



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
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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
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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
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Arm title	Roflumilast 250 µg OD then 500 µg OD
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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]
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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
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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]
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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
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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
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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
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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]
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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]
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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
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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)
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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	0 / 441 (0.00%)	0 / 437 (0.00%)	0 / 443 (0.00%)
occurrences (all)	0	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 441 (0.00%)	0 / 437 (0.00%)	0 / 443 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	6 / 441 (1.36%)	4 / 437 (0.92%)	9 / 443 (2.03%)
occurrences (all)	7	4	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	100 / 441 (22.68%)	105 / 437 (24.03%)	129 / 443 (29.12%)
occurrences (all)	201	204	251
Hypokalaemia			
subjects affected / exposed	0 / 441 (0.00%)	0 / 437 (0.00%)	0 / 443 (0.00%)
occurrences (all)	0	0	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	0 / 27 (0.00%)	0 / 39 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	1 / 27 (3.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 27 (3.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 39 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

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