Clinical trial results:
Effect of Roflumilast 500 g Tablets Once Daily at Acute COPD Exacerbations Treated With Standard Therapy of Oral Steroids and Antibiotics. A Randomised, Double-blind, Placebo-controlled, Parallel-group Trial

Summary

EudraCT number	2011-002905-31
Trial protocol	GB
Global end of trial date	16 April 2014

Results information

Result version number	v1
This version publication date	04 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	RO-2455-405-RD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01473758
WHO universal trial number (UTN)	U1111-1137-4023

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, 1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, Takeda, 1 877-825-3327, trialdisclosures@takeda.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	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2014
Global end of trial reached?	Yes
Global end of trial date	16 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to investigate if roflumilast can reduce the neutrophilic inflammation at acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD). In addition, the potential benefit of roflumilast on severity and recovery periods of acute COPD exacerbations will be assessed using patient diaries and questionnaires.

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	16 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	18
From 65 to 84 years	57
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 1 investigative site in the United Kingdom from 16 February 2012 to 25 March 2014.

Pre-assignment

Screening details:

Patients with Chronic Obstructive (COPD) were enrolled equally in 1 of 2 treatment groups, once a day placebo or roflumilast 500 µg in Cycle 1. With Amendment 5, patients previously enrolled in the trial were allowed to be re-enrolled with a new exacerbation, if they reached a stable disease status since completing the first treatment cycle.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast 500 µg

Arm description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.

Arm type	Active comparator
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks.

Arm title	Placebo

Arm description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.

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

Dosage and administration details:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast.

Number of subjects in period 1	Roflumilast 500 µg	Placebo
Started	38	43
Completed	27	40
Not completed	11	3
Adverse event, non-fatal	10	2
Withdrawal by Subject	1	1

Period 2	
Period 2 title	Cycle 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast 500 µg

Arm description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations.

Arm type	Active comparator
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks.

Arm title	Placebo

Arm description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. therapy for acute COPD exacerbations.

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

Dosage and administration details:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast.

Number of subjects in period 2[1]	Roflumilast 500 µg	Placebo
Started	10	4
Completed	5	4
Not completed	5	0
Adverse event, non-fatal	5	-

Notes:

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

Justification: With Amendment 5, patients previously enrolled in the trial were allowed to be re-enrolled with a new exacerbation, if they reached a stable disease status since completing the first treatment cycle.

Baseline characteristics

Reporting groups	
Reporting group title	Roflumilast 500 µg
Reporting group description:	
Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.	
Reporting group title	Placebo
Reporting group description:	
Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.	

Reporting group values	Roflumilast 500 µg	Placebo	Total
Number of subjects	38	43	81
Age categorical Units: Subjects			
≤ 65 years	7	11	18
> 65 years	31	32	63
Gender categorical Units: Subjects			
Female	16	15	31
Male	22	28	50
Race/Ethnicity, Customized Units: Subjects			
Asian	2	1	3
White	36	42	78
Smoking Status Units: Subjects			
Non-smoker	0	0	0
Current smoker	8	11	19
Former smoker	30	32	62
Baseline COPD Assessment Test (CAT) Total Score Units: Subjects			
< 10	2	3	5
≥ 10	16	25	41
Missing	20	15	35
Weight Category by Body Mass Index (BMI) Units: Subjects			
Underweight	3	0	3
Normal Weight	15	18	33
Overweight	11	15	26
Obese	9	9	18
Missing	0	1	1
Chronic Bronchitis Units: Subjects			
No	14	17	31

Yes	24	26	50
Historical Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Units: Subjects			
< 2	28	28	56
≥ 2	10	15	25

End points

End points reporting groups

Reporting group title	Roflumilast 500 µg

Reporting group description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.

Reporting group title	Placebo

Reporting group description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Eligible participants were rerandomized to receive either roflumilast 500 µg or placebo for 4 weeks in Cycle 2.

Reporting group title	Roflumilast 500 µg

Reporting group description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations.

Reporting group title	Placebo

Reporting group description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. therapy for acute COPD exacerbations.

Subject analysis set title	Roflumilast 500 µg
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast for 4 weeks added on to standard therapy for acute COPD exacerbations. therapy for acute COPD exacerbations. .

Primary: Change From Baseline in Sputum Neutrophil Counts at Day 14 Post Exacerbation (Initial Approach)

End point title	Change From Baseline in Sputum Neutrophil Counts at Day 14 Post Exacerbation (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) were determined using a Neubauer hemocytometer. A negative change from Baseline indicates improvement. An Analysis of Covariance (ANCOVA) model was used with neutrophil count at Baseline and treatment as independent variables, fixed effects.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Primary

End point timeframe:

Baseline and Day 14

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	37		
Units: 10^6 cells/gram sputum				
least squares mean (standard error)	-18.705 (± 2.263)	-20.109 (± 1.995)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
Comparison groups	Placebo v Roflumilast 500 µg
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6491 [1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.731
upper limit	7.538
Variability estimate	Standard error of the mean
Dispersion value	3.07

Notes:

[1] - The model contains neutrophil count at Baseline and treatment as independent variables, fixed effects.

Primary: Change From Baseline in Sputum Neutrophil Counts at Day 14 Post Exacerbation (Extended Approach)

End point title	Change From Baseline in Sputum Neutrophil Counts at Day 14 Post Exacerbation (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) were determined using a Neubauer hemocytometer. A negative change from Baseline indicates improvement. An Analysis of Covariance (ANCOVA) model was used with neutrophil count at Baseline and treatment as independent variables, fixed effects.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Primary

End point timeframe:

Baseline and Day 14

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	39		
Units: 10^6 cells/gram sputum				
least squares mean (standard error)	-19.569 (± 1.906)	-19.157 (± 1.855)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis
Comparison groups	Placebo v Roflumilast 500 µg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8786 [2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.766
upper limit	4.943
Variability estimate	Standard error of the mean
Dispersion value	2.687

Notes:

[2] - The model contains neutrophil count at Baseline and treatment as independent variables, fixed effects.

Secondary: Percentage of Participants Whose Sputum Neutrophil Counts Returned to Stable State at Day 14 (Initial Approach)

End point title	Percentage of Participants Whose Sputum Neutrophil Counts Returned to Stable State at Day 14 (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) and were determined with a Neubauer hemocytometer.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Day 14

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	29		
Units: percentage of participants				
number (confidence interval 95%)	37.5 (15.2 to 64.6)	55.2 (35.7 to 73.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Whose Sputum Neutrophil Counts Returned to Stable State at Day 14 (Extended Approach)

End point title	Percentage of Participants Whose Sputum Neutrophil Counts Returned to Stable State at Day 14 (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) and were determined with a Neubauer hemocytometer.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Day 14

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	31		
Units: percentage of participants				
number (confidence interval 95%)	45 (23.1 to 68.5)	51.6 (33.1 to 69.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Total Cells (Initial Approach)

End point title	Change from Baseline in Sputum Marker Total Cells (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) were determined using a Neubauer hemocytometer. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: 10^6 cells/gram sputum				
least squares mean (standard error)				
Change at Day 7 (n=35, 39)	-25.559 (± 3.529)	-27.563 (± 3.334)		
Change at Day 14 (n=32, 38)	-21.813 (± 2.706)	-25.111 (± 2.505)		
Change at Day 28 (n=25, 37)	-29.2 (± 4.022)	-22.218 (± 3.362)		
Change at Day 56 (n=24, 33)	-24.477 (± 2.708)	-26.474 (± 2.341)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Total Cells (Extended Approach)

End point title	Change from Baseline in Sputum Marker Total Cells (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Total cell count (absolute number of nonsquamous cells per gram of the original sputum sample) were determined using a Neubauer hemocytometer. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	46		
Units: 10^6 cells/gram sputum				
least squares mean (standard error)				
Change at Day 7 (n=45, 43)	-26.634 (± 3.03)	-26.335 (± 3.124)		
Change at Day 14 (n=41, 42)	-23.512 (± 2.448)	-25.332 (± 2.471)		
Change at Day 28 (n=30, 40)	-29.023 (± 3.347)	-22.92 (± 2.947)		
Change at Day 56 (n=28, 36)	-19.551 (± 3.92)	-26.855 (± 3.536)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Neutrophils (Initial Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Neutrophils (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of neutrophils was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	43		
Units: percentage of neutrophils				
least squares mean (standard error)				
Change at Day 7 (n=30, 35)	-11.325 (± 3.837)	-14.484 (± 3.559)		
Change at Day 14 (n=31, 37)	-16.77 (± 3.983)	-20.346 (± 3.55)		
Change at Day 28 (n=24, 34)	-27.76 (± 5.275)	-13.837 (± 4.498)		
Change at Day 56 (n=16, 30)	-19.663 (± 5.561)	-17.047 (± 4.229)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Neutrophils (Extended Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Neutrophils (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of neutrophils was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction. A negative change from Baseline indicates improvement.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of neutrophils				
least squares mean (standard error)				
Change at Day 7 (n=37, 39)	-14.637 (± 3.748)	-16.06 (± 3.713)		
Change at Day 14 (n=39, 40)	-20.69 (± 3.758)	-21.052 (± 3.678)		
Change at Day 28 (n=29, 36)	-29.848 (± 4.721)	-14.664 (± 4.371)		
Change at Day 56 (n=20, 32)	-21.327 (± 5.009)	-17.328 (± 4.188)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Macrophages (Initial Approach)

End point title	Change from Baseline in Sputum Marker Percentage of

	Macrophages (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of macrophages was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	43		
Units: percentage of macrophages				
least squares mean (standard error)				
Change at Day 7 (n=30, 35)	11.393 (± 3.837)	15.43 (± 3.559)		
Change at Day 14 (n=31, 37)	16.062 (± 3.929)	20.774 (± 3.506)		
Change at Day 28 (n=24, 34)	27.535 (± 5.284)	13.382 (± 4.503)		
Change at Day 56 (n=16, 30)	16.593 (± 5.539)	15.877 (± 4.171)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Macrophages (Extended Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Macrophages (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of macrophages was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of macrophages				
least squares mean (standard error)				
Change at Day 7 (n=37, 39)	14.679 (± 3.74)	17.228 (± 3.704)		
Change at Day 14 (n=39, 40)	20.331 (± 3.745)	21.599 (± 3.667)		
Change at Day 28 (n=29, 36)	29.51 (± 4.717)	14.463 (± 4.367)		
Change at Day 56 (n=20, 32)	19.075 (± 5.003)	16.322 (± 4.156)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Eosinophils (Initial Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Eosinophils (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of eosinophils was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	43		
Units: percentage of eosinophils				
least squares mean (standard error)				
Change at Day 7 (n=30, 35)	-0.259 (± 0.245)	-0.1 (± 0.225)		
Change at Day 14 (n=31, 37)	-0.11 (± 0.326)	-0.188 (± 0.288)		

Change at Day 28 (n=24, 34)	0.043 (± 1.209)	1.597 (± 1.02)		
Change at Day 56 (n=16, 30)	2.187 (± 2.278)	1.086 (± 1.766)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Eosinophils (Extended Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Eosinophils (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of eosinophils was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of macrophages				
least squares mean (standard error)				
Change at Day 7 (n=37, 39)	-0.341 (± 0.206)	-0.141 (± 0.202)		
Change at Day 14 (n=39, 40)	-0.174 (± 0.271)	-0.214 (± 0.263)		
Change at Day 28 (n=29, 36)	0.031 (± 1.044)	1.518 (± 0.952)		
Change at Day 56 (n=20, 32)	1.714 (± 1.969)	0.913 (± 1.655)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Lymphocyte (Initial Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Lymphocyte (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of lymphocytes was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	43		
Units: percentage of lymphocytes				
least squares mean (standard error)				
Change at Day 7 (n=30, 35)	0.229 (± 0.353)	0.182 (± 0.326)		
Change at Day 14 (n=31, 37)	0.43 (± 0.254)	0.295 (± 0.225)		
Change at Day 28 (n=24, 34)	0.039 (± 0.183)	-0.325 (± 0.155)		
Change at Day 56 (n=16, 30)	-0.095 (± 0.187)	-0.051 (± 0.137)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Percentage of Lymphocytes (Extended Approach)

End point title	Change from Baseline in Sputum Marker Percentage of Lymphocytes (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Aliquots of a cell suspension prepared from the sputum sample were used to prepare cytospin slides that were stained with Diff-Quik for differential cell counts. 100 cells were counted and the percentage of lymphocytes was determined. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: percentage of lymphocytes				
least squares mean (standard error)				
Change at Day 7 (n=37, 39)	0.109 (± 0.308)	-0.015 (± 0.303)		
Change at Day 14 (n=39, 40)	0.309 (± 0.25)	0.195 (± 0.243)		
Change at Day 28 (n=29, 36)	-0.118 (± 0.173)	-0.431 (± 0.158)		
Change at Day 56 (n=20, 32)	-0.203 (± 0.164)	-0.208 (± 0.132)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-6 (Initial Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-6 (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker IL-6 was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	42		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=31, 38)	-1317.4 (± 143.748)	-934.624 (± 133.217)		
Change at Day 14 (n=30, 35)	-822.715 (± 221.328)	-695.955 (± 206.201)		

Change at Day 28 (n=22, 35)	-1232.93 (± 212.663)	-955.365 (± 174.734)		
Change at Day 56 (n=22, 29)	-1042.1 (± 225.619)	-996.485 (± 196.729)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-6 (Extended Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-6 (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker IL-6 was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 42)	-1207.68 (± 133.298)	-923.325 (± 130.533)		
Change at Day 14 (n=36, 39)	-725.454 (± 195.921)	-705.849 (± 192.89)		
Change at Day 28 (n=26, 38)	-1115.74 (± 200.367)	-877.871 (± 172.95)		
Change at Day 56 (n=26, 32)	-860.191 (± 206.289)	-962.342 (± 189.817)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-8 (Initial Approach)

End point title	Change from Baseline in Sputum Marker Concentration of

	Interleukin (IL)-8 (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker IL-8 was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction. A negative change from Baseline indicates improvement.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	42		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=31, 38)	-174718 (± 45481.71)	-227275 (± 41821.02)		
Change at Day 14 (n=30, 35)	-149198 (± 47388.83)	-199516 (± 43965.79)		
Change at Day 28 (n=22, 35)	-255317 (± 70915.15)	-160587 (± 57944.79)		
Change at Day 56 (n=21, 29)	-204731 (± 50404.33)	-223918 (± 43039.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-8 (Extended Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Interleukin (IL)-8 (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker IL-8 was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 42)	-193223 (± 39595.2)	-215296 (± 38432.42)		
Change at Day 14 (n=36, 39)	-172070 (± 41341.33)	-195751 (± 40449.87)		
Change at Day 28 (n=26, 38)	-264788 (± 62440.42)	-160441 (± 53963.53)		
Change at Day 56 (n=25, 32)	-168205 (± 51760.36)	-205823 (± 46476.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Myeloperoxidase (MPO) (Initial Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Myeloperoxidase (MPO) (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker MPO was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	42		
Units: ng/mL				
least squares mean (standard error)				
Change at Day 7 (n=31, 38)	-9253.79 (± 1997.077)	-4521.4 (± 1863.867)		
Change at Day 14 (n=30, 35)	-8072.78 (± 2144.895)	-6318.88 (± 2002.939)		

Change at Day 28 (n=22, 35)	-13744.8 (± 2476.123)	-5944.18 (± 2041.587)		
Change at Day 56 (n=22, 29)	-10248.6 (± 2578.146)	-9478.46 (± 2234.238)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Myeloperoxidase (MPO) (Extended Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Myeloperoxidase (MPO) (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker MPO was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: ng/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 42)	-8606.36 (± 1747.094)	-4380.8 (± 1713.047)		
Change at Day 14 (n=36, 39)	-8380.85 (± 1871.93)	-5929.78 (± 1843.806)		
Change at Day 28 (n=26, 38)	-12692.3 (± 2220.374)	-5351 (± 1933.964)		
Change at Day 56 (n=26, 32)	-9424.23 (± 2275.981)	-8527.77 (± 2078.411)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Neutrophil Elastase (Initial Approach)

End point title	Change from Baseline in Sputum Marker Concentration of

	Neutrophil Elastase (Initial Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker Neutrophil Elastase was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	42		
Units: µg/mL				
least squares mean (standard error)				
Change at Day 7 (n=31, 38)	-222995 (± 14887.25)	-224606 (± 13669.99)		
Change at Day 14 (n=30, 35)	-149211 (± 39523.47)	-125385 (± 36629.96)		
Change at Day 28 (n=22, 35)	-200905 (± 25432.98)	-149866 (± 20549.57)		
Change at Day 56 (n=21, 30)	-141986 (± 28278.57)	-169390 (± 23767.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sputum Marker Concentration of Neutrophil Elastase (Extended Approach)

End point title	Change from Baseline in Sputum Marker Concentration of Neutrophil Elastase (Extended Approach)

End point description:

Sputum samples were collected and processed at the investigational site according to their standard procedures. Sputum inflammatory marker Neutrophil Elastase was quantified by commercial sandwich enzyme-linked immunosorbent assays (ELISA). A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	45		
Units: µg/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 42)	-202235 (± 12993.51)	-206912 (± 12543.14)		
Change at Day 14 (n=36, 39)	-143832 (± 34043.87)	-110144 (± 33211.58)		
Change at Day 28 (n=26, 38)	-183452 (± 22560.24)	-130613 (± 19255.85)		
Change at Day 56 (n=25, 33)	-118129 (± 25397.04)	-156544 (± 22550.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Interleukin (IL)-6 (Initial Approach)

End point title	Change from Baseline in Blood Biomarker Interleukin (IL)-6 (Initial Approach)

End point description:

Blood was collected and serum biomarker IL-6 was quantified using commercial sandwich ELISA. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	-12.469 (± 0.782)	-11.904 (± 0.742)		
Change at Day 14 (n=33, 41)	-1.973 (± 1.918)	-5.728 (± 1.73)		
Change at Day 28 (n=28, 40)	-8.108 (± 2.36)	-7.243 (± 1.997)		

Change at Day 56 (n=27, 40)	-11.665 (± 1.129)	-9.431 (± 0.937)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Interleukin (IL)-6 (Extended Approach)

End point title	Change from Baseline in Blood Biomarker Interleukin (IL)-6 (Extended Approach)

End point description:

Blood was collected and serum biomarker IL-6 was quantified using commercial sandwich ELISA. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	-12.314 (± 0.652)	-11.802 (± 0.665)		
Change at Day 14 (n=43, 45)	1.607 (± 2.543)	-6.069 (± 2.49)		
Change at Day 28 (n=33, 44)	-7.587 (± 2.088)	-7.619 (± 1.838)		
Change at Day 56 (n=32, 44)	-10.811 (± 1.064)	-9.604 (± 0.918)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Interleukin-1 Beta (IL-1β) (Initial Approach)

End point title	Change from Baseline in Blood Biomarker Interleukin-1 Beta (IL-1β) (Initial Approach)

End point description:

Blood was collected and serum biomarker IL-1β was quantified using commercial sandwich ELISA. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	1.274 (± 0.682)	0.378 (± 0.647)		
Change at Day 14 (n=33, 41)	0.217 (± 0.359)	0.495 (± 0.324)		
Change at Day 28 (n=28, 40)	0.657 (± 0.431)	0.541 (± 0.366)		
Change at Day 56 (n=27, 40)	-0.003 (± 0.329)	0.464 (± 0.288)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker IL-1β (Extended Approach)

End point title	Change from Baseline in Blood Biomarker IL-1β (Extended Approach)

End point description:

Blood was collected and serum biomarker IL-1β was quantified using commercial sandwich ELISA. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: pg/mL				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	0.35 (± 0.59)	-1.002 (± 0.602)		
Change at Day 14 (n=43, 45)	-0.394 (± 0.355)	-0.841 (± 0.349)		
Change at Day 28 (n=33, 44)	-0.139 (± 0.414)	-0.757 (± 0.368)		
Change at Day 56 (n=32, 44)	-0.799 (± 0.333)	-0.806 (± 0.312)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker C-reactive protein (CRP) (Initial Approach)

End point title	Change from Baseline in Blood Biomarker C-reactive protein (CRP) (Initial Approach)

End point description:

Blood was collected and serum biomarker CRP was measured using Roche Modular Analytics E 170 Module. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: mg/liter(L)				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	-15.579 (± 0.485)	-16.518 (± 0.461)		
Change at Day 14 (n=33, 41)	4.836 (± 4.249)	-4.369 (± 3.812)		
Change at Day 28 (n=28, 38)	-9.179 (± 4.11)	-8.018 (± 3.533)		
Change at Day 56 (n=26, 40)	-14.889 (± 1.395)	-13.057 (± 1.133)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker C-reactive protein (CRP) (Extended Approach)

End point title	Change from Baseline in Blood Biomarker C-reactive protein (CRP) (Extended Approach)

End point description:

Blood was collected and serum biomarker CRP was measured using Roche Modular Analytics E 170 Module. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: mg/L				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	-16.166 (± 0.41)	-16.901 (± 0.417)		
Change at Day 14 (n=43, 45)	5.72 (± 3.6)	-5.257 (± 3.518)		
Change at Day 28 (n=33, 42)	-8.25 (± 3.802)	-9.254 (± 3.375)		
Change at Day 56 (n=31, 44)	-15.152 (± 1.219)	-13.793 (± 1.034)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Fibrinogen (Initial Approach)

End point title	Change from Baseline in Blood Biomarker Fibrinogen (Initial Approach)

End point description:

Biomarker Plasma fibrinogen was determined using the method described by Clauss. A negative change

from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	42		
Units: umol/L				
least squares mean (standard error)				
Change at Day 7 (n=34, 39)	-3.916 (± 0.286)	-3.976 (± 0.261)		
Change at Day 14 (n=33, 38)	0.404 (± 0.625)	-0.184 (± 0.571)		
Change at Day 28 (n=27, 36)	0.21 (± 0.676)	0.014 (± 0.567)		
Change at Day 56 (n=26, 38)	-2.127 (± 0.625)	-1.144 (± 0.515)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Fibrinogen (Extended Approach)

End point title	Change from Baseline in Blood Biomarker Fibrinogen (Extended Approach)

End point description:

Biomarker Plasma fibrinogen was determined using the method described by Clauss. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	46		
Units: umol/L				
least squares mean (standard error)				
Change at Day 7 (n=44, 43)	-3.971 (± 0.246)	-3.839 (± 0.244)		
Change at Day 14 (n=43, 42)	0.051 (± 0.521)	-0.148 (± 0.519)		
Change at Day 28 (n=32, 40)	0.147 (± 0.599)	-0.091 (± 0.524)		
Change at Day 56 (n=31, 42)	-2.155 (± 0.533)	-1.162 (± 0.462)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Glucose (Initial Approach)

End point title	Change from Baseline in Blood Biomarker Glucose (Initial Approach)

End point description:

Blood was collected and analyzed for serum glucose levels. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	43		
Units: mmol/L				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	1.617 (± 0.426)	1.027 (± 0.397)		
Change at Day 14 (n=33, 41)	1 (± 0.3)	0.432 (± 0.27)		
Change at Day 28 (n=28, 40)	0.067 (± 0.156)	-0.02 (± 0.129)		
Change at Day 56 (n=27, 40)	0.255 (± 0.272)	0.226 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Blood Biomarker Glucose (Extended Approach)

End point title	Change from Baseline in Blood Biomarker Glucose (Extended Approach)

End point description:

Blood was collected and analyzed for serum glucose levels. A negative change from Baseline indicated improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: mmol/L				
least squares mean (standard error)				
Change at Day 7 (n=46, 45)	1.767 (± 0.408)	0.973 (± 0.408)		
Change at Day 14 (n=42, 45)	0.942 (± 0.254)	0.364 (± 0.246)		
Change at Day 28 (n=33, 44)	0.061 (± 0.139)	-0.008 (± 0.119)		
Change at Day 56 (n=32, 43)	0.189 (± 0.235)	0.215 (± 0.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Forced Expiratory Volume (FEV1) (Initial Approach)

End point title	Change from Baseline in Forced Expiratory Volume (FEV1) (Initial Approach)

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. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	43		
Units: liters				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	0.051 (± 0.031)	0.01 (± 0.029)		
Change at Day 14 (n=33, 41)	0.083 (± 0.035)	0.028 (± 0.031)		
Change at Day 28 (n=28, 40)	0.095 (± 0.037)	0.001 (± 0.031)		
Change at Day 56 (n=27, 40)	0.064 (± 0.039)	0.01 (± 0.033)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Forced Expiratory Volume (FEV1) (Extended Approach)

End point title	Change from Baseline in Forced Expiratory Volume (FEV1) (Extended Approach)

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. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: liters				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	0.063 (± 0.027)	0.012 (± 0.028)		
Change at Day 14 (n= 43, 45)	0.062 (± 0.029)	0.018 (± 0.029)		

Change at Day 28 (n=33, 44)	0.084 (± 0.031)	-0.003 (± 0.028)		
Change at Day 56 (n=32, 44)	0.05 (± 0.034)	0.005 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Forced Vital Capacity (FVC) (Initial Approach)

End point title	Change from Baseline in Forced Vital Capacity (FVC) (Initial Approach)

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. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	43		
Units: liters				
least squares mean (standard error)				
Change at Day 7 (n=37, 41)	0.002 (± 0.06)	0.057 (± 0.056)		
Change at Day 14 (n=33, 41)	0.039 (± 0.062)	0.166 (± 0.056)		
Change at Day 28 (n=28, 40)	0.039 (± 0.072)	0.075 (± 0.062)		
Change at Day 56 (n=27, 40)	0.044 (± 0.072)	0.086 (± 0.062)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Forced Vital Capacity (FVC) (Extended Approach)

End point title	Change from Baseline in Forced Vital Capacity (FVC) (Extended Approach)

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. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: liters				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	0.048 (± 0.052)	0.062 (± 0.053)		
Change at Day 14 (n=43, 45)	0.046 (± 0.054)	0.146 (± 0.053)		
Change at Day 28 (n=33, 44)	0.053 (± 0.062)	0.067 (± 0.057)		
Change at Day 56 (n=32, 44)	0.034 (± 0.065)	0.084 (± 0.058)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FEV1/FVC (Initial Approach)

End point title	Change from Baseline in FEV1/FVC (Initial Approach)

End point description:

FEV1/FVC is the percentage of the vital capacity which is expired in the first second of maximal expiration. In healthy patients the FEV1/FVC is usually around 70%. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	43		
Units: percent				
least squares mean (standard error)				
Change from Baseline at Day 7 (n=37, 41)	1.575 (± 0.933)	-1.064 (± 0.87)		
Change from Baseline at Day 14 (n=33, 41)	1.874 (± 1.012)	-1.796 (± 0.914)		
Change from Baseline at Day 28 (n=28, 40)	2.35 (± 1.138)	-1.029 (± 0.982)		
Change from Baseline at Day 56 (n=27, 40)	1.636 (± 0.951)	-1.669 (± 0.828)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FEV1/FVC (Extended Approach)

End point title	Change from Baseline in FEV1/FVC (Extended Approach)

End point description:

FEV1/FVC is the percentage of the vital capacity which is expired in the first second of maximal expiration. In healthy patients the FEV1/FVC is usually around 70%. A positive change from Baseline indicates an improvement. A Mixed Model Repeated Measurement (MMRM) was used for analysis with Baseline value, treatment, visit, and treatment by visit interaction as covariates.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Day 7, Day 14, Day 28 and Day 56

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: percent				
least squares mean (standard error)				
Change at Day 7 (n=47, 45)	1.282 (± 0.795)	-1.128 (± 0.799)		
Change at Day 14 (n=43, 45)	1.394 (± 0.85)	-1.83 (± 0.834)		
Change at Day 28 (n=33, 44)	2.045 (± 0.974)	-1.198 (± 0.888)		
Change at Day 56 (n=32, 44)	1.393 (± 0.827)	-1.881 (± 0.765)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Initial Approach)

End point title	Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Initial Approach)

End point description:

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status. It comprises 8 questions that cover a broad range of effects of COPD on patients' health. Each question is scored in a range between 0 and 5, with the higher end indicating a higher impact of COPD on the patient's wellbeing. The CAT Total score ranges from 0 best) to 40 (Worst).

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=27, 34)	19.4 (± 6.65)	19.2 (± 7.2)		
Week 2 (n=28, 36)	17.1 (± 7.86)	17.1 (± 7.48)		
Week 3 (n=24, 37)	15.9 (± 7.84)	16 (± 7.9)		
Week 4 (n=23, 38)	15.1 (± 7.85)	15.8 (± 8.42)		
Week 5 (n=21, 37)	14.2 (± 7.41)	14.9 (± 8.04)		
Week 6 (n=19, 37)	12.9 (± 6.85)	15.4 (± 8.23)		
Week 7 (n=20, 33)	13.9 (± 8.93)	14.7 (± 8.48)		
Week 8 (n=18, 30)	12.8 (± 7.85)	15.6 (± 8.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Extended Approach)

End point title	Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Extended Approach)

End point description:

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status. It comprises 8 questions that cover a broad range of effects of COPD on patients' health. Each question is scored in a range between 0 and 5, with the higher end indicating a higher impact of COPD on the patient's wellbeing. The CAT Total score ranges from 0 best) to 40 (Worst).

Participants from the Intent-to-treat population, all randomized participants, with data available at the

given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=37, 38)	20.4 (± 7.26)	19.3 (± 7.03)		
Week 2 (n=37, 40)	18.2 (± 8.54)	17.2 (± 7.32)		
Week 3 (n=29, 41)	16.2 (± 8.08)	16.1 (± 7.73)		
Week 4 (n=27, 42)	16 (± 8.21)	15.9 (± 8.26)		
Week 5 (n=25, 41)	14 (± 7.28)	15.1 (± 7.93)		
Week 6 (n=23, 41)	12.9 (± 6.58)	15.4 (± 8.12)		
Week 7 (n=24, 37)	13.5 (± 8.38)	14.8 (± 8.44)		
Week 8 (n=19, 30)	13 (± 7.68)	15.6 (± 8.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Initial Approach)

End point title	Change from Stable State in Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Initial Approach)

End point description:

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status. It comprises 8 questions that cover a broad range of effects of COPD on patients' health. Each question is scored in a range between 0 and 5, with the higher end indicating a higher impact of COPD on the patient's wellbeing. The CAT Total score ranges from 0 best) to 40 (Worst). A negative change from Baseline indicates improvement. Covariates for MMRM are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=27, 34)	6.448 (± 1.503)	2.695 (± 1.096)		
Change at Week 2 (n=28, 36)	3.778 (± 1.239)	0.804 (± 0.911)		
Change at Week 3 (n=24, 37)	2.002 (± 0.915)	0.278 (± 0.669)		
Change at Week 4 (n=23, 38)	0.559 (± 0.739)	0.277 (± 0.536)		
Change at Week 5 (n=21, 37)	-0.412 (± 0.613)	-0.392 (± 0.448)		
Change at Week 6 (n=19, 37)	-0.924 (± 0.411)	-0.062 (± 0.297)		
Change at Week 7 (n=20, 33)	-0.228 (± 0.342)	0.048 (± 0.253)		
Change at Week 8 (n=18, 30)	0.002 (± 0.059)	-0.048 (± 0.044)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Stable State in Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Extended Approach)

End point title	Change From Stable State in Chronic Obstructive Pulmonary Assessment Test (CAT) Weekly Averages (Extended Approach)

End point description:

The CAT is a short, validated, patient-completed questionnaire to assess the impact of COPD on health status. It comprises 8 questions that cover a broad range of effects of COPD on patients' health. Each question is scored in a range between 0 and 5, with the higher end indicating a higher impact of COPD on the patient's wellbeing. The CAT Total score ranges from 0 best) to 40 (Worst). A negative change from Baseline indicates improvement. Covariates for MMRM are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: scores on a scale				
least squares mean (standard error)				

Week 1 (n=37, 38)	6.232 (± 1.424)	3.009 (± 1.052)		
Week 2 (n=37, 40)	3.558 (± 1.178)	1.074 (± 0.876)		
Week 3 (n=29, 41)	2.044 (± 0.847)	0.458 (± 0.627)		
Week 4 (n=27, 42)	0.545 (± 0.732)	0.429 (± 0.534)		
Week 5 (n=25, 41)	-0.347 (± 0.621)	-0.17 (± 0.459)		
Week 6 (n=23, 41)	-0.668 (± 0.402)	-0.043 (± 0.295)		
Week 7 (n=24, 37)	-0.121 (± 0.31)	0.014 (± 0.232)		
Week 8 (n=19, 30)	-0.01 (± 0.061)	-0.031 (± 0.045)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Initial Approach)

End point title	Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Initial Approach)

End point description:

The EXACT-PRO questionnaire is a new, validated, and standardized measure to evaluate the frequency, severity, and duration of COPD exacerbations. It is a 14-item daily diary, and scores range from 0 to 100, with higher scores indicating worse health status.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=25, 35)	45.2 (± 8.54)	45.1 (± 8.5)		
Week 2 (n=28, 36)	41.2 (± 11.39)	42.4 (± 9.07)		
Week 3 (n=24, 38)	38.8 (± 11.22)	40 (± 10.22)		
Week 4 (n=23, 38)	38.3 (± 11)	40.2 (± 11.26)		
Week 5 (n=21, 37)	35.9 (± 11.11)	39.1 (± 10.55)		
Week 6 (n=19, 37)	35.1 (± 9.75)	39.4 (± 11.05)		
Week 7 (n=20, 34)	35.6 (± 13.69)	38.7 (± 12.05)		
Week 8 (n=18, 32)	34.4 (± 11.5)	39.4 (± 11.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Extended Approach)

End point title	Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Extended Approach)

End point description:

The EXACT-PRO questionnaire is a new, validated, and standardized measure to evaluate the frequency, severity, and duration of COPD exacerbations. It is a 14-item daily diary, and scores range from 0 to 100, with higher scores indicating worse health status.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n=35, 39)	45.6 (± 9.19)	45 (± 8.39)		
Week 2 (n=37, 40)	42 (± 11.07)	42.3 (± 8.81)		
Week 3 (n=29, 42)	39 (± 11.27)	39.9 (± 9.82)		
Week 4 (n=27, 42)	38.8 (± 11.37)	40.3 (± 10.9)		
Week 5 (n=25, 41)	35.3 (± 11.03)	39.1 (± 10.13)		
Week 6 (n=23, 41)	33.9 (± 10.45)	39.4 (± 10.62)		
Week 7 (n=24, 38)	34.3 (± 13.09)	38.7 (± 11.52)		
Week 8 (n=19, 33)	34 (± 11.3)	39.6 (± 11.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Initial Approach)

End point title	Change from Stable State in Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Initial

	Approach)

End point description:

The EXACT-PRO questionnaire is a new, validated, and standardized measure to evaluate the frequency, severity, and duration of COPD exacerbations. It is a 14-item daily diary, and scores range from 0 to 100, with higher scores indicating worse health status. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, time point, treatment by time point and baseline by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=25, 35)	6.182 (± 3.271)	4.753 (± 2.385)		
Change at Week 2 (n=28, 36)	4.423 (± 2.538)	1.558 (± 1.864)		
Change at Week 3 (n=24, 38)	2.08 (± 2.041)	0.317 (± 1.494)		
Change from at Week 4 (n=23, 38)	0.002 (± 2.003)	0.657 (± 1.459)		
Change at Week 5 (n=21, 37)	-1.058 (± 1.748)	-0.307 (± 1.276)		
Change at Week 6 (n=19, 37)	-1.688 (± 1.015)	-0.002 (± 0.738)		
Change at Week 7 (n=20, 34)	-0.773 (± 0.698)	0.002 (± 0.514)		
Change at Week 8 (n=18, 32)	-0.19 (± 0.259)	-0.154 (± 0.191)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Stable State in Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Extended Approach)

End point title	Change From Stable State in Exacerbations of Chronic Pulmonary Disease Test (EXACT-PRO) Weekly Averages (Extended Approach)

End point description:

The EXACT-PRO questionnaire is a new, validated, and standardized measure to evaluate the frequency, severity, and duration of COPD exacerbations. It is a 14-item daily diary, and scores range from 0 to 100, with higher scores indicating worse health status. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are baseline value, treatment, time point, treatment by time point and baseline by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: score on a scale				
least squares mean (standard error)				
Week 1 (n=35, 39)	7.163 (± 2.859)	4.697 (± 2.077)		
Week 2 (n=37, 40)	4.839 (± 2.259)	1.433 (± 1.652)		
Week 3 (n=29, 42)	2.988 (± 1.87)	0.179 (± 1.363)		
Week 4 (n=27, 42)	0.909 (± 1.861)	0.743 (± 1.344)		
Week 5 (n=25, 41)	-0.657 (± 1.554)	-0.318 (± 1.129)		
Week 6 (n=23, 41)	-0.889 (± 0.976)	-0.14 (± 0.706)		
Week 7 (n=24, 38)	-0.311 (± 0.654)	-0.075 (± 0.479)		
Week 8 9n=19, 33)	-0.24 (± 0.244)	-0.115 (± 0.178)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Peak Expiratory Flow (PEF) Weekly Average (Initial Approach)

End point title	Change from Stable State in Diaries Peak Expiratory Flow (PEF) Weekly Average (Initial Approach)

End point description:

Morning post-medication PEF (the best of 3 attempts measured with a mini-Wright peak-flow meter) was recorded in a daily diary. A positive change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: liters/minute				
least squares mean (standard error)				
Change at Week 1 (n=37, 38)	-16.551 (± 5.144)	-9.915 (± 4.442)		
Change at Week 2 (n=35, 40)	-6.067 (± 4.564)	-0.304 (± 3.899)		
Change at Week 3 (n=35, 40)	-4.996 (± 3.914)	0.687 (± 3.36)		
Change at Week 4 (n=29, 39)	-4.595 (± 3.421)	-0.42 (± 2.737)		
Change at Week 5 (n=28, 38)	-3.557 (± 4.061)	-1.224 (± 3.287)		
Change at Week 6 (n=27, 37)	-3.795 (± 4.546)	-5.559 (± 3.68)		
Change at Week 7 (n=27, 36)	-7.178 (± 5.212)	-4.186 (± 4.264)		
Change at Week 8 (n=27, 35)	-2.887 (± 5.388)	-0.956 (± 4.418)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Peak Expiratory Flow (PEF) Weekly Average (Extended Approach)

End point title	Change from Stable State in Diaries Peak Expiratory Flow (PEF) Weekly Average (Extended Approach)

End point description:

Morning post-medication PEF (the best of 3 attempts measured with a mini-Wright peak-flow meter) was recorded in a daily diary. A positive change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: liters/minute				
least squares mean (standard error)				
Change at Week 1 (n=46, 42)	-13.958 (± 4.147)	-8.447 (± 3.865)		
Change at Week 2 (n=44, 44)	-5.776 (± 3.772)	1.029 (± 3.488)		
Change at Week 3 (n=44, 44)	-5.36 (± 3.676)	2.038 (± 3.421)		
Change at Week 4 (n=37, 43)	-6.66 (± 3.546)	1.133 (± 3.126)		
Change at Week 5 (n=33, 42)	-5.568 (± 3.847)	0.269 (± 3.396)		
Change at Week 6 (n=32, 41)	-2.186 (± 3.515)	-4.596 (± 3.076)		
Change at Week 7 (n=31, 40)	-8.513 (± 4.544)	-1.974 (± 3.952)		
Change at Week 8 (n=31, 39)	-4.563 (± 4.741)	0.95 (± 4.091)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Symptom Score Weekly Average (Initial Approach)

End point title	Change from Stable State in Diaries Symptom Score Weekly Average (Initial Approach)

End point description:

Any increase in the following respiratory symptoms: dyspnea, sputum purulence, sputum amount, wheeze, sore throat, cough, fever, symptoms of a common cold, ie, nasal congestion and discharge over the previous 24 hours were recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=38, 42)	2.93 (± 0.286)	2.587 (± 0.254)		

Change at Week 2 (n=37, 42)	1.13 (± 0.314)	1.331 (± 0.272)		
Change at Week 3 (n=35, 42)	0.906 (± 0.299)	0.79 (± 0.258)		
Change at Week 4 (n=30, 40)	0.552 (± 0.298)	0.922 (± 0.248)		
Change at Week 5 (n=29, 39)	0.413 (± 0.305)	0.882 (± 0.254)		
Change at Week 6 (n=28, 39)	0.141 (± 0.31)	0.681 (± 0.258)		
Change at Week 7 (n=27, 37)	0.442 (± 0.0294)	0.673 (± 0.243)		
Change at Week 8 (n=27, 36)	0.626 (± 0.361)	0.612 (± 0.297)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Symptom Score Weekly Average (Extended Approach)

End point title	Change from Stable State in Diaries Symptom Score Weekly Average (Extended Approach)

End point description:

Any increase in the following respiratory symptoms: dyspnea, sputum purulence, sputum amount, wheeze, sore throat, cough, fever, symptoms of a common cold, ie, nasal congestion and discharge over the previous 24 hours were recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=48, 46)	3.11 (± 0.257)	2.593 (± 0.246)		
Change at Week 2 (n=47, 46)	1.171 (± 0.285)	1.402 (± 0.267)		
Change at Week 3 (n=44, 46)	0.85 (± 0.267)	0.802 (± 0.25)		
Change at Week 4 (n=38, 44)	0.751 (± 0.312)	0.924 (± 0.282)		
Change at Week 5 (n=34, 43)	0.437 (± 0.287)	0.907 (± 0.259)		

Change at Week 6 (n=33, 43)	0.041 (± 0.257)	0.661 (± 0.231)		
Change at Week 7 (n=31, 41)	0.503 (± 0.247)	0.533 (± 0.216)		
Change at Week 8 (n=31, 40)	0.451 (± 0.274)	0.53 (± 0.237)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Treatment Score Weekly Average (Initial Approach)

End point title	Change from Stable State in Diaries Treatment Score Weekly Average (Initial Approach)

End point description:

Any changes in the participant's usual treatment were recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=38, 42)	0.849 (± 0.194)	0.769 (± 0.174)		
Change at Week 2 (n=37, 42)	0.682 (± 0.19)	0.804 (± 0.167)		
Change at Week 3 (n=35, 42)	0.281 (± 0.115)	0.188 (± 0.099)		
Change at Week 4 (n=30, 40)	0.185 (± 0.118)	0.217 (± 0.099)		
Change at Week 5 (n=29, 39)	0.13 (± 0.123)	0.263 (± 0.103)		
Change at Week 6 (n=28, 39)	0.128 (± 0.13)	0.204 (± 0.108)		
Change at Week 7 (n=27, 37)	0.112 (± 0.117)	0.135 (± 0.097)		
Change at Week 8 (n=27, 36)	0.122 (± 0.101)	0.127 (± 0.084)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Treatment Score Weekly Average (Extended Approach)

End point title	Change from Stable State in Diaries Treatment Score Weekly Average (Extended Approach)

End point description:

Any changes in the participant's usual treatment were recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 1 (n=48, 46)	0.787 (± 0.17)	0.73 (± 0.162)		
Change at Week 2 (n=47, 46)	0.767 (± 0.172)	0.78 (± 0.161)		
Change at Week 3 (n=44, 46)	0.338 (± 0.103)	0.177 (± 0.095)		
Change at Week 4 (n=38, 44)	0.379 (± 0.144)	0.206 (± 0.129)		
Change at Week 5 (n=34, 43)	0.191 (± 0.107)	0.244 (± 0.096)		
Change at Week 6 (n=33, 43)	0.127 (± 0.107)	0.196 (± 0.096)		
Change at Week 7 (n=31, 41)	0.179 (± 0.116)	0.156 (± 0.103)		
Change at Week 8 (n=31, 40)	0.084 (± 0.086)	0.171 (± 0.075)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Hours Out of the Home Weekly Average (Initial Approach)

End point title	Change from Stable State in Diaries Hours Out of the Home Weekly Average (Initial Approach)

End point description:

Estimates of the length of time the participants were out of their own home on the previous day were

recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: hours				
least squares mean (standard error)				
Change at Week 1 (n=34, 34)	-1.313 (± 0.416)	-0.105 (± 0.391)		
Change at Week 2 (n=34, 38)	-0.974 (± 0.359)	-0.328 (± 0.333)		
Change at Week 3 (n=34, 40)	-1.077 (± 0.374)	0.226 (± 0.335)		
Change at Week 4 (n=28, 39)	-1.131 (± 0.414)	-0.306 (± 0.354)		
Change at Week 5 (n=26, 38)	-0.826 (± 0.465)	0.28 (± 0.407)		
Change at Week 6 (n=25, 35)	-1.154 (± 0.448)	-0.062 (± 0.386)		
Change at Week 7 (n=26, 35)	-1.194 (± 0.449)	-0.34 (± 0.394)		
Change at Week 8 (n=26, 34)	-0.812 (± 0.532)	0.037 (± 0.458)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Stable State in Diaries Hours Out of the Home Weekly Average (Extended Approach)

End point title	Change from Stable State in Diaries Hours Out of the Home Weekly Average (Extended Approach)

End point description:

Estimates of the length of time the participants were out of their own home on the previous day were recorded in a daily diary. A negative change from Baseline indicates improvement. Covariates for Mixed Model Repeated Measurement (MMRM) are stable state value, treatment, time point, and treatment by time point interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 3, 4, 5, 6, 7 and 8

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: hours				
least squares mean (standard error)				
Change at Week 1 (n=42, 38)	-1.472 (± 0.353)	-0.276 (± 0.344)		
Change at Week 2 (n=43, 42)	-1.305 (± 0.319)	-0.472 (± 0.307)		
Change at Week 3 (n=42, 44)	-1.314 (± 0.343)	0.099 (± 0.0324)		
Change at Week 4 (n=35, 43)	-1.328 (± 0.357)	-0.266 (± 0.325)		
Change at Week 5 (n=31, 42)	-0.833 (± 0.402)	0.158 (± 0.369)		
Change at Week 6 (n=30, 39)	-1.271 (± 0.372)	-0.247 (± 0.344)		
Change at Week 7 (n=30, 39)	-1144 (± 0.363)	-0.478 (± 0.333)		
Change at Week 8 (n=30, 38)	-0.714 (± 0.433)	-0.068 (± 0.401)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exacerbation Length (Initial Approach)

End point title	Exacerbation Length (Initial Approach)

End point description:

Exacerbation length is the period from start of increased symptoms to end of increased symptoms; the last day of an exacerbation was to be followed by 2 days without symptom entries in the diary.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

8 Weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	43		
Units: days				
median (confidence interval 95%)	12 (8 to 18)	14 (10 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Exacerbation Length (Extended Approach)

End point title	Exacerbation Length (Extended Approach)

End point description:

Exacerbation length is the period from start of increased symptoms to end of increased symptoms; the last day of an exacerbation was to be followed by 2 days without symptom entries in the diary.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

8 Weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	47		
Units: days				
median (confidence interval 95%)	13 (9 to 19)	14 (11 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Aortic Pulse Wave Velocity in a Subset of Participants (Initial Approach)

End point title	Change from Baseline in Aortic Pulse Wave Velocity in a Subset of Participants (Initial Approach)

End point description:

Carotid-femoral aortic pulse wave velocity (aPWV) will be measured in a subset of participants to determine changes in arterial stiffness. A negative change from Baseline indicates improvement. Covariates for MMRM are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat (ITT) population, all randomized participants, with data available at the given time-point. Initial Approach Analysis included all participants who received treatment in Cycle 1.

End point type	Secondary

End point timeframe:

Baseline and Days 14 and 28

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: meters/second				
least squares mean (standard error)				
Change at Day 14 (n=18, 24)	-0.047 (± 0.337)	-0.343 (± 0.29)		
Change at Day 28 (n=14, 24)	-0.38 (± 0.413)	-0.474 (± 0.321)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Aortic Pulse Wave Velocity in a Subset of Participants (Extended Approach)

End point title	Change from Baseline in Aortic Pulse Wave Velocity in a Subset of Participants (Extended Approach)

End point description:

Carotid-femoral aortic pulse wave velocity (aPWV) will be measured in a subset of participants to determine changes in arterial stiffness. A negative change from Baseline indicates improvement. Covariates for MMRM are baseline value, treatment, visit, and treatment by visit interaction.

Participants from the Intent-to-treat population, all randomized participants, with data available at the given time-point. Extended Approach Analysis included all participants who received treatment in Cycle 1 and participants who were re-randomized and received treatment in Cycle 2.

End point type	Secondary

End point timeframe:

Baseline and Days 14 and 28

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	32		
Units: meters/second				
least squares mean (standard error)				
Change at Day 14 (n=28, 28)	-0.128 (± 0.247)	-0.326 (± 0.245)		
Change at Day 28 (n=19, 28)	-0.316 (± 0.323)	-0.511 (± 0.273)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Signing of informed consent until Follow-up Visit (Up to 56 days)

Adverse event reporting additional description:

AEs were analyzed using an Initial Approach (all patients treated in Cycle 1) and an Extended Approach (all patients treated in Cycle 1 and patients re-randomized and treated in Cycle 2). The data from the 2 approaches are entered in one table. Please note: a result of 0 corresponds to no patients with AEs for the preferred term > the 5% threshold.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Roflumilast 500 µg (Initial Approach)

Reporting group description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Initial Approach Arm includes all participants who received treatment in Cycle 1.

Reporting group title	Placebo (Initial Approach)

Reporting group description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Initial Approach Arm includes all participants who received treatment in Cycle 1.

Reporting group title	Roflumilast 500 µg (Extended Approach)

Reporting group description:

Roflumilast 500 µg tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Extended Approach Arm includes all participants who received treatment in Cycle 1 and those participants who were re-randomized and received treatment in Cycle 2.

Reporting group title	Placebo (Extended Approach)

Reporting group description:

Placebo matching roflumilast tablet, once daily, orally in the morning after breakfast added on to standard therapy for acute COPD exacerbations. Extended Approach Arm includes all participants who received treatment in Cycle 1 and those participants who were re-randomized and received treatment in Cycle 2.

Serious adverse events	Roflumilast 500 µg (Initial Approach)	Placebo (Initial Approach)	Roflumilast 500 µg (Extended Approach)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	1 / 43 (2.33%)	4 / 48 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	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			
subjects affected / exposed	0 / 38 (0.00%)	1 / 43 (2.33%)	0 / 48 (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
Pulmonary embolism			
subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (Extended Approach)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Roflumilast 500 µg (Initial Approach)	Placebo (Initial Approach)	Roflumilast 500 µg (Extended Approach)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	25 / 43 (58.14%)	44 / 48 (91.67%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 38 (15.79%)	1 / 43 (2.33%)	6 / 48 (12.50%)
occurrences (all)	6	1	6
Headache			
subjects affected / exposed	3 / 38 (7.89%)	2 / 43 (4.65%)	4 / 48 (8.33%)
occurrences (all)	3	2	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 43 (2.33%)	0 / 48 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	25 / 38 (65.79%)	10 / 43 (23.26%)	32 / 48 (66.67%)
occurrences (all)	27	10	34
Flatulence			

subjects affected / exposed	2 / 38 (5.26%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	1 / 43 (2.33%)	3 / 48 (6.25%)
occurrences (all)	2	1	3
Nausea			
subjects affected / exposed	6 / 38 (15.79%)	3 / 43 (6.98%)	9 / 48 (18.75%)
occurrences (all)	6	3	9
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	0 / 43 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	17 / 38 (44.74%)	13 / 43 (30.23%)	19 / 48 (39.58%)
occurrences (all)	17	14	20
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 38 (31.58%)	2 / 43 (4.65%)	14 / 48 (29.17%)
occurrences (all)	12	2	14
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 38 (5.26%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Oral candidiasis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 38 (10.53%)	2 / 43 (4.65%)	6 / 48 (12.50%)
occurrences (all)	4	2	6

Non-serious adverse events	Placebo (Extended Approach)		

Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 47 (59.57%)		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 1 / 47 (2.13%) 1 2 / 47 (4.26%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 0 / 47 (0.00%) 0 11 / 47 (23.40%) 11 0 / 47 (0.00%) 0 1 / 47 (2.13%) 1 3 / 47 (6.38%) 3 1 / 47 (2.13%) 1		
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	 15 / 47 (31.91%) 16		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 47 (4.26%) 2		

Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	 0 / 47 (0.00%) 0		
Infections and infestations Cellulitis subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all)	 0 / 47 (0.00%) 0 0 / 47 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 2 / 47 (4.26%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2011	• Oxygen therapy (less than 8 hours daily) was added as allowed concomitant medication in Section 6.8 of the protocol at the request of the Research Ethics Committee. Exclusion criterion E6 'Oxygen therapy (more than 8 hours daily)' remained unchanged, because patients who received home oxygen therapy (more than 8 hours daily) were to be excluded due to possible severe hypoxemia during COPD exacerbation.
16 May 2012	• A further objective to investigate the effect of roflumilast on changes in arterial stiffness during recovery from an exacerbation was added. Changes in arterial stiffness from Visit V0 to Visit V2 and Visit V3 were to be measured in a subset of 60 patients by aPWV. A separate patient information sheet and IC were to be signed by patients in this subset. Arterial stiffness has been shown to increase in COPD patients from stable state to exacerbation presentation and remain elevated during the recovery period of the acute exacerbation. As arterial stiffness is a validated measure of cardiovascular risk, and roflumilast is associated with a lower risk of major adverse cardiovascular events, the addition of arterial stiffness measurement was intended to enable exploration of a potential anti-inflammatory effect of roflumilast. • Additional information on standard antibiotic exacerbation treatment was added to include use of antibiotics other than penicillin and clarithromycin in case of allergy or intolerance of these antibiotics. • Additional laboratory parameters were added for standard clinical hematology, coagulation, blood chemistry, and endocrinology tests (erythrocyte mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration, prothrombin time, prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen, serum urea, estimated glomerular filtration rate, serum albumin, adjusted serum calcium, inorganic blood phosphate, total cholesterol:high density lipoprotein ratio, serum C reactive protein, serum troponin T, and NT-proBNP). These were to provide additional information on the health status of each patient. Troponin T and NT-proBNP are biomarkers for cardiovascular disease and were of interest for the added arterial stiffness measurements.
16 May 2012	• Additional planned statistical analyses were added: aPWV was to be analyzed by MMRM with change from Visit V0 to Visit V2 and Visit V3 as the dependent variable, and the Visit V0 value, treatment indicator, scheduled visit, and treatment-by-visit interaction as independent variables; serum troponin T and NT-proBNP were to be analyzed by ANCOVA with change from Visit V0 to Visit V3 as the dependent variable, and the Visit V0 value and the treatment group as independent variables.
02 November 2012	• The potential ADR 'angioedema' was added to the description of the IMP based on a cumulative review of post-marketing reports in which rare (≥1/10,000 to <1/1,000) cases of angioedema were noted with roflumilast in COPD studies (Updated in accordance with IB V6e, 05 October 2012) • The exclusion criterion E6 'Oxygen therapy (more than 8 hours daily)' was removed because new data were available on the tolerability and safety of roflumilast, indicating that roflumilast could be used in patients with more severe COPD, ie, patients who required long-term oxygen therapy. This information was obtained from the 38 patients randomized in the trial to this point: only 2 withdrawals due to tolerability had occurred, and these were related to insomnia and diarrhea. Allowed concomitant medication 'oxygen therapy (less than 8 hours daily)' was updated to 'oxygen therapy'.
23 November 2012	• As a consequence of the merger of Nycomed GmbH with Takeda Pharmaceutical Company Ltd. on 31 October 2011, the sponsor of the trial changed in name and legal entity to Takeda Pharma A/S (Denmark).

28 August 2013	• The recruitment period was extended to 2 years. • Exclusion criterion E21 was changed: patients previously enrolled in the trial were allowed to re-enroll with a new exacerbation, provided they had reached a stable disease status since completing the first cycle of trial treatment. Patients with recurrent exacerbations within 8 weeks of a previous exacerbation, and hence unstable disease, could not be re-enrolled. • A new approach to the statistical analyses was introduced, to reflect the change to exclusion criterion E21: the primary and confirmatory analyses were to be performed as originally planned, using the data from patients' first cycle of trial treatment only; all analyses were to be repeated in an exploratory manner including data from both the first cycle and, for re-enrolled patients, the second cycle, and treating re-enrolled patients as if they were new patients. • Storage conditions were specified: IMP was to be stored below 30°

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 April 2014	Study was terminated due to difficulty in identifying further eligible patients for this exploratory study within a reasonable time.	-

Notes:

Limitations and caveats

None reported