FEV1) | | | |
| Pre-bronchodilator FEV1 data was available for 440, 436 and 443 participants in each treatment arm, respectively. | | | |
| Units: Liters | | | |
| arithmetic mean | 1.022 | 1.028 | 1.018 |
| standard deviation | ± 0.3177 | ± 0.3173 | ± 0.3289 |
| Pre-Bronchodilator Forced Vital Capacity (FVC) | | | |
| Pre-Bronchodilator FVC data was available for 440, 436 and 443 participants in each treatment arm, respectively. | | | |
| Units: Liters | | | |
| arithmetic mean | 2.304 | 2.303 | 2.314 |
| standard deviation | ± 0.7418 | ± 0.7091 | ± 0.6822 |
| Reporting group values | Total | | |
| Number of subjects | 1321 | | |

| | | | |
|---|------|--|--|
| Age, Customized Units: participants | | | |
| 40-64 years | 668 | | |
| 65-84 years | 651 | | |
| 85 years and over | 2 | | |
| Age Continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender, Male/Female Units: participants | | | |
| Female | 338 | | |
| Male | 983 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 8 | | |
| Not Hispanic or Latino | 1277 | | |
| Missing | 36 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 1 | | |
| Asian | 94 | | |
| Black or African American | 9 | | |
| Native Hawaiian/Other Pacific Islander | 8 | | |
| White | 1209 | | |
| Smoking Classification Units: Subjects | | | |
| Current Smoker | 607 | | |
| Ex-smoker | 714 | | |
| Region of Enrollment Units: Subjects | | | |
| Bulgaria | 84 | | |
| Germany | 52 | | |
| Greece | 20 | | |
| Hungary | 235 | | |
| Korea, Republic Of | 46 | | |
| Philippines | 30 | | |
| Poland | 199 | | |
| Romania | 144 | | |
| Russia | 140 | | |
| Slovakia | 105 | | |
| South Africa | 61 | | |
| Spain | 5 | | |
| Thailand | 17 | | |
| Ukraine | 168 | | |
| United Kingdom | 15 | | |
| Height Units: cm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weight | | | |

| | | | |
|---|---|--|--|
| Units: kg arithmetic mean standard deviation | - | | |
| Body Mass Index (BMI) Units: kg/m ² arithmetic mean standard deviation | - | | |
| Number of Cigarette Pack-Years | | | |
| Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked | | | |
| Units: pack-years arithmetic mean standard deviation | - | | |
| Pre-bronchodilator Forced Expiratory Volume in the First Second (FEV1) | | | |
| Pre-bronchodilator FEV1 data was available for 440, 436 and 443 participants in each treatment arm, respectively. | | | |
| Units: Liters arithmetic mean standard deviation | - | | |
| Pre-Bronchodilator Forced Vital Capacity (FVC) | | | |
| Pre-Bronchodilator FVC data was available for 440, 436 and 443 participants in each treatment arm, respectively. | | | |
| Units: Liters arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Roflumilast 250 µg OD then 500 µg OD |
| Reporting group description: Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Reporting group title | Roflumilast 500 µg EOD then 500 µg OD |
| Reporting group description: Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Reporting group title | Roflumilast 500 µg OD |
| Reporting group description: Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period. | |
| Reporting group title | Roflumilast 250 µg OD then 500 µg OD |
| Reporting group description: Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Reporting group title | Roflumilast 500 µg EOD then 500 µg OD |
| Reporting group description: Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Reporting group title | Roflumilast 500 µg OD |
| Reporting group description: Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period. | |
| Subject analysis set title | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the roflumilast 250 µg once daily (OD) then 500 µg OD who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Subject analysis set title | Roflumilast 500 µg EOD_Down-Titration Period |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the roflumilast 500 µg, every other day (EOD) treatment arm who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Subject analysis set title | Roflumilast 500 µg OD_Down Titration Period |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Participants in the roflumilast 500 µg once daily (OD) treatment arm who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period. | |
| Subject analysis set title | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants in the roflumilast 250 µg once daily (OD) then 500 µg OD who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | All PK Participants_Roflumilast |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

All PK participants who received any dose of roflumilast. Results for roflumilast.

| | |
|----------------------------|---|
| Subject analysis set title | All PK Participants_Roflumilast N-oxide |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

All PK participants who received any dose of roflumilast. Results for roflumilast N-oxide.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Roflumilast 500 µg EOD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, every other day (EOD) in the Main Period.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Roflumilast 250 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 250 µg tablets, orally, once daily in the Main Period.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Roflumilast 250 µg Down-Titration |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Roflumilast 250 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg at least one dose in the Main Period followed by Roflumilast 250 µg tablets, orally, once daily in the Down -Titration Period.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Roflumilast 250 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 250 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Roflumilast 500 µg EOD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, orally, every other day (EOD) at least 1 dose in the Main Period

| | |
|----------------------------|--|
| Subject analysis set title | Roflumilast 500 µg OD_CFB in FEV1 @ Week 4 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, once daily (OD) for 12 weeks. Results for Change from Baseline in FEV1 at Week 4.

| | |
|----------------------------|---|
| Subject analysis set title | Roflumilast 500 µg OD_CFB in FEV1 @ Week 12 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, once daily (OD) for 12 weeks. Results for Change from Baseline in FEV1 at Week 12.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Roflumilast 500 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Roflumilast 500 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, once daily (OD) at least 1 dose in the Main Period.

| | |
|----------------------------|---------------------------------------|
| Subject analysis set title | Roflumilast 500 µg EOD then 500 µg OD |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

Primary: Percentage of Participants Prematurely Discontinuing Study Treatment due to any Reason

| | |
|-----------------|--|
| End point title | Percentage of Participants Prematurely Discontinuing Study Treatment due to any Reason |
|-----------------|--|

End point description:

The primary endpoint is the percentage of participants prematurely discontinuing study treatment for any reason during the Main Period from Visit 1 (V1) to Last Visit (Vend). Discontinuation is defined as permanently stopping randomized treatment; participants who resume randomized treatment after an interval will not be counted as having discontinued. The analysis used discontinuations occurring during the Main Period, irrespective of whether a participant subsequently entered into the Down-Titration Period.

Safety Analysis Set (SAS) included all randomized participants who took at least one dose of study medication.

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

End point timeframe:

Baseline to Week 12 (Main Period)

| End point values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | Roflumilast 500 µg OD | |
|-----------------------------------|--------------------------------------|---------------------------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 441 | 437 | 443 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 18.4 | 20.1 | 24.6 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Analyses were performed using a hierarchical testing procedure.

| | |
|---|--|
| Comparison groups | Roflumilast 250 µg OD then 500 µg OD v Roflumilast 500 µg OD |
| Number of subjects included in analysis | 884 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.017 ^[1] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.66 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.93 |

Notes:

[1] - Study treatment, country and baseline forced expiratory volume in the first second (FEV1) as explanatory variables.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analyses were performed using a hierarchical testing procedure.

| | |
|---|--|
| Comparison groups | Roflumilast 250 µg OD then 500 µg OD v Roflumilast 500 µg OD |
| Number of subjects included in analysis | 884 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.68 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.92 |

Notes:

[2] - Cox proportional hazards model with study treatment and country as class effects, and baseline FEV1 as a continuous variable.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analyses were performed using a hierarchical testing procedure.

| | |
|---|---|
| Comparison groups | Roflumilast 500 µg EOD then 500 µg OD v Roflumilast 500 µg OD |
| Number of subjects included in analysis | 880 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.114 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.76 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.07 |

Notes:

[3] - Study treatment, country and baseline forced expiratory volume in the first second (FEV1) as explanatory variables.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analyses were performed using a hierarchical testing procedure.

| | |
|-------------------|---|
| Comparison groups | Roflumilast 500 µg EOD then 500 µg OD v Roflumilast 500 µg OD |
|-------------------|---|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 880 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.02 |

Notes:

[4] - Cox proportional hazards model with study treatment and country as class effects, and baseline FEV1 as a continuous variable.

Secondary: Percentage of Participants with Adverse Events of Interest

| | |
|------------------------|---|
| End point title | Percentage of Participants with Adverse Events of Interest |
| End point description: | Adverse events (AEs) of interest to evaluate tolerability are defined as diarrhea, nausea, headache, decreased appetite, insomnia and abdominal pain. SAS included all randomized participants who took at least one dose of study medication. |
| End point type | Secondary |
| End point timeframe: | Baseline to Week 12 (Main Period) |

| End point values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | Roflumilast 500 µg OD | |
|-----------------------------------|--------------------------------------|---------------------------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 441 | 437 | 443 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 45.4 | 48.3 | 54.2 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | Analyses were performed using a hierarchical testing procedure. |
| Comparison groups | Roflumilast 250 µg OD then 500 µg OD v Roflumilast 500 µg OD |
| Number of subjects included in analysis | 884 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 ^[5] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.63 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.83 |

Notes:

[5] - Study treatment, country and baseline forced expiratory volume in the first second (FEV1) as explanatory variables.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analyses were performed using a hierarchical testing procedure.

| | |
|---|---|
| Comparison groups | Roflumilast 500 µg EOD then 500 µg OD v Roflumilast 500 µg OD |
| Number of subjects included in analysis | 880 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.091 ^[6] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.78 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.04 |

Notes:

[6] - Study treatment, country and baseline forced expiratory volume in the first second (FEV1) as explanatory variables.

Secondary: Change from Baseline (V0DT) in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) to Final Visit of the Down-Titration Period

| | |
|-----------------|---|
| End point title | Change from Baseline (V0DT) in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) to Final Visit of the Down-Titration Period |
|-----------------|---|

End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement.

Participants from the Down-Titration Period Full Analysis Set (FAS), all randomized participants who entered this period, regardless of whether they took study medication, with data available for analysis.

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

End point timeframe:

Baseline (V0DT) [assessment at end of main period] and Final Visit of Down-Titration Period (Up to Day 56)

| End point values | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 26 | 39 | 38 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | 0.03 (± 0.2294) | 0.055 (± 0.417) | 0.007 (± 0.3555) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Prematurely Discontinuing Study Treatment due to Any Reason During Down-Titration Period

| | |
|---|---|
| End point title | Percentage of Participants Prematurely Discontinuing Study Treatment due to Any Reason During Down-Titration Period |
| End point description: Down-Titration Period Full Analysis Set (FAS) included all randomized participants who entered this period, regardless of whether they took study medication. | |
| End point type | Secondary |
| End point timeframe: Baseline DT (Day 1 of Down-Titration Period) to Week 8 (Down-Titration Period) | |

| End point values | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | |
|-----------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 39 | 38 | 27 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 28.2 | 18.4 | 25.9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) during the Down-Titration Period

| | |
|---|---|
| End point title | Change from Baseline in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) during the Down-Titration Period |
| End point description: FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement. | |

Participants from the Down-Titration Period Full Analysis Set (FAS), all randomized participants who entered this period, regardless of whether they took study medication, with data available for analysis.

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

End point timeframe:

Baseline DT (Day 1 of Down-Titration Period) to Days 14, 28 and 56 (Down-Titration Period)

| End point values | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 39 | 38 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 14 (n=20, 32, 34) | 0.128 (± 0.3708) | 0.223 (± 0.4101) | 0.097 (± 0.2532) | |
| Day 28 (n=20, 29, 31) | 0.162 (± 0.4274) | 0.218 (± 0.4443) | 0.07 (± 0.2067) | |
| Day 56 (n=26, 39, 38) | 0.162 (± 0.3311) | 0.261 (± 0.4616) | 0.127 (± 0.3334) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) during the Main Period

| | |
|-----------------|--|
| End point title | Change from Baseline in Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) during the Main Period ^[7] |
|-----------------|--|

End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement.

Main Period FAS included all randomized participants, regardless of whether they took study medication. "n" in each of the categories is the number of participants with data available at the given time-point.

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

End point timeframe:

Baseline (Day 1 of Main Period) to Days 15, 29, 57 and 84 (Main Period)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all Baseline period arms are applicable to this endpoint.

| End point values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | |
|--------------------------------------|--------------------------------------|-----------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 441 | 443 | 439 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|--------------------------|------------------|------------------|------------------|--|
| Day 15 (n=409, 406, 386) | 0.067 (± 0.2299) | 0.094 (± 0.2566) | 0.094 (± 0.2573) | |
| Day 29 (n=402, 389, 365) | 0.099 (± 0.2605) | 0.116 (± 0.244) | 0.115 (± 0.2629) | |
| Day 57 (n=376, 367, 352) | 0.104 (± 0.2659) | 0.133 (± 0.2705) | 0.161 (± 0.2765) | |
| Day 84 (n=402, 411, 409) | 0.117 (± 0.269) | 0.122 (± 0.2705) | 0.141 (± 0.2882) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC) during the Main Period

| | |
|-----------------|--|
| End point title | Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC) during the Main Period ^[8] |
|-----------------|--|

End point description:

Forced vital capacity is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement.

Main Period FAS included all randomized participants, regardless of whether they took study medication. "n" in each of the categories is the number of participants with data available at the given time-point.

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

End point timeframe:

Baseline (Day 1 of Main Period) to Days 15, 29, 57 and 84 (Main Period)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Not all Baseline period arms are applicable to this endpoint.

| End point values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | |
|--------------------------------------|--------------------------------------|-----------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 441 | 443 | 439 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 (n=409, 406, 386) | 0.096 (± 0.4053) | 0.104 (± 0.4166) | 0.112 (± 0.4168) | |
| Day 29 (n=402, 389, 365) | 0.139 (± 0.3826) | 0.149 (± 0.4173) | 0.143 (± 0.4172) | |
| Day 57 (n=376, 367, 352) | 0.156 (± 0.4346) | 0.162 (± 0.4341) | 0.194 (± 0.4974) | |
| Day 84 (n=402, 411, 409) | 0.157 (± 0.4746) | 0.147 (± 0.4555) | 0.207 (± 0.4925) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC)

during the Down-Titration Period

| | |
|-----------------|---|
| End point title | Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC) during the Down-Titration Period |
|-----------------|---|

End point description:

Forced vital capacity is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement.

Down-Titration Period Full Analysis Set (FAS) included all randomized participants who entered this period, regardless of whether they took study medication.

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

End point timeframe:

Baseline DT (Day 1 of Down-Titration Period) to Days 14, 28 and 56 (Down-Titration Period)

| End point values | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 39 | 38 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 14 (n=20, 32, 34) | 0.087 (± 0.5392) | 0.303 (± 0.5103) | 0.104 (± 0.4568) | |
| Day 28 (n=20, 29, 31) | 0.125 (± 0.6151) | 0.191 (± 0.478) | 0.067 (± 0.3522) | |
| Day 56 (n=26, 39, 38) | 0.167 (± 0.5492) | 0.133 (± 0.51) | 0.029 (± 0.4628) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Treatment Satisfaction Scores during the Main Period

| | |
|-----------------|---|
| End point title | Change from Baseline in Treatment Satisfaction Scores during the Main Period ^[9] |
|-----------------|---|

End point description:

Participants will be asked to assess their satisfaction with their COPD therapy at each visit. The participants will rate their treatment satisfaction on a 7-point scale where 0=very satisfied, 1=satisfied, 2=somewhat satisfied, 3=neither satisfied nor dissatisfied, 4=somewhat dissatisfied, 5=dissatisfied and 6=very dissatisfied. A negative change from Baseline indicates improvement.

Main Period FAS included all randomized participants, regardless of whether they took study medication. "n" in each of the categories is the number of participants with data available at the given time-point.

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

End point timeframe:

Baseline (Day 1 of Main Period) to Days 15, 29, 57 and 84 (Main Period)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not all Baseline period arms are applicable to this endpoint.

| End point values | Roflumilast 250 µg OD then 500 µg OD | Roflumilast 500 µg OD | Roflumilast 500 µg EOD then 500 µg OD | |
|--------------------------------------|--------------------------------------|-----------------------|---------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 441 | 443 | 439 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 (n=410, 408, 386) | -0.4 (± 1.12) | -0.3 (± 1.07) | -0.3 (± 1.15) | |
| Day 29 (n=403, 390, 366) | -0.5 (± 1.23) | -0.5 (± 1.22) | -0.5 (± 1.16) | |
| Day 57 (n=375, 369, 351) | -0.6 (± 1.24) | -0.5 (± 1.29) | -0.6 (± 1.26) | |
| Day 84 (n=407, 416, 412) | -0.5 (± 1.43) | -0.3 (± 1.52) | -0.5 (± 1.51) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Treatment Satisfaction Scores during the Down-Titration Period

| | |
|-----------------|--|
| End point title | Change from Baseline in Treatment Satisfaction Scores during the Down-Titration Period |
|-----------------|--|

End point description:

Participants will be asked to assess their satisfaction with their COPD therapy at each visit. The participants will rate their treatment satisfaction on a 7-point scale where 0=very satisfied, 1=satisfied, 2=somewhat satisfied, 3=neither satisfied nor dissatisfied, 4=somewhat dissatisfied, 5=dissatisfied and 6=very dissatisfied. A negative change from Baseline indicates improvement.

Down-Titration Period Full Analysis Set (FAS) included all randomized participants who entered this period, regardless of whether they took study medication. "n" in each of the categories is the number of participants with data available at the given time-point.

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

End point timeframe:

Baseline DT (Day 1 of Down-Titration Period) to Days 14, 28 and 56 (Down-Titration Period)

| End point values | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 39 | 38 | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 14 (n=20, 32, 34) | -1.1 (± 1.85) | -0.8 (± 1.57) | -0.8 (± 1.84) | |
| Day 28 (n=20, 29, 31) | -1.2 (± 2.01) | -0.8 (± 1.75) | -0.9 (± 1.81) | |
| Day 56 (n=26, 39, 38) | -0.8 (± 2.23) | -0.3 (± 2.15) | -0.4 (± 2.26) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Model Point Estimate for Absorption Rate Constant (Ka) of Roflumilast and Roflumilast N-oxide

| | |
|-----------------|---|
| End point title | Population PK Model Point Estimate for Absorption Rate Constant (Ka) of Roflumilast and Roflumilast N-oxide |
|-----------------|---|

End point description:

PK model point estimates for Ka are calculated using all available PK data for all doses of roflumilast combined and are presented for roflumilast and metabolite roflumilast N-oxide. Results are reported for the overall population as well as for the subgroups defined according to the covariates (weight, age, smoking status and sex) included in the final model.

Pharmacokinetic (PK) Set included all participants who had at least 1 quantifiable PK concentration.

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

End point timeframe:

Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours at weeks 2 or 8

| End point values | All PK Participants_Roflumilast | All PK Participants_Roflumilast N-oxide | | |
|-----------------------------|---------------------------------|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1238 | 1238 | | |
| Units: units per hour (1/h) | | | | |
| number (not applicable) | | | | |
| Weight=33.5 kg | 0.9 | 0.57 | | |
| Weight=70 kg | 0.9 | 0.57 | | |
| Weight=160 kg | 0.9 | 0.57 | | |
| Age=40 | 0.9 | 0.57 | | |
| Age=60 | 0.9 | 0.57 | | |
| Age=92 | 0.9 | 0.57 | | |
| Smoking=former | 0.9 | 0.57 | | |
| Smoking=current | 0.9 | 0.57 | | |
| Sex=female | 0.9 | 0.57 | | |
| Sex=male | 0.9 | 0.57 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Model Point Estimate for Apparent Oral Clearance (CL/F) of Roflumilast and Roflumilast N-oxide

| | |
|-----------------|--|
| End point title | Population PK Model Point Estimate for Apparent Oral Clearance (CL/F) of Roflumilast and Roflumilast N-oxide |
|-----------------|--|

End point description:

PK model point estimates for CL/F are calculated using all available PK data for all doses of roflumilast combined and are presented for roflumilast and metabolite roflumilast N-oxide. Results are reported for the overall population as well as for the subgroups defined according to the covariates (weight, age, smoking status and sex) included in the final model.

Pharmacokinetic (PK) Set included all participants who had at least 1 quantifiable PK concentration.

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

End point timeframe:

Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours at weeks 2 or 8

| End point values | All PK Participants_Ro flumilast | All PK Participants_Ro flumilast N- oxide | | |
|------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1238 | 1238 | | |
| Units: liters per hour (L/h) | | | | |
| number (not applicable) | | | | |
| Weight=33.5 kg | 5.64 | 0.73 | | |
| Weight=70 kg | 5.64 | 0.89 | | |
| Weight=160 kg | 5.64 | 1.12 | | |
| Age=40 | 7.23 | 1.11 | | |
| Age=60 | 5.64 | 0.89 | | |
| Age=92 | 4.35 | 0.71 | | |
| Smoking=former | 5.64 | 0.89 | | |
| Smoking=current | 6.5 | 1.03 | | |
| Sex=female | 5.64 | 0.89 | | |
| Sex=male | 5.64 | 0.79 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Model Point Estimate for Apparent Central Volume (Vc/F) of Roflumilast and Roflumilast N-oxide

| | |
|-----------------|--|
| End point title | Population PK Model Point Estimate for Apparent Central Volume (Vc/F) of Roflumilast and Roflumilast N-oxide |
|-----------------|--|

End point description:

PK model point estimates for Vc/F are calculated using all available PK data for all doses of roflumilast combined and are presented for roflumilast and metabolite roflumilast N-oxide. Results are reported for the overall population as well as for the subgroups defined according to the covariates (weight, age, smoking status and sex) included in the final model.

Pharmacokinetic (PK) Set included all participants who had at least 1 quantifiable PK concentration.

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

End point timeframe:

Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours at weeks 2 or 8

| End point values | All PK Participants_Ro flumilast | All PK Participants_Ro flumilast N- oxide | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1238 | 1238 | | |
| Units: liters (L) | | | | |
| number (not applicable) | | | | |
| Weight=33.5 kg | 26 | 4.5 | | |
| Weight=70 kg | 63.9 | 11 | | |
| Weight=160 kg | 175.2 | 30.2 | | |
| Age=40 | 63.9 | 11 | | |
| Age=60 | 63.9 | 11 | | |
| Age=92 | 63.9 | 11 | | |
| Smoking=former | 63.9 | 11 | | |
| Smoking=current | 63.9 | 11 | | |
| Sex=female | 63.9 | 11 | | |
| Sex=male | 63.9 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Population PK Model Point Estimate for Apparent Peripheral Volume (Vp/F) of Roflumilast and Roflumilast N-oxide

| | |
|--|---|
| End point title | Population PK Model Point Estimate for Apparent Peripheral Volume (Vp/F) of Roflumilast and Roflumilast N-oxide |
| End point description: | |
| PK model point estimates for Vp/F are calculated using all available PK data for all doses of roflumilast combined and are presented for roflumilast and metabolite roflumilast N-oxide. Results are reported for the overall population as well as for the subgroups defined according to the covariates (weight, age, smoking status and sex) included in the final model. | |
| Pharmacokinetic (PK) Set included all participants who had at least 1 quantifiable PK concentration. | |
| End point type | Secondary |
| End point timeframe: | |
| Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours at weeks 2 or 8 | |

| End point values | All PK Participants_Ro flumilast | All PK Participants_Ro flumilast N- oxide | | |
|-----------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1238 | 1238 | | |
| Units: Liters | | | | |
| number (not applicable) | | | | |
| Weight=33.5 kg | 69.6 | 5 | | |
| Weight=70 kg | 171 | 12.4 | | |
| Weight=160 kg | 468.8 | 34 | | |
| Age=40 | 171 | 12.4 | | |
| Age=60 | 171 | 12.4 | | |

| | | | | |
|-----------------|-----|------|--|--|
| Age=92 | 171 | 12.4 | | |
| Smoking=former | 171 | 12.4 | | |
| Smoking=current | 171 | 12.4 | | |
| Sex=female | 171 | 12.4 | | |
| Sex=male | 171 | 12.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total PDE4 Inhibitory Activity (tPDE4i)

| | |
|---|---|
| End point title | Total PDE4 Inhibitory Activity (tPDE4i) ^[10] |
| End point description: | |
| tPDE4i of roflumilast and roflumilast N-oxide was derived using in-vitro constants for protein binding and biochemical activity (IC50). tPDE4i is reported for a set of reference participants defined according to the covariates included in the final model. Participants from the PK Set, all participants who had at least 1 quantifiable PK concentration, with data available. Measured values are predicted values reported as median and 90% prediction interval. | |
| End point type | Secondary |
| End point timeframe: | |
| Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours post-dose at Days 15 and 57. Down-titration: Pre-dose and 1,2,3,4,6 hours post-dose at Days 1 and 14 and pre-dose at Days 28 and 56. | |
| Notes: | |
| [10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. | |
| Justification: Not all Baseline period arms are applicable to this endpoint. | |

| End point values | Roflumilast 500 µg OD | Roflumilast 500 µg EOD | Roflumilast 250 µg OD | Roflumilast 250 µg Down-Titration |
|-------------------------------------|-----------------------|------------------------|------------------------|-----------------------------------|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 392 | 399 | 404 | 101 |
| Units: unitless | | | | |
| median (confidence interval 90%) | | | | |
| Overall | 1.17 (0.366 to 2.05) | 0.608 (0.227 to 1.03) | 0.563 (0.157 to 1.01) | 0.583 (0.21 to 1.24) |
| Age < 65 (n=198,187,229,45) | 1.06 (0.323 to 1.85) | 0.559 (0.237 to 0.998) | 0.518 (0.16 to 0.958) | 0.511 (0.205 to 0.984) |
| Age ≥ 65 to < 75 (n=146,159,136,39) | 1.24 (0.55 to 2.08) | 0.66 (0.177 to 1.04) | 0.614 (0.138 to 1.1) | 0.683 (0.207 to 1.23) |
| Age ≥ 75 (n=48,53,39,17) | 1.24 (0.318 to 2.31) | 0.676 (0.188 to 1.12) | 0.616 (0.195 to 1.01) | 0.712 (0.3 to 1.32) |
| Weight < 60 kg (n=56,78,73,17) | 1.34 (0.591 to 2.64) | 0.755 (0.258 to 1.22) | 0.653 (0.156 to 1.12) | 0.934 (0.325 to 1.39) |
| Weight ≥ 60 kg (n=336,321,331,84) | 1.12 (0.339 to 1.99) | 0.592 (0.223 to 1.01) | 0.552 (0.158 to 0.971) | 0.538 (0.202 to 1.02) |
| Males (n=300,297,290,66) | 1.12 (0.363 to 1.96) | 0.585 (0.226 to 0.994) | 0.558 (0.145 to 0.998) | 0.575 (0.213 to 1.14) |
| Females (n=92,102,114,35) | 1.29 (0.468 to 2.38) | 0.696 (0.26 to 1.15) | 0.618 (0.189 to 1.01) | 0.626 (0.217 to 1.25) |
| Current Smoker (n=179,183,200,45) | 1.04 (0.327 to 1.88) | 0.568 (0.247 to 0.976) | 0.514 (0.101 to 0.949) | 0.554 (0.228 to 1.21) |

| | | | | |
|----------------------------------|----------------------|-----------------------|----------------------|----------------------|
| Former Smoker (n=213,216,204,56) | 1.25 (0.416 to 2.15) | 0.632 (0.186 to 1.09) | 0.626 (0.196 to 1.1) | 0.624 (0.207 to 1.3) |
|----------------------------------|----------------------|-----------------------|----------------------|----------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Summary Statistics of Predicted Total PDE4 Inhibitory Activity (tPDE4i)

| | |
|--|---|
| End point title | Summary Statistics of Predicted Total PDE4 Inhibitory Activity (tPDE4i) |
| End point description: | |
| tPDE4i of roflumilast and roflumilast N-oxide was derived using in-vitro constants for protein binding and biochemical activity (IC50). An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) is defined as an AE with an onset that occurs after receiving study drug. Adverse Events of Interest (AEI) for PK analyses included: headache, diarrhea, nausea, vomiting, abdominal pain, appetite disorders, sleep disorders, angioedema, psychiatric disorders (anxiety, nervousness), psychiatric disorders (depression, suicidal ideation, behaviour) and weight loss. 99999=NA (no participants analyzed). Measured values are predicted values reported as median and 90% prediction interval. PK Set . "n" in the category is the number of participants with available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours post-dose at Days 15 and 57. Down-titration: Pre-dose and 1,2,3,4,6 hours post-dose at Days 1 and 14 and pre-dose at Days 28 and 56. | |

| End point values | Roflumilast 250 µg OD | Roflumilast 500 µg OD | | |
|--|------------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 76 | 1114 | | |
| Units: unitless | | | | |
| median (confidence interval 90%) | | | | |
| All Participants (n=76,1114) | 0.611 (0.197 to 1.243) | 1.17 (0.352 to 2.03) | | |
| Discontinuation due to Any AEI=Yes (n=62,67) | 0.647 (0.201 to 1.239) | 1.28 (0.427 to 2.22) | | |
| Discontinuation due to Any AEI=No (n=14,1047) | 0.436 (0.212 to 1.069) | 1.16 (0.339 to 2.02) | | |
| Discontinuation due to Any AE=Yes (n=64,77) | 0.647 (0.204 to 1.237) | 1.29 (0.464 to 2.1) | | |
| Discontinuation due to Any AE=No (n=12,1037) | 0.408 (0.209 to 1.006) | 1.16 (0.337 to 2.02) | | |
| Discontinuation Due to Any Reason=Yes (n=75,106) | 0.6 (0.197 to 1.243) | 1.23 (0.416 to 2.06) | | |
| Discontinuation Due to Any Reason=No (n=1,1008) | 0.626 (0.626 to 0.626) | 1.16 (0.332 to 2.02) | | |
| At Least 1 AEI=Yes (n=75,536) | 0.6 (0.197 to 1.243) | 1.23 (0.453 to 2.09) | | |
| At Least 1 AEI=No (1,578) | 0.929 (0.929 to 0.929) | 1.12 (0.297 to 1.98) | | |

| | | | | |
|------------------------------|------------------------|----------------------|--|--|
| At Least 1 AE=Yes (n=76,693) | 0.611 (0.197 to 1.243) | 1.22 (0.416 to 2.07) | | |
| At Least 1 AE=No (n=0,421) | 99999 (99999 to 99999) | 1.08 (0.294 to 1.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median Predicted Percentage of Participants with Adverse Events of Interest

| | |
|-----------------|---|
| End point title | Median Predicted Percentage of Participants with Adverse Events of Interest |
|-----------------|---|

End point description:

The PK model predicted the total PDE4 inhibitory activity and the median percentage of participants with Adverse Events of Interest during 12 weeks of treatment based on 1000 participants simulated. Results are reported for the set of reference participants defined according to the covariates [weight, smoking status, sex, age and long acting muscarinic antagonist (LAMA)] included in the final model and tPDE4i. Adverse Events of Interest (AEI) for PK analyses included: headache, diarrhea, nausea, vomiting, abdominal pain, appetite disorders, sleep disorders, angioedema, psychiatric disorders (anxiety, nervousness), psychiatric disorders (depression, suicidal ideation, behaviour) and weight loss. PK Set included all participants who had at least 1 quantifiable PK concentration. Number of participants analyzed is the number of participants simulated. Measured values are predicted values.

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

End point timeframe:

Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours post-dose at Days 15 and 57.

| End point values | Roflumilast 250 µg OD | Roflumilast 500 µg EOD | Roflumilast 500 µg OD | |
|--|-----------------------|------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 1000 | 1000 | 1000 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Weight=48 kg (tPDE4i=0.72,0.72,1.45) | 53.2 | 53.2 | 61.8 | |
| Weight=74 kg (tPDE4i=0.65,0.65,1.30) | 52.3 | 52.3 | 60.1 | |
| Weight=105 kg (tPDE4i=0.60,0.60,1.19) | 51.7 | 51.7 | 58.8 | |
| Former Smoker (tPDE4i=0.65,0.65,1.30) | 52.3 | 52.3 | 60.1 | |
| Current Smoker (tPDE4i=0.56,0.56,1.13) | 42.5 | 42.5 | 49.2 | |
| Male (tPDE4i=0.65,0.65,1.30) | 52.3 | 52.3 | 60.1 | |
| Female (tPDE4i=0.72,0.72,1.45) | 53.2 | 53.2 | 61.8 | |
| Age=51 (tPDE4i=0.58,0.58,1.15) | 51.4 | 51.4 | 58.4 | |
| Age=64 (tPDE4i=0.65,0.65,1.30) | 52.3 | 52.3 | 60.1 | |
| Age=77 (tPDE4i=0.72,0.72,1.44) | 53.2 | 53.2 | 61.7 | |
| With LAMA (tPDE4i=0.65,0.65,1.30) | 52.3 | 52.3 | 60.1 | |
| Without LAMA (tPDE4i=0.65,0.65,1.30) | 43.5 | 43.5 | 51.4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median Predicted Absolute Change from Baseline in FEV1 at Weeks 4 and 12

| | |
|--|--|
| End point title | Median Predicted Absolute Change from Baseline in FEV1 at Weeks 4 and 12 |
| End point description: | |
| <p>The PK model predicted the total PDE4 inhibitory activity and the median Change from Baseline (CFB) in FEV1 at Week 4 and the Change from Baseline in FEV1 at Week 12 during 12 weeks of treatment with roflumilast 500 µg OD based on 1000 participants simulated. Results are reported for the set of reference participants defined according to the covariates [weight, smoking status, sex, age, race, COPD severity, concomitant long acting muscarinic antagonist (LAMA) and Percent FEV1 reversibility] included in the final model and tPDE4i. FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Pulmonary function testing was performed using spirometry prior to taking study medication. A positive change from Baseline indicates improvement. PK Set included all participants who had at least 1 quantifiable PK concentration. The number of participants analyzed is the number of participants simulated. Measured values are predicted values.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Main period: Pre-dose and 1,2,3,4,6 hours post-dose or pre-dose and 2 hours post-dose at Days 15 and 57. | |

| End point values | Roflumilast 500 µg OD_CFB in FEV1 @ Week 4 | Roflumilast 500 µg OD_CFB in FEV1 @ Week 12 | | |
|---|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1000 | 1000 | | |
| Units: milliliters (mL) | | | | |
| number (not applicable) | | | | |
| Weight=33.5 kg (tPDE4i=1.012,1.012) | 50 | 32 | | |
| Weight=70 kg (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| Weight=160 kg (tPDE4i=0.681,0.681) | 108 | 157 | | |
| Current Smoker (tPDE4i=0.729,0.729) | 99.5 | 96.5 | | |
| Former/Never Smoker (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| Male (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| Female (tPDE4i=0.937,0.937) | 53.2 | 49.8 | | |
| Age=40 years (tPDE4i=0.675,0.675) | 57.6 | 52.2 | | |
| Age=60 years (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| Age=92 years (tPDE4i=1.06,1.06) | 56.4 | 53.3 | | |
| Asian (tPDE4i=0.839,0.839) | 56.1 | 52 | | |
| non-Asian (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| COPD_Not Very Severe (tPDE4i=0.839,0.839) | 60.5 | 56 | | |

| | | | | |
|--|------|------|--|--|
| COPD_Very Severe (tPDE4i=0.839,0.839) | 42.2 | 39.1 | | |
| LAMA=Yes (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| LAMA=No (tPDE4i=0.839,0.839) | 63.5 | 58.8 | | |
| %FEV1 Reversibility=-28% (tPDE4i=0.839,0.839) | 68.1 | 63.1 | | |
| %FEV1 Reversibility=10% (tPDE4i=0.839,0.839) | 60.5 | 56 | | |
| %FEV1 Reversibility=147% (tPDE4i=0.839,0.839) | 32.9 | 30.5 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main Treatment Period: First dose of study drug to 30 days past last dose or first dose in the Down-Titration Period (Up to 114 Days). Down-Titration Period: First dose of study drug to 30 days past the last dose of study drug (Up to 86 Days).

Adverse event reporting additional description:

Due to the design of the study, the most common ($\geq 2\%$) non-serious adverse events were determined separately for each period, the blinded Main Treatment Period and the open-label Down-Titration Period. A result of 0 means that the event did not meet the $\geq 2\%$ threshold for that study period but did meet the threshold for the other study period.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Roflumilast 250 µg OD then 500 µg OD_Main Treatment Period |
|-----------------------|--|

Reporting group description:

Roflumilast 250 µg, tablets, orally, once daily (OD) for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|---|
| Reporting group title | Roflumilast 500 µg EOD then 500 µg OD_Main Treatment Period |
|-----------------------|---|

Reporting group description:

Roflumilast 500 µg, tablets, orally, every other day (EOD), and roflumilast placebo-matching tablets, orally, every other day on non-treatment days, for 4 weeks, followed by roflumilast 500 µg, tablets, orally, once daily, for 8 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|---|
| Reporting group title | Roflumilast 500 µg OD_Main Treatment Period |
|-----------------------|---|

Reporting group description:

Roflumilast 500 µg tablets, orally, once daily for 12 weeks in the Main Treatment Period. Any participants not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|--|
| Reporting group title | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period |
|-----------------------|--|

Reporting group description:

Participants in the roflumilast 250 µg once daily (OD) then 500 µg OD who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|--|
| Reporting group title | Roflumilast 500 µg EOD_Down-Titration Period |
|-----------------------|--|

Reporting group description:

Participants in the roflumilast 500 µg, every other day (EOD) treatment arm who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| | |
|-----------------------|---|
| Reporting group title | Roflumilast 500 µg OD_Down Titration Period |
|-----------------------|---|

Reporting group description:

Participants in the roflumilast 500 µg once daily (OD) treatment arm who were not tolerating study treatment were prematurely discontinued and received roflumilast 250 µg, tablets, orally, once daily for 8 weeks in the open-label Down-Titration Period.

| Serious adverse events | Roflumilast 250 µg OD then 500 µg OD_Main Treatment Period | Roflumilast 500 µg EOD then 500 µg OD_Main Treatment Period | Roflumilast 500 µg OD_Main Treatment Period |
|---|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 441 (4.31%) | 22 / 437 (5.03%) | 20 / 443 (4.51%) |
| number of deaths (all causes) | 3 | 1 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung adenocarcinoma | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg OD and is not related (previous AE included concurrent moderate haemoptysis). | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |

| | | | |
|---|---|-----------------|-----------------|
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg OD and is not related (previous AE included severe syncope). | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included moderate COPD). | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included moderate COPD). | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Sciatica | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal mass | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral hernia incarcerated | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---|------------------|-----------------|
| disorders | | | |
| Chronic obstructive pulmonary disease | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included concurrent moderate pneumonia). | | |
| subjects affected / exposed | 8 / 441 (1.81%) | 13 / 437 (2.97%) | 7 / 443 (1.58%) |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 14 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 441 (0.68%) | 0 / 437 (0.00%) | 3 / 443 (0.68%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg EOD then 500 µg OD and is not related. | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 441 (0.45%) | 1 / 437 (0.23%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 441 (0.23%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Upper respiratory tract infection subjects affected / exposed | 0 / 441 (0.00%) | 1 / 437 (0.23%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period |
|--|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung adenocarcinoma | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg OD and is not related (previous AE included concurrent moderate haemoptysis). | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Transitional cell carcinoma | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg OD and is not related (previous AE included severe syncope). | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Atrial fibrillation | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included moderate COPD). | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Cardiopulmonary failure | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included moderate COPD). | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal mass | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Femoral hernia incarcerated | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | Additional description: One treatment-emergent death occurred during treatment with roflumilast 250 µg OD then 500 µg OD and is not related (previous AE included concurrent moderate pneumonia). | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |

| | | | |
|---|---|----------------|----------------|
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Pneumothorax spontaneous | Additional description: One treatment-emergent death occurred during treatment with roflumilast 500 µg EOD then 500 µg OD and is not related. | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Acute sinusitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (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 |
| Gout | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 39 (0.00%) | 0 / 38 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Roflumilast 250 µg OD then 500 µg OD_Main Treatment Period | Roflumilast 500 µg EOD then 500 µg OD_Main Treatment Period | Roflumilast 500 µg OD_Main Treatment Period |
|--|---|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 239 / 441 (54.20%) | 248 / 437 (56.75%) | 272 / 443 (61.40%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 441 (0.91%) | 10 / 437 (2.29%) | 5 / 443 (1.13%) |
| occurrences (all) | 4 | 10 | 9 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 34 / 441 (7.71%) | 39 / 437 (8.92%) | 38 / 443 (8.58%) |
| occurrences (all) | 38 | 41 | 45 |
| Dyspnoea | | | |
| subjects affected / exposed | 15 / 441 (3.40%) | 13 / 437 (2.97%) | 11 / 443 (2.48%) |
| occurrences (all) | 15 | 13 | 11 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 97 / 441 (22.00%) | 100 / 437 (22.88%) | 106 / 443 (23.93%) |
| occurrences (all) | 253 | 252 | 234 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 10 / 441 (2.27%) | 9 / 437 (2.06%) | 17 / 443 (3.84%) |
| occurrences (all) | 10 | 9 | 17 |
| Blood glucose increased | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 441 (0.00%) 0 | 0 / 437 (0.00%) 0 | 0 / 443 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural dizziness | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 107 / 441 (24.26%) | 115 / 437 (26.32%) | 115 / 443 (25.96%) |
| occurrences (all) | 278 | 279 | 271 |
| Dizziness | | | |
| subjects affected / exposed | 16 / 441 (3.63%) | 20 / 437 (4.58%) | 14 / 443 (3.16%) |
| occurrences (all) | 16 | 20 | 18 |
| Tremor | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Amnesia | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Chalazion | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 107 / 441 (24.26%) | 113 / 437 (25.86%) | 134 / 443 (30.25%) |
| occurrences (all) | 216 | 233 | 259 |
| Nausea | | | |

| | | | |
|---|-------------------|-------------------|--------------------|
| subjects affected / exposed | 87 / 441 (19.73%) | 92 / 437 (21.05%) | 110 / 443 (24.83%) |
| occurrences (all) | 183 | 201 | 192 |
| Abdominal pain | | | |
| subjects affected / exposed | 69 / 441 (15.65%) | 58 / 437 (13.27%) | 64 / 443 (14.45%) |
| occurrences (all) | 145 | 126 | 141 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 19 / 441 (4.31%) | 15 / 437 (3.43%) | 27 / 443 (6.09%) |
| occurrences (all) | 29 | 27 | 34 |
| Bowel movement irregularity | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 20 / 441 (4.54%) | 21 / 437 (4.81%) | 20 / 443 (4.51%) |
| occurrences (all) | 24 | 23 | 23 |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 441 (1.81%) | 7 / 437 (1.60%) | 9 / 443 (2.03%) |
| occurrences (all) | 8 | 7 | 10 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 441 (1.59%) | 11 / 437 (2.52%) | 12 / 443 (2.71%) |
| occurrences (all) | 8 | 11 | 12 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 441 (0.00%) | 0 / 437 (0.00%) | 0 / 443 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |

| | | | |
|--|---------------------------|---------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 0 / 441 (0.00%) 0 | 0 / 437 (0.00%) 0 | 0 / 443 (0.00%) 0 |
| Viral pharyngitis subjects affected / exposed occurrences (all) | 0 / 441 (0.00%) 0 | 0 / 437 (0.00%) 0 | 0 / 443 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 6 / 441 (1.36%) 7 | 4 / 437 (0.92%) 4 | 9 / 443 (2.03%) 9 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 100 / 441 (22.68%) 201 | 105 / 437 (24.03%) 204 | 129 / 443 (29.12%) 251 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 441 (0.00%) 0 | 0 / 437 (0.00%) 0 | 0 / 443 (0.00%) 0 |

| Non-serious adverse events | Roflumilast 250 µg OD then 500 µg OD_Down Titration Period | Roflumilast 500 µg EOD_Down-Titration Period | Roflumilast 500 µg OD_Down Titration Period |
|---|---|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 13 / 27 (48.15%) | 21 / 39 (53.85%) | 25 / 38 (65.79%) |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Feeling hot subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Malaise subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Reproductive system and breast disorders Postmenopausal haemorrhage subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|------------------------|------------------------|
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 3 | 3 / 39 (7.69%) 3 | 1 / 38 (2.63%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 4 | 10 / 39 (25.64%) 15 | 6 / 38 (15.79%) 10 |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 2 / 38 (5.26%) 2 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 1 / 39 (2.56%) 1 | 0 / 38 (0.00%) 0 |
| Injury, poisoning and procedural complications Procedural dizziness subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Skin abrasion subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | 7 / 39 (17.95%) 9 | 10 / 38 (26.32%) 21 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | 1 / 39 (2.56%) 1 | 0 / 38 (0.00%) 0 |
| Amnesia | | | |

| | | | |
|--|----------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 1 / 39 (2.56%) 1 | 0 / 38 (0.00%) 0 |
| Eye disorders Chalazion subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 4 | 6 / 39 (15.38%) 8 | 11 / 38 (28.95%) 18 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 5 / 39 (12.82%) 8 | 8 / 38 (21.05%) 11 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 6 / 39 (15.38%) 10 | 5 / 38 (13.16%) 6 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 3 / 39 (7.69%) 4 | 3 / 38 (7.89%) 5 |
| Bowel movement irregularity subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Duodenitis subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |

| | | | |
|--|----------------------|-----------------------|-----------------------|
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 3 / 38 (7.89%) 3 |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 2 / 38 (5.26%) 2 |
| Candida infection subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Viral pharyngitis subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 1 / 38 (2.63%) 1 |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 39 (0.00%) 0 | 0 / 38 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 27 (11.11%) 4 | 8 / 39 (20.51%) 12 | 9 / 38 (23.68%) 15 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 1 / 39 (2.56%) 1 | 0 / 38 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 08 August 2014 | Amendment 1: • All procedures outlined in the V(end) visit were to be performed at V(ODT) for participants continuing into the open label Down-Titration Period of the study. • Clarified that the 'Liver Function Test (LFT) Abnormalities' were not be a separate participant discontinuation/withdrawal category. • Clarified that an additional dose of study drug was not to be provided at Vend for participants discontinuing prematurely from the Main Period without continuing into the Down-Titration Period, and that only 1 PK sample was to be taken at this visit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported