Clinical trial results:
Effect of Roflumilast on Exacerbation Rate in Patients With COPD Treated With Fixed Combinations of LABA and ICS. A 52-week, Randomised Double-blind Trial With Roflumilast 500 µg Versus Placebo. The REACT Trial

Summary

EudraCT number	2010-019685-87
Trial protocol	GB BE DE AT DK GR NL HU SK IT ES
Global end of trial date	27 May 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	RO-2455-404-RD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01329029
WHO universal trial number (UTN)	U1111-1141-7422

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	11 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2014
Global end of trial reached?	Yes
Global end of trial date	27 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the REACT trial is to investigate the effect of roflumilast 500 µg tablets once daily versus placebo on exacerbation rate and pulmonary function in COPD patients who are concomitantly treated with a fixed combination of long-acting β2-agonists (LABA) and inhaled glucocorticosteroids (ICS). In addition, data on safety and tolerability of roflumilast will be obtained. An additional objective is to further characterize the population pharmacokinetic profile of roflumilast and roflumilast N oxide and to further characterize their pharmacokinetics/pharmacodynamics (PK/PD) relationship in terms of efficacy and relevant safety aspects. Patients to be included are required to have severe COPD associated with chronic bronchitis and a history of frequent exacerbations and must be concomitantly treated with a fixed combination of LABA and ICS. Two parallel treatment arms (roflumilast 500 µg once daily and placebo) are included.

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 May 2011
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	Netherlands: 19
Country: Number of subjects enrolled	Poland: 176
Country: Number of subjects enrolled	Slovakia: 58
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	United Kingdom: 50
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 133
Country: Number of subjects enrolled	Greece: 68
Country: Number of subjects enrolled	Hungary: 236
Country: Number of subjects enrolled	Italy: 115
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Brazil: 80
Country: Number of subjects enrolled	Canada: 26

Country: Number of subjects enrolled	Israel: 240
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Russian Federation: 358
Country: Number of subjects enrolled	South Africa: 53
Country: Number of subjects enrolled	Turkey: 96
Worldwide total number of subjects	1935
EEA total number of subjects	1039

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)	961
From 65 to 84 years	965
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 203 investigative sites in Australia, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Korea (Republic of), Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Turkey and United Kingdom from 28 May 2011 to 27 May 2014.

Pre-assignment

Screening details:

Participants with a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) entered a 4 week baseline period during which all patients received placebo then were enrolled equally in 1 of 2 treatment groups, once a day placebo or roflumilast 500 µg.

Pre-assignment period milestones

Number of subjects started	1945[1]
Number of subjects completed	1935

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not receive treatment: 10

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 10 participants did not receive study medication and therefore were not accounted for in the
worldwide number enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast 500 µg

Arm description:

Roflumilast 500 µg tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.

Arm type	Experimental
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, orally, once daily for 52 weeks.

Arm title	Placebo

Arm description:

Placebo-matching roflumilast tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.

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, orally, once daily for 52 weeks.

Number of subjects in period 1	Roflumilast 500 µg	Placebo
Started	969	966
Full Analysis Set (FAS)	969	966
Completed	704	780
Not completed	265	186
Met Pre-defined Discontinuation Criteria	5	1
Physician decision	16	13
Adverse Event	82	29
Death	16	19
Other	10	14
COPD Exacerbation	11	18
Withdrawal by Subject	117	87
Lost to follow-up	8	5

Baseline characteristics

Reporting groups	
Reporting group title	Roflumilast 500 µg
Reporting group description:	
Roflumilast 500 µg tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching roflumilast tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.	

Reporting group values	Roflumilast 500 µg	Placebo	Total
Number of subjects	969	966	1935
Age categorical Units: Subjects			
≤ 65 years	527	542	1069
> 65 years	442	424	866
Age continuous Units: years			
arithmetic mean	64.7	64.7	
standard deviation	± 8.38	± 8.37	-
Gender categorical Units: Subjects			
Female	251	241	492
Male	718	725	1443
Race/Ethnicity, Customized Units: Subjects			
Asian	20	16	36
Black or African American	6	5	11
White	940	943	1883
Other	3	2	5
Region of Enrollment Units: Subjects			
Australia	9	16	25
Austria	11	3	14
Belgium	19	18	37
Brazil	42	38	80
Canada	14	12	26
Denmark	15	19	34
France	16	13	29
Germany	70	63	133
Greece	38	30	68
Hungary	111	125	236
Israel	114	126	240
Italy	64	51	115
Korea, Republic of	11	7	18
Netherlands	11	8	19
Poland	88	88	176

Russia Federation	177	181	358
Slovakia	25	33	58
South Africa	23	30	53
Spain	37	33	70
Turkey	52	44	96
United Kingdom	22	28	50
Chronic Obstructive Pulmonary Disease (COPD) Severity			
COPD severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guideline (2009) as: - Very severe COPD: baseline post-bronchodilator FEV1 %predicted < 30% - Severe COPD: baseline post-bronchodilator FEV1 %predicted ≥ 30% to < 50% - Moderate COPD: baseline post-bronchodilator FEV1 %predicted ≥ 50% to < 80% - Mild COPD: baseline post-bronchodilator FEV1 %predicted ≥ 80%.			
Units: Subjects			
Mild	2	0	2
Moderate	18	16	34
Severe	658	677	1335
Very Severe	291	273	564
COPD Disease Characteristics Units: Subjects			
Pure emphysema	4	2	6
Predominantly chronic bronchitis	338	330	668
Combined emphysema and chronic bronchitis	626	634	1260
Missing	1	0	1
Global Initiative for Chronic Obstructive Lung Disease (GOLD) Patient Group			
Patients were classified based on spirometry, symptoms and exacerbation risk.			
Units: Subjects			
A: low risk, less symptoms	0	0	0
B: low risk, more symptoms	0	0	0
C: high risk, less symptoms	62	57	119
D: high risk, more symptoms	905	907	1812
Missing	2	2	4
Smoking Status Units: Subjects			
Current smoker	411	432	843
Former smoker	558	534	1092
Non-smoker	0	0	0
Height Units: cm			
arithmetic mean	168.2	168.33	
standard deviation	± 8.652	± 8.198	-
Weight Units: kg			
arithmetic mean	75.07	75.6	
standard deviation	± 17.275	± 17.238	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	26.45	26.58	
standard deviation	± 5.474	± 5.359	-
Cigarette Pack Years Units: pack years			

arithmetic mean	47.6	47.6	
standard deviation	± 24.55	± 23.56	-
Pre-bronchodilator Forced Expiratory Volume in the First Second (FEV1)			
Number of participants for whom pre-bronchodilator FEV1 data was available was 938 and 937 in each treatment arm, respectively.			
Units: Liters			
arithmetic mean	0.999	1.016	
standard deviation	± 0.3149	± 0.3209	-
Post-bronchodilator FEV1			
Units: Liters			
arithmetic mean	1.066	1.078	
standard deviation	± 0.3317	± 0.3244	-
Pre-bronchodilator FEV1 Predicted			
Number of participants for whom pre-bronchodilator FEV1 data was available was 938 and 933 in each treatment arm, respectively.			
Units: percent predicted			
arithmetic mean	33.259	33.562	
standard deviation	± 9.0781	± 9.0043	-
Post-bronchodilator FEV1 Predicted			
Units: percent predicted			
arithmetic mean	35.392	35.532	
standard deviation	± 9.2484	± 8.7573	-
FEV1 Reversibility % Increase			
FEV reversibility (%) = (post-bronchodilator FEV minus pre-bronchodilator FEV) / pre-bronchodilator FEV * 100. Number of participants for whom FEV1 reversibility % increase data was available was 912 and 915 in each treatment arm, respectively.			
Units: percent reversibility			
arithmetic mean	7.465	7.383	
standard deviation	± 11.2559	± 12.0752	-
FEV1 Reversibility Increase			
Number of participants for whom FEV1 reversibility increase data was available was 912 and 915 in each treatment arm, respectively.			
Units: mL			
arithmetic mean	65.2	65.4	
standard deviation	± 108.72	± 121.55	-
Post-bronchodilator FEV1/Forced Vital Capacity (FVC)			
Calculated as FEV1/FVC * 100			
Units: FEV1/FVC percent			
arithmetic mean	40.2	40.1	
standard deviation	± 10.81	± 10.26	-

End points

End points reporting groups

Reporting group title	Roflumilast 500 µg
Reporting group description:	
Roflumilast 500 µg tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching roflumilast tablet, orally, once daily for 52 weeks. Background therapy concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Placebo-matching roflumilast tablet, orally, once daily for 52 weeks (following a 4 week placebo run-in period) and concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.	

Primary: Rate of Moderate or Severe COPD Exacerbations Per Patient Per Year

End point title	Rate of Moderate or Severe COPD Exacerbations Per Patient Per Year
End point description:	
A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. COPD exacerbations were categorized as follows: Severe=Requiring hospitalization and/or leading to death; Moderate=Requiring oral or parenteral glucocorticosteroid therapy. The defined number of days a patient was in the trial was divided by 365.25, in order to express the duration as a fraction of 1 year.	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: exacerbations per patient per year				
arithmetic mean (confidence interval 95%)	0.805 (0.724 to 0.895)	0.927 (0.843 to 1.02)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Estimation comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.	
Comparison groups	Roflumilast 500 µg v Placebo

Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0529 [1]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.753
upper limit	1.002
Variability estimate	Standard error of the mean
Dispersion value	0.0633

Notes:

[1] - Level of significance: 5% 2-sided
Poisson regression model (estimates of exacerbation rates using time in trial as model offset).

Secondary: Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in the First Second (FEV1)

End point title	Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in the First Second (FEV1)

End point description:

Pulmonary function testing was performed using centralised spirometry. FEV1 is the maximum amount of air that can be forcefully exhaled in one second. Least-squares means is from Analysis of Covariance (ANCOVA) including treatment by time interaction. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	928	941		
Units: liters				
least squares mean (standard error)	0.052 (± 0.0064)	-0.004 (± 0.0062)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo

Number of subjects included in analysis	1869
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.0089

Notes:

[2] - Analysis of Covariance (ANCOVA) including treatment by time interaction.

Secondary: Rate of Severe COPD Exacerbations Per Patient Per Year

End point title	Rate of Severe COPD Exacerbations Per Patient Per Year

End point description:

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. Severe COPD exacerbations were categorized as requiring hospitalization and/or leading to death. The defined number of days a patient was in the trial was divided by 365.25, in order to express the duration as a fraction of 1 year.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: exacerbations per patient per year				
arithmetic mean (confidence interval 95%)	0.239 (0.201 to 0.283)	0.315 (0.27 to 0.368)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo

Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0175 [3]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.757
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.601
upper limit	0.952
Variability estimate	Standard error of the mean
Dispersion value	0.0889

Notes:

[3] - Analyzed using a negative binomial regression model excluding a correction for overdispersion.

Secondary: Rate of COPD Exacerbations Per Patient Per Year All Categories

End point title	Rate of COPD Exacerbations Per Patient Per Year All Categories

End point description:

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. COPD exacerbations were categorized as follows: Severe=Requiring hospitalization and/or leading to death; Moderate=Requiring oral or parenteral glucocorticosteroid therapy. The defined number of days a patient was in the trial was divided by 365.25, in order to express the duration as a fraction of 1 year.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: exacerbations per patient per year				
arithmetic mean (confidence interval 95%)				
Moderate	0.574 (0.508 to 0.648)	0.627 (0.561 to 0.702)		
Mild, Moderate or Severe	3.078 (2.723 to 3.479)	3.879 (3.492 to 4.31)		
Leading to Hospitalisation	0.238 (0.2 to 0.283)	0.313 (0.268 to 0.365)		
Glucocorticosteroids and/or Antibiotics treatment	0.794 (0.716 to 0.88)	0.929 (0.847 to 1.019)		
Moderate or Severe and/or treated with Antibiotics	1.012 (0.922 to 1.11)	1.21 (1.115 to 1.313)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Moderate COPD Exacerbations
Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2875 [4]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.914
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.775
upper limit	1.078
Variability estimate	Standard error of the mean
Dispersion value	0.0771

Notes:

[4] - Level of significance: 5% 2-sided
Poisson regression model (estimates of exacerbation rates using time in trial as model offset).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mild, Moderate or Severe COPD Exacerbations
Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [5]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.794
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.675
upper limit	0.933
Variability estimate	Standard error of the mean
Dispersion value	0.0654

Notes:

[5] - Level of significance: 5% 2-sided
Poisson regression model (estimates of exacerbation rates using time in trial as model offset).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

COPD Exacerbations treated with Glucocorticosteroids and/or Antibiotics
Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo

Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0262 [7]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.854
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.744
upper limit	0.982
Variability estimate	Standard error of the mean
Dispersion value	0.0605

Notes:

[6] - Level of significance: 5% 2-sided

[7] - Poisson regression model (estimates of exacerbation rates using time in trial as model offset).

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Moderate or Severe COPD Exacerbations and/or treated with Antibiotics
Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047 [8]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.739
upper limit	0.947
Variability estimate	Standard error of the mean
Dispersion value	0.0528

Notes:

[8] - Level of significance: 5% 2-sided
Poisson regression model (estimates of exacerbation rates using time in trial as model offset).

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Leading to Hospitalisation
Estimation Comments: A rate ratio of < 1 represents a favourable outcome for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209 [9]
Method	Generalized Linear Regression
Parameter estimate	Rate ratio
Point estimate	0.761

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.604
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	0.0899

Notes:

[9] - Level of significance: 5% 2-sided.
Negative binomial regression model (estimates of exacerbation rates)

Secondary: Percentage of Participants Experiencing at Least 1 COPD Exacerbation

End point title	Percentage of Participants Experiencing at Least 1 COPD Exacerbation

End point description:

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of participants				
number (not applicable)	55.2	60.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First COPD Exacerbation All Categories

End point title	Time to First COPD Exacerbation All Categories

End point description:

Time to event was calculated as date of onset of event — date of first intake of double-blind study drug + 1 day for all events: mild, moderate or severe. A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (confidence interval 95%)	218 (189 to 259)	180 (147 to 200)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.	
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1461 [10]
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.815
upper limit	1.031
Variability estimate	Standard error of the mean
Dispersion value	0.0549

Notes:

[10] - Level of significance: 5% 2-sided.

Secondary: Time to Second Moderate or Severe COPD Exacerbation

End point title	Time to Second Moderate or Severe COPD Exacerbation

End point description:

Time to event was calculated as date of onset of event — date of first intake of double-blind study drug + 1 day for events: moderate or severe. A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. COPD exacerbations were categorized as Severe: Requiring hospitalization and/or leading to death; Moderate: Requiring oral or parenteral glucocorticosteroid therapy.
Result Comment: 99999=Not Available (NA). Roflumilast arm: 95% confidence interval upper limit not estimated. Placebo arm: parameters not estimated-data did not reach the median.

End point type	Secondary

End point timeframe:

52 weeks [some participants extended treatment beyond 52 Weeks and are included in the analysis]

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (confidence interval 95%)	421 (413 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Estimation Comments: A hazard ratio of <1 represents a favourable outcome for the test treatment	
Comparison groups	Placebo v Roflumilast 500 µg
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [11]
Method	Wei-Lin-Weissfeld Method
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.641
upper limit	0.974
Variability estimate	Standard error of the mean
Dispersion value	0.0842

Notes:

[11] - Level of significance: 5% 2-sided

Secondary: Time to Third Moderate or Severe COPD Exacerbation

End point title	Time to Third Moderate or Severe COPD Exacerbation

End point description:

Time to event was calculated as date of onset of event — date of first intake of double-blind study drug + 1 day for events: moderate or severe. A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. COPD exacerbations were categorized as Severe: Requiring hospitalization and/or leading to death; Moderate: Requiring oral or parenteral glucocorticosteroid therapy.
Result Comment: 99999=Not Available (NA). Parameters not estimated-data did not reach the median.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Estimation Comments: A hazard ratio of <1 represents a favourable outcome for the test treatment.	
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0731 [12]
Method	Wei-Lin-Weissfeld Method
Parameter estimate	Hazard ratio (HR)
Point estimate	0.749
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	1.027
Variability estimate	Standard error of the mean
Dispersion value	0.1209

Notes:

[12] - Level of significance: 5% 2-sided

Secondary: Number of Patients Needed to Treat to Avoid 1 Moderate or Severe COPD Exacerbation Derived from Exacerbation per Patient per Year

End point title	Number of Patients Needed to Treat to Avoid 1 Moderate or Severe COPD Exacerbation Derived from Exacerbation per Patient per Year

End point description:

The number needed to treat (NNT) analysis is a simple, concise method to quantify directly the benefits that alternative treatment options have on disease outcomes in terms of the number of patients who need to be treated before a benefit is observed. Risk reduction: Rate(Placebo)— Rate (Roflumilast 500 µg), Number needed to treat for benefit (NNTB): 1/(Risk reduction). A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. COPD exacerbations were categorized as Severe: Requiring hospitalization and/or leading to death; Moderate: Requiring oral or parenteral glucocorticosteroid therapy.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: exacerbation per patient per year				
number (not applicable)	0.805	0.927		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	NNTB
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	31

Secondary: Number of Moderate or Severe COPD Exacerbation Days

End point title	Number of Moderate or Severe COPD Exacerbation Days

End point description:

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management. The number of exacerbation days per patient is the sum of durations (stop date of exacerbation — start date of exacerbation + 1) of all exacerbations within the category.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	380	432		
Units: days				
arithmetic mean (standard deviation)	26.9 (± 23.09)	30.9 (± 29.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Moderate or Severe COPD Exacerbations Per Participant

End point title	Duration of Moderate or Severe COPD Exacerbations Per Participant

End point description:

A COPD exacerbation is an event in the natural course of the disease characterized by a worsening in the patient's baseline dyspnoea, cough, and/or sputum production beyond day to day variability sufficient to warrant a change in management.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	380	432		
Units: days				
arithmetic mean (standard deviation)	15.9 (± 10.59)	16.6 (± 14.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator Forced Vital Capacity (FVC)

End point title	Change From Baseline in Post-Bronchodilator Forced Vital Capacity (FVC)

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. Least-squares means was from ANCOVA including treatment by time interaction. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	928	941		
Units: liters				
least squares mean (standard error)	0.036 (± 0.0114)	-0.057 (± 0.0111)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1869
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Repeated measurement model
Parameter estimate	Least Square Mean Difference
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.124
Variability estimate	Standard error of the mean
Dispersion value	0.0159

Notes:

[13] - Level of significance: 5% 2-sided.
Unstructured covariance structure and restricted maximum likelihood (REML).

Secondary: Change From Baseline in Post-Bronchodilator Forced Expiratory Flow at 25% to 75% of Vital Capacity (FEF25-75%)

End point title	Change From Baseline in Post-Bronchodilator Forced Expiratory Flow at 25% to 75% of Vital Capacity (FEF25-75%)

End point description:

Forced expiratory flow 25-75% (FEF25-75%) is the flow (or speed) of air coming out of the lung during the middle half of a forced expiration. Pulmonary function testing was performed using centralized spirometry. Least-squares means was from ANCOVA including treatment by time interaction. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	928	941		
Units: liters/second				
least squares mean (standard error)	0.035 (± 0.0044)	0.009 (± 0.0043)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1869
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Repeated measurement model
Parameter estimate	LS Mean Difference
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.038
Variability estimate	Standard error of the mean
Dispersion value	0.0062

Notes:

[14] - Level of significance: 5% 2-sided.
Unstructured covariance structure and REML.

Secondary: Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in the First 6 Seconds (FEV6)

End point title	Change From Baseline in Post-Bronchodilator Forced Expiratory Volume in the First 6 Seconds (FEV6)

End point description:

FEV6 is the amount of air which can be forcibly exhaled from the lungs in the first six seconds of a forced exhalation. Pulmonary function testing was performed using centralized spirometry. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	924	937		
Units: liters				
least squares mean (standard error)	0.061 (± 0.0093)	-0.033 (± 0.0091)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1861
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Repeated measurement model
Parameter estimate	LS Mean Difference
Point estimate	0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.0131

Notes:

[15] - Level of significance: 5% 2-sided.
Unstructured covariance structure and REML.

Secondary: Change From Baseline in Post-Bronchodilator FEV1/FVC

End point title	Change From Baseline in Post-Bronchodilator FEV1/FVC

End point description:

The FEV1/FVC ratio represents the percentage of vital capacity expelled from the lungs during the first second of a forced exhalation. Pulmonary function testing was performed using centralized spirometry. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	701	780		
Units: percent				
arithmetic mean (standard deviation)	1.17 (± 7.0339)	0.58 (± 6.8405)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Use of Rescue Medication From Daily Diary

End point title	Change From Baseline in Use of Rescue Medication From Daily Diary

End point description:

Salbutamol metered dose inhaler was available as rescue medication during the study. The participant recorded the use of rescue medication in a daily diary. A negative change from Baseline indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	848	896		
Units: puffs per day				
least squares mean (standard error)	-0.109 (± 0.0676)	0.173 (± 0.0654)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1744
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027 [16]
Method	Repeated measurement model
Parameter estimate	LS Mean Difference
Point estimate	-0.283
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.467
upper limit	-0.098
Variability estimate	Standard error of the mean
Dispersion value	0.0941

Notes:

[16] - Level of significance: 5% 2-sided.
Compound symmetry covariance structure and REML.

Secondary: Change From Baseline in COPD Symptom Score From Daily Diary

End point title	Change From Baseline in COPD Symptom Score From Daily Diary

End point description:

Participants recorded COPD symptoms cough and sputum production in a daily diary. Cough was assessed using a 4-point scale where 0=No cough to 3=severe cough and sputum was assessed using a 4-point scale where 0=no sputum production to 3=severe sputum production. Least-squares means from ANCOVA including treatment by time interaction. A negative change from Baseline indicates improvement. Total symptom score is the sum of cough and sputum scores, ranging from 0 (best possible outcome) to 6 (worst possible outcome).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	897	932		
Units: score on a scale				
least squares mean (standard error)	-0.412 (± 0.0315)	-0.398 (± 0.0306)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1829
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7392 [17]
Method	Repeated measurement model
Parameter estimate	LS Mean Difference
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.101
upper limit	0.071
Variability estimate	Standard error of the mean
Dispersion value	0.0439

Notes:

[17] - Level of significance: 5% 2-sided.
Compound symmetry covariance structure and REML.

Secondary: Percentage of Symptom-Free Days

End point title	Percentage of Symptom-Free Days

End point description:

Symptoms of COPD (cough, sputum) were recorded in a daily diary. The percentage of days without symptoms is reported.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of days				
arithmetic mean (standard deviation)	7.09 (± 17.119)	6.88 (± 16.185)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Rescue Medication-Free Days

End point title	Percentage of Rescue Medication-Free Days

End point description:

Participants recorded their use of rescue medication in a daily diary. The percentage of days without rescue medication use.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of days				
arithmetic mean (standard deviation)	23.25 (± 33.734)	22.77 (± 33.141)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in COPD Assessment Test (CAT) Total Score

End point title	Change From Baseline in COPD Assessment Test (CAT) Total Score

End point description:

Participants completed the CAT questionnaire at Baseline and after 52 Weeks of Treatment. The CAT questionnaire measures the impact of COPD on wellbeing and daily life. Participants answer 8 questions on a scale from 0 (best) to 5 (worst). The total score ranges from 0 to 40 with higher scores indicating more impact. A negative change from Baseline indicates improvement. Least-squares means from ANCOVA including treatment by time interaction.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	924	940		
Units: score on a scale				
arithmetic mean (standard error)	-1.27 (± 0.1556)	-0.985 (± 0.1518)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1909 [18]
Method	Repeated measurement model
Parameter estimate	LS Mean Difference
Point estimate	-0.285
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.711
upper limit	0.142
Variability estimate	Standard error of the mean
Dispersion value	0.2175

Notes:

[18] - Level of significance: 5% 2-sided.
Unstructured covariance structure and REML.

Secondary: Percentage of Participants With Improvement in CAT

End point title	Percentage of Participants With Improvement in CAT

End point description:

Participants completed the CAT questionnaire at Baseline and after 52 Weeks of treatment. The CAT questionnaire measures the impact of COPD on wellbeing and daily life. Participants answer 8 questions on a scale from 0 (best) to 5 (worst). The total score ranges from 0 to 40 with higher scores indicating more impact. Improvement was defined as a CAT Total Score reduction from Baseline > 1.6.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of participants				
number (not applicable)	71.2	72.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Mortality Due to Any Reason During the Treatment Period Score

End point title	Time to Mortality Due to Any Reason During the Treatment Period Score

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.
Result Comment: 99.99999=Not Available (NA). Data did not reach the median.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99.99999 (44 to 381)	99.99999 (21 to 293)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9414 [19]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.528
upper limit	1.99
Variability estimate	Standard error of the mean
Dispersion value	0.3468

Notes:

[19] - Level of significance: 5% 2-sided.

Secondary: Time to Mortality Due to COPD Exacerbation During the Treatment Period

End point title	Time to Mortality Due to COPD Exacerbation During the Treatment Period

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.
Result Comment: 99.99999=Not Available (NA). Data did not reach the median.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99.99999 (44 to 322)	99.99999 (25 to 293)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8876 [20]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.378
upper limit	3.075

Variability estimate	Standard error of the mean
Dispersion value	0.5765

Notes:

[20] - Level of significance: 5% 2-sided.

Secondary: Time to Withdrawal During the Treatment Period

End point title	Time to Withdrawal During the Treatment Period

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	420 (5 to 428)	444 (1 to 444)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.529
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.268
upper limit	1.845
Variability estimate	Standard error of the mean
Dispersion value	0.1463

Notes:

[21] - Level of significance: 5% 2-sided.

Secondary: Time to Withdrawal Due to COPD Exacerbation During the Treatment Period

End point title	Time to Withdrawal Due to COPD Exacerbation During the Treatment Period

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.
Result Comment: 99.99999=Not Available (NA). Data did not reach the median.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99.99999 (25 to 371)	99.99999 (12 to 319)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3477 [22]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.695
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.326
upper limit	1.484
Variability estimate	Standard error of the mean
Dispersion value	0.2691

Notes:

[22] - Level of significance: 5% 2-sided.

Secondary: Percentage of Participants With Major Adverse Cardiovascular Event (MACE) During the Treatment Period

End point title	Percentage of Participants With Major Adverse Cardiovascular Event (MACE) During the Treatment Period

End point description:

Composite MACE is a combined endpoint (cardiovascular death [including death due to undetermined cause], nonfatal myocardial infarction, and nonfatal stroke).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of participants				
number (not applicable)	1.7	1.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Major Adverse Cardiovascular Event (MACE) During the Treatment Period

End point title	Time to First Major Adverse Cardiovascular Event (MACE) During the Treatment Period

End point description:

Composite MACE is a combined endpoint(cardiovascular death [including death due to undetermined cause], nonfatal myocardial infarction, and nonfatal stroke). Time to event was calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.
Result Comment: 99.99999=Not Available (NA). Data did not reach the median.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99.99999 (52 to 415)	99.99999 (50 to 365)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments: A hazards ratio of < 1 represents a lower hazard for the test treatment.

Comparison groups	Roflumilast 500 µg v Placebo

Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8208 [23]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.542
upper limit	2.167
Variability estimate	Standard error of the mean
Dispersion value	0.3832

Notes:

[23] - Level of significance: 5% 2-sided.

Secondary: Percentage of Participant With All-Cause Hospitalisation During the Treatment Period

End point title	Percentage of Participant With All-Cause Hospitalisation During the Treatment Period

End point description:

Percentage of patients with at least one hospital admission due to any cause.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: percentage of participants				
number (not applicable)	24.9	29.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hospitalisation Due to Any Cause During the Treatment Period

End point title	Time to First Hospitalisation Due to Any Cause During the Treatment Period

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (confidence interval 95%)	400 (387 to 415)	408 (391 to 420)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Roflumilast 500 µg v Placebo
Number of subjects included in analysis	1935
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7943 [24]
Method	Cox-proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.977
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.821
upper limit	1.162
Variability estimate	Standard error of the mean
Dispersion value	0.0865

Notes:

[24] - Level of significance: 5% 2-sided.

Secondary: Time to Trial Withdrawal Due to an Adverse Event

End point title	Time to Trial Withdrawal Due to an Adverse Event

End point description:

Time to event will be calculated as date of onset of event — date of first intake of double-blind study drug + 1 day.
Result Comment: 99.99999=Not Available (NA). Data did not reach the median.

End point type	Secondary

End point timeframe:

52 Weeks (some participants extended treatment beyond 52 Weeks and are included in the analysis)

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	969	966		
Units: days				
median (full range (min-max))	99.99999 (7 to 420)	99.99999 (13 to 444)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced at Least 1 Treatment Emergent Adverse Event (TEAE)

End point title	Percentage of Participants Who Experienced at Least 1 Treatment Emergent Adverse Event (TEAE)[25]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug.

End point type	Secondary

End point timeframe:

52 weeks

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Subject Analysis Set Placebo was used for this endpoint and includes all participants who received at least one dose of placebo.

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	968	967		
Units: percentage of participants				
number (not applicable)	66.9	59.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight

End point title	Change From Baseline in Body Weight

End point description:

Least Square Means was from an ANCOVA model including Last Observation Carried Forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	938	944		
Units: kilograms (kg)				
least squares mean (standard error)	-2.66 (± 0.13)	-0.14 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI)

End point title	Change From Baseline in Body Mass Index (BMI)

End point description:

Body mass index (BMI) is a measure of body fat based on height and weight. Least Square Means was from an ANCOVA model including LOCF.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Roflumilast 500 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	938	944		
Units: kg/m^2				
least squares mean (standard error)	-0.94 (± 0.046)	-0.04 (± 0.046)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 Weeks

Adverse event reporting additional description:

Safety Population included all randomized participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Roflumilast 500 µg

Reporting group description:

Roflumilast 500 µg tablet, orally, once daily for 52 weeks (following a 4 week placebo run-in period) and concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.

Reporting group title	Placebo

Reporting group description:

Placebo-matching roflumilast tablet, orally, once daily for 52 weeks (following a 4 week placebo run-in period) and concomitant medication: fixed combination of long-acting β2-agonist and inhaled glucocorticosteroid.

Serious adverse events	Roflumilast 500 µg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	249 / 968 (25.72%)	285 / 967 (29.47%)	
number of deaths (all causes)	21	24	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign lung neoplasm			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bile duct cancer			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder adenocarcinoma stage unspecified			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder neoplasm			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 968 (0.10%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon neoplasm			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid tumour			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric neoplasm			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kaposi's sarcoma			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 968 (0.10%)	4 / 967 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic squamous cell carcinoma			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	4 / 968 (0.41%)	4 / 967 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal neoplasm			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic occlusion			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	3 / 968 (0.31%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 968 (0.21%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Alcohol detoxification			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 968 (0.31%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Drug ineffective			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 968 (0.21%)	3 / 967 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal obstruction			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 968 (0.21%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	144 / 968 (14.88%)	184 / 967 (19.03%)	
occurrences causally related to treatment / all	0 / 186	1 / 259	
deaths causally related to treatment / all	0 / 8	0 / 7	
Chronic respiratory failure			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 968 (0.31%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung infiltration			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum disorder			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	5 / 968 (0.52%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 968 (0.10%)	3 / 967 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Sleep apnoea syndrome			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant evaluation			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	4 / 968 (0.41%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rib fracture			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Accessory auricle			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitello-intestinal duct remnant			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 968 (0.21%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 968 (0.10%)	5 / 967 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 968 (0.62%)	6 / 967 (0.62%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 968 (0.21%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 968 (0.31%)	5 / 967 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 968 (0.41%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 968 (0.31%)	5 / 967 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid sinus syndrome			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 968 (0.31%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal nerve disorder			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder due to a general medical condition			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Acute vestibular syndrome			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 968 (0.10%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 968 (0.41%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	2 / 968 (0.21%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia haemorrhagic			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 968 (0.10%)	3 / 967 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	3 / 968 (0.31%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melaena			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perivascular dermatitis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyrotoxic crisis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 968 (0.10%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 968 (0.21%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	3 / 968 (0.31%)	7 / 967 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	0 / 968 (0.00%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 968 (0.21%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasopharyngitis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	33 / 968 (3.41%)	37 / 967 (3.83%)	
occurrences causally related to treatment / all	0 / 35	0 / 39	
deaths causally related to treatment / all	0 / 0	0 / 6	
Pneumonia moraxella			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 968 (0.10%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 968 (0.21%)	2 / 967 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 968 (0.10%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tracheobronchitis			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection viral			

subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 968 (0.21%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 968 (0.00%)	1 / 967 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 968 (0.10%)	0 / 967 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Roflumilast 500 µg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	228 / 968 (23.55%)	114 / 967 (11.79%)	
Investigations			
Weight decreased			
subjects affected / exposed	84 / 968 (8.68%)	27 / 967 (2.79%)	
occurrences (all)	86	27	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	97 / 968 (10.02%)	33 / 967 (3.41%)	
occurrences (all)	108	35	
Nausea			
subjects affected / exposed	55 / 968 (5.68%)	15 / 967 (1.55%)	
occurrences (all)	59	16	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	52 / 968 (5.37%)	52 / 967 (5.38%)	
occurrences (all)	68	59	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2012	Protocol Amendment 1 • MACE included as an additional efficacy endpoint • Re-enrollment allowed of patients not presenting with postbronchodilator FEV1 ≤50% of predicted after at least 4 weeks • LABA and ICS pretreatment fixed combinations at a constant (maximum) dose were only required for 3 months instead of 12 months. • Physical exercise maintenance was allowed during the trial. • Rate of severe exacerbations per patient per year is a key secondary endpoint. • PK samples were to be analysed at PPD. Update in changes in drug safety and trial management responsibilities and labelling of rescue medication.
17 October 2012	Protocol Amendment 2 Nycomed GmbH merged with Takeda Pharma and assumed sponsorship of the study from 30 November 2012.
12 September 2013	Protocol Amendment 3 • Clarification of AE and SAE reporting. • Clarification that European Medicines Agency Guidelines, 'no special storage requirements' for roflumilast = 15°C to 30°C. • Clarification for analysis of plasma PK samples.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Please Note: At this time the EudraCT system does not recognize "NA" as a viable result for an Endpoint. When this system error is corrected the results will be re-submitted with the proper data.

Notes: