Clinical trial results:
Effects of ROFLUMILAST on markers of subclinical atherosclerosis In stable COPD; the ELASTIC-trial

Summary

EudraCT number	2011-004152-19
Trial protocol	AT
Global end of trial date	18 January 2016

Results information

Result version number	v1 (current)
This version publication date	12 February 2018
First version publication date	12 February 2018

Trial information

Trial identification

Sponsor protocol code	ELASTIC2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01630200
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology
Sponsor organisation address	Sanatoriumstrasse 2, Vienna, Austria, 1140
Public contact	Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, 0043 019106041007, matthias.urban@wienkav.at
Scientific contact	Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, 0043 019106041007, matthias.urban@wienkav.at

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	24 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2016
Global end of trial reached?	Yes
Global end of trial date	18 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effects of ROFLUMILAST 500µg once daily on arterial stiffness in patients with COPD

Protection of trial subjects:

Blood samples were taken at visit2 and 4 to rule a potential impairment of liver - or renal function
During 6 minute walk test dyspnea scores were assessed to quantify patients subjective amount of dyspnea and excertion

Background therapy:

not applicable

Evidence for comparator:

not applicable

Actual start date of recruitment	02 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	40
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from an outpatient database of the Department of Respiratory and Critical Care Medicine in the Otto Wagner Hospital in Vienna. Recruitement started in April 2012 and lasted until July 2015.

Pre-assignment

Screening details:

A total of 240 patients were assessed for eligibility. Patients went through a 4 weeks run-in period to check for medication compliance. The primary reason for screening failure were comorbid diseases consistent with a predefined exclusion criteria. 80 patients were randomized to the study groups.

Period 1

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

Blinding implementation details:

The study was conducted in a double-blinded manner. All responsible persons, those administering the interventions or assessing the outcomes, and elementally all experimental and control patients were blinded to group assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast arm

Arm description:

After Randomization patients from the Roflumilast arm received the study medication (IMP: Roflumilast, 500µg, once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Roflumilast arm were equivalent to the Placebo arm.

Arm type	Experimental
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	R03DX07
Other name	Daxas® (EU), Daliresp® (USA)
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

500µg triangular coated tablet, administered oral once daily, in the morning

Arm title	Placebo arm

Arm description:

After Randomization patients from the Placebo arm received Placebo (once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Placebo arm were equivalent to the Placebo arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	not applicable
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

500µg triangular coated tablet, administered oral once daily, in the morning

Number of subjects in period 1	Roflumilast arm	Placebo arm
Started	40	40
Completed	33	34
Not completed	7	6
Adverse event, serious fatal	2	1
Consent withdrawn by subject	2	3
Adverse event, non-fatal	2	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Roflumilast arm
Reporting group description:	
After Randomization patients from the Roflumilast arm received the study medication (IMP: Roflumilast, 500µg, once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Roflumilast arm were equivalent to the Placebo arm.	
Reporting group title	Placebo arm
Reporting group description:	
After Randomization patients from the Placebo arm received Placebo (once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Placebo arm were equivalent to the Placebo arm.	

Reporting group values	Roflumilast arm	Placebo arm	Total
Number of subjects	40	40	80
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age of participants was evaluated on individual level at Visit 1 based on date of birth assessed via a survey			
Units: years			
median	64.5	64.5	
inter-quartile range (Q1-Q3)	61 to 69.5	56 to 72	-
Gender categorical			
Gender of participants was evaluated on individual level at Visit 1 based on anthropometric data			
Units: Subjects			
Female	22	16	38
Male	18	24	42
Ethnicity			
Units: Subjects			
Caucasian	40	40	80
Body Mass Index			
Body Mass Index of participants was evaluated on individual level at Visit 1 based on the equation: [Bodyweight in kilograms divided by height in meters squared]			
Units: points			
median	26.5	26.8	
inter-quartile range (Q1-Q3)	21.7 to 31.8	14.2 to 29.4	-
Smoking History			
Smoking history of participants was evaluated on individual level at Visit 1 based on the equation:			

(number of cigarettes smoked per day/20) × number of years smoked			
Units: Pack Years			
median	50	50	
inter-quartile range (Q1-Q3)	40 to 80	30 to 75	-
Exacerbation rate			
Exacerbation Rate of participants was evaluated on individual level at Visit 1 based on the number of COPD-exacerbations during the last years, characterized as a worsing of respiratory symptoms exceeding the usual day-to-day variability and the demand for intensified administration of bronchodilatory medication plus oral corticosteroids and/or antibiotics.			
Units: counts			
median	3	3	
inter-quartile range (Q1-Q3)	2 to 4	2 to 4	-
CAT score			
CAT (COPD assessement test) of participants was assessed on individual level at Visit 1 via the standardised and validated questionnaire containing 8 questions to quantify subjects COPD related symptoms via a scoe ranging from 0-5			
Units: points			
median	21	21	
inter-quartile range (Q1-Q3)	15.5 to 26.5	13 to 26	-
6-Minute Walk Test			
6-Minute Walk Test of participants was measured on individual level at Visit 1 based on the maximum distance walked on a 30 meters level ground during a time period of 6 minutes			
Units: meters			
median	428	456	
inter-quartile range (Q1-Q3)	340 to 558	364 to 570	-
FVC			
FVC (forced vital capacity) of participants was measured on individual level at baseline visit via standardized spirometry			
Units: percent of individual predicted value			
median	66.6	69.4	
inter-quartile range (Q1-Q3)	58.5 to 79.2	59.5 to 75.1	-
FEV1			
FEV1 (forced expiratory volume in 1 second) of participants was measured on individual level at baseline visit via standardized spirometry			
Units: percent of individual predicted value			
median	34.5	35.3	
inter-quartile range (Q1-Q3)	25.5 to 48.6	27 to 46.8	-
FEV1/FVC ratio			
FEV1FVC ratio: (forced expiratory volume in 1 second/forced vital capacity ratio) of participants was measured on individual level at baseline visit via standardized spirometry			
Units: ratio			
median	42	40.6	
inter-quartile range (Q1-Q3)	35.8 to 51	35.5 to 53	-
Cholesterol			
Cholesterol of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: mg/dl			
median	216	218	
inter-quartile range (Q1-Q3)	190 to 246	183 to 254	-
Triglycerides			
Triglycerides of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: mg/dl			
median	129	127	

inter-quartile range (Q1-Q3)	95 to 184	85.5 to 163	-
Blood Glucose			
Blood glucose of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: mg/dl			
median	101	97.5	
inter-quartile range (Q1-Q3)	92 to 115	91 to 122	-
Creatinine			
Creatinine of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: mg/dl			
median	0.8	0.8	
inter-quartile range (Q1-Q3)	0.7 to 0.9	0.6 to 0.9	-
Neutrophils			
Neutrophil counts were measured on individual level at baseline visit via collection of venous blood samples and and subsequent quantification in whole blood			
Units: Giga/l			
median	6.13	5.69	
inter-quartile range (Q1-Q3)	5.22 to 8.18	4.99 to 7.05	-
CRP			
CRP (C-reactive protein) of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: mg/dl			
median	5.2	3.85	
inter-quartile range (Q1-Q3)	3.1 to 9.5	1.65 to 8.2	-
IL-6			
IL6 (Interleukin-6) of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: pg/ml			
median	10.9	8.9	
inter-quartile range (Q1-Q3)	5.87 to 14.75	5.4 to 13.6	-
TNF-alpha			
TNF-lpha (tumor necrosis factor alpha) of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: pg/ml			
median	17.7	14.7	
inter-quartile range (Q1-Q3)	13.8 to 22.6	12 to 20.9	-
ADMA			
ADMA (asymmetric dimethylarginine) of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: ng/ml			
median	0.71	0.71	
inter-quartile range (Q1-Q3)	0.55 to 0.88	0.56 to 0.86	-
MMP-9			
MMP-9 (matrix metalloproteinase-9) of participants was measured on individual level at baseline visit via collection of venous blood samples and quantification in serum			
Units: ng/ml			
median	1575	1443	
inter-quartile range (Q1-Q3)	949 to 2179	964 to 1887	-
Systolic Blood Pressure			
Arterial Systolic Blood Pressure of participants was measured on individual level at baseline visit via a sphygmomanometric cuff at the right upper arm			
Units: mmHg			
median	139	138	
inter-quartile range (Q1-Q3)	128 to 150	125 to 156	-

Diastolic Blood Pressure			
Arterial Diastolic Blood Pressure of participants was measured on individual level at baseline visit via a sphygmomanometric cuff at the right upper arm			
Units: mmHg			
median	79	79.5	
inter-quartile range (Q1-Q3)	72 to 86	73 to 88.5	-
Heart Rate			
Heart Rate of participants was measured on individual level at baseline visit via a 12-lead electrocardiogramm			
Units: beets per minute			
median	90	78.5	
inter-quartile range (Q1-Q3)	77.5 to 99.5	71 to 90	-
AIx			
AIx (Augmentation Index) of participants was measured on individual level at baseline visit via applanation tonometry at the radial artery of the right arm			
Units: percent			
median	23	27	
inter-quartile range (Q1-Q3)	19 to 33	17 to 36	-
RHI			
RHI (Reactive Hyperemia Index) of participants was measured on individual level at baseline visit via the validated plethysmographic Endopat device at patients right arm			
Units: index			
median	1.56	1.64	
inter-quartile range (Q1-Q3)	1.38 to 2.32	1.46 to 2	-
PWV			
PWV (carotid-femoral pulse wave velocity) of participants was measured on individual level at baseline visit via ECG-gated applanation tonometry at the right carotid and femoral artery			
Units: m/s			
median	9.7	9.8	
inter-quartile range (Q1-Q3)	8.4 to 11.2	8.05 to 11.05	-

End points

End points reporting groups

Reporting group title	Roflumilast arm

Reporting group description:

After Randomization patients from the Roflumilast arm received the study medication (IMP: Roflumilast, 500µg, once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Roflumilast arm were equivalent to the Placebo arm.

Reporting group title	Placebo arm

Reporting group description:

After Randomization patients from the Placebo arm received Placebo (once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Placebo arm were equivalent to the Placebo arm.

Primary: Change in Pulse Wave Velocity between Baseline and Final Visit

End point title	Change in Pulse Wave Velocity between Baseline and Final Visit

End point description:

Difference in the change of log Pulse Wave Velocity between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Primary

End point timeframe:

Measurement of Pulse Wave Velocity was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: m/s				
least squares mean (confidence interval 95%)	1.07 (0.98 to 1.17)	0.99 (0.91 to 1.08)		

Statistical analyses

Statistical analysis title	Intergroup comparison of primary endpoint

Statistical analysis description:

Primary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of cf-PWV from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of cf-PWV the analysis were calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 5
Method	ANCOVA

Secondary: change from baseline RHI

End point title	change from baseline RHI

End point description:

Difference in the change of Reactive Hyperemia Index between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Reactive Hyperemia Index was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: units				
least squares mean (confidence interval 95%)	0.99 (0.88 to 1.11)	1.02 (0.91 to 1.15)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of RHI from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of RHI the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: change from baseline AIx

End point title	change from baseline AIx

End point description:

Difference in the change of Augmentation Index between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Augmentation Index was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: percent				
least squares mean (confidence interval 95%)	-1.11 (-5.33 to 3.11)	-1.99 (-6.12 to 2.14)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of AIx from final visit for baseline as well as for GOLD stage. Due to a normal distribution of AIx the analysis was calculated unlogarythmised, resulting in an absolute difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline MMP-9

End point title	Change from baseline MMP-9

End point description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of MMP-9 from final visit for baseline as well as for GOLD stage. Due to a normal distribution of AIx the analysis was calculated unlogarythmised, resulting in an absolute difference.

End point type	Secondary

End point timeframe:

Measurement of Matrix Metalloproteinase-9 was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: ng/ml				
least squares mean (confidence interval 95%)	-143 (-370 to 84.6)	-77 (-301 to 146)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of MMP-9 from final visit for baseline as well as for GOLD stage. Due to a normal distribution of MMP-9 the analysis was calculated unlogarythmised, resulting in an absolute difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline ADMA

End point title	Change from baseline ADMA

End point description:

Difference in the change of Asymmetric Dimethyarginine between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Asymmetric Dimethyarginine was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: µmol/l				
least squares mean (confidence interval 95%)	0.97 (0.88 to 1.06)	0.91 (0.83 to 1)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of ADMA from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of ADMA the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline TNF-alpha

End point title	Change from baseline TNF-alpha

End point description:

Difference in the change of Tumor Necrosis Factor-alpha between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Tumor Necrosis Factor-alpha was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: pg/ml				
least squares mean (confidence interval 95%)	0.95 (0.82 to 1.08)	1.06 (0.92 to 1.22)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of TNF-alpha from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of TNF-alpha the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline IL-6

End point title	Change from baseline IL-6

End point description:

Difference in the change of Interleukin-6 between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Interleukin-6 was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: pg/ml				
least squares mean (confidence interval 95%)	1.22 (1.01 to 1.47)	1.03 (0.85 to 1.25)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of IL-6 from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of IL-6 the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline CRP

End point title	Change from baseline CRP

End point description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of CRP from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of CRP the analysis was calculated under a log-scale, resulting in percentage difference.

End point type	Secondary

End point timeframe:

Measurement of C-reactive Protein was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: mg/dl				
least squares mean (confidence interval 95%)	0.83 (0.63 to 1.1)	1.21 (0.92 to 1.6)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of CRP from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of CRP the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline FEV1

End point title	Change from baseline FEV1

End point description:

Difference in the change of FEV1 between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of Forced Espiratory Volume in 1 Seocnd was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: % predicted				
least squares mean (confidence interval 95%)	1.02 (0.96 to 1.08)	1.01 (0.96 to 1.07)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of FEV1 from final visit for baseline as well as for GOLD stage. Due to a right-skewed distribution of FEV1 the analysis was calculated under a log-scale, resulting in percentage difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline 6MWT

End point title	Change from baseline 6MWT

End point description:

Difference in the change of 6-Minute Walk Test between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of 6-Minute Walk Test was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: meter				
least squares mean (confidence interval 95%)	59.2 (18.3 to 100)	0.69 (-39.7 to 42.1)		

Statistical analyses

Statistical analysis title	Change from baseline 6MWT

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of 6MWT from final visit for baseline as well as for GOLD stage. Due to a normal distribution of 6MWT the analysis was calculated unlogarythmised, resulting in an absolute difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Change from baseline CAT

End point title	Change from baseline CAT

End point description:

Difference in the change of CAT between the study groups (Roflumilast versus Placebo) after the 24 weeks study period

End point type	Secondary

End point timeframe:

Measurement of COPD Assessment Test was conducted firstly at the intial visit (following randomisation) and secondly after a study period of 24 weeks

End point values	Roflumilast arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: points				
least squares mean (confidence interval 95%)	0.42 (-1.36 to 2.19)	1.2 (-0.57 to 2.98)		

Statistical analyses

Statistical analysis title	Intergroup comparison of secondary endpoint

Statistical analysis description:

Secondary endpoint was calculated via analysis of covariance (ANCOVA) with adjustment of the intergroup comparison of CAT from final visit for baseline as well as for GOLD stage. Due to a normal distribution of CAT the analysis was calculated unlogarythmised, resulting in an absolute difference.

Comparison groups	Roflumilast arm v Placebo arm
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported during the 24 weeks active study phase starting with randomization and ending with the final visit.

Adverse event reporting additional description:

Adverse events were collected routinely during every study visit. Moreover, patients were instructed to appraise the study team about potential adverse events intermittently via phone calls.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Roflumilast arm

Reporting group description:

After Randomization patients from the Roflumilast arm received the study medication (IMP: Roflumilast, 500µg, once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Roflumilast arm were equivalent to the Placebo arm.

Reporting group title	Placebo arm

Reporting group description:

After Randomization patients from the Placebo arm received Placebo (once daily, oral administration) in a double-blinded manner for a period of 24 weeks. Apart from the study medication, study related procedures in Placebo arm were equivalent to the Placebo arm.

Serious adverse events	Roflumilast arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 40 (32.50%)	9 / 40 (22.50%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic macroangiopathy			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death	Additional description: death of unknown etiology (pat was found dead at home)		
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polypectomy			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
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			
Bronchoscopic lung volume reduction			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			

subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchoscopy	Additional description: Assessment of previously diagnosed bronchiectasis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic coma			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 40 (7.50%)	5 / 40 (12.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: Acute exacerbation of COPD		
subjects affected / exposed	5 / 40 (12.50%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (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: 0 %

Non-serious adverse events	Roflumilast arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 40 (67.50%)	22 / 40 (55.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	

Nausea			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Weight decreased			
subjects affected / exposed	6 / 40 (15.00%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Appetite disorder	Additional description: Loss of appetite		
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Pulmonary embolism			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease	Additional description: acute exacerbation of COPD		
subjects affected / exposed	14 / 40 (35.00%)	16 / 40 (40.00%)	
occurrences (all)	19	24	
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue			

disorders			
Convulsions local	Additional description: Muscular cramps of the upper or lower extremities		
subjects affected / exposed	4 / 40 (10.00%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Infections and infestations			
Influenza like illness			
subjects affected / exposed	5 / 40 (12.50%)	4 / 40 (10.00%)	
occurrences (all)	6	6	
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported