EU Clinical Trials Register

Clinical trial results:
A 16-Week, Randomized, Placebo-Controlled, Double Blind, and Parallel Group Trial to Assess the Anti-Inflammatory Effects of Roflumilast in Chronic Obstructive Pulmonary Disease.
The ROBERT Study
(Roflumilast Biopsy European Research Trial)

Summary

EudraCT number	2011-000582-13
Trial protocol	DE GB SE PL DK
Global end of trial date	11 February 2016

Results information

Result version number	v1 (current)
This version publication date	08 February 2017
First version publication date	08 February 2017

Trial information

Trial identification

Sponsor protocol code	RO-2455-402-RD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01509677
WHO universal trial number (UTN)	-
Other trial identifiers	Register Identifier: U1111-1155-8767

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	1800 Concord Pike, PO Box 15437, Wilmington, United States, DE 19850
Public contact	AstraZeneca Clinical Study Information Center, AstraZeneca, 001 18772409479 x, information.center@astrazeneca.com
Scientific contact	AstraZeneca Clinical Study Information Center, AstraZeneca, 001 18772409479 x, information.center@astrazeneca.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	24 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2016
Global end of trial reached?	Yes
Global end of trial date	11 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of roflumilast 500 µg tablets once daily versus placebo on inflammation parameters in bronchial biopsy tissue specimen.

Protection of trial subjects:

SABA or SAMA could be used as rescue medication according to the individual needs of a patient.

Background therapy:

Therapy consisting of any bronchodilator such as SABA, SAMA, LABA, or LAMA starting at least 6 weeks prior to V0 was allowed. The treatment had to remain stable in the course of the whole study, that is, 6 weeks of single-blind placebo administration (run-in) and 16 weeks of double-blind treatment period.

Evidence for comparator: -

Actual start date of recruitment	04 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	United Kingdom: 61
Worldwide total number of subjects	158
EEA total number of subjects	158

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)	83
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

N=281

Pre-assignment period milestones

Number of subjects started	281[1]
Number of subjects completed	158

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 123

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: According to the CSR, 296 subject where screened, of these 15 subjects were re-enrolled in the study. This gives us 281 unique patients.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	R500

Arm description:

Roflumilast 500 µg

Arm type	Experimental
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

500 µg tablet once daily, oral administration

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

tablet, once daily, oral administration

Number of subjects in period 1	R500	Placebo
Started	79	79
Completed	76	73
Not completed	3	6
Consent withdrawn by subject	-	3
Adverse event, non-fatal	3	3

Baseline characteristics

Reporting groups

Reporting group title	R500
Reporting group description:	
Roflumilast 500 µg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	R500	Placebo	Total
Number of subjects	79	79	158
Age categorical			
Units: Subjects			
Adults (18-64 years)	37	46	83
65 years and over	42	33	75
Age Continuous |			
Units: Years			
arithmetic mean	64	62.5	
standard deviation	± 8.23	± 8.43	-
Gender, Male/Female			
Units: Participants			
Female	19	18	37
Male	60	61	121
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	1	1
Black or African American	1	0	1
White	77	77	154
Other	1	1	2
Age, Customized			
Units: Subjects			
Between 18 and 65 years	37	46	83
>=65 years	42	33	75
Region of Enrollment			
Units: Subjects			
Europe	79	79	158

End points

End points reporting groups

Reporting group title	R500
Reporting group description:	
Roflumilast 500 µg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: Number of CD8+ inflammatory cells in bronchial biopsy tissue.

End point title	Number of CD8+ inflammatory cells in bronchial biopsy

End point description:

End point type	Primary

End point timeframe:

16 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses colected.

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
arithmetic mean (standard deviation)	442.4 (± 312.74)	427.1 (± 261.42)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of CD8+ inflammatory cells in bronchial biopsy tissue

End point title	Number of CD8+ inflammatory cells in bronchial biopsy tissue

End point description:

End point type	Primary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
arithmetic mean (standard deviation)	13.4 (± 302.69)	29.4 (± 298.88)		

Statistical analyses

Statistical analysis title	Number of CD8+ inflammatory cells
Statistical analysis description:	
2-sided test at 5% significant level	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7922
Method	Poisson regression model

Secondary: CD68+ Count in Biopsied Material (submucosa)

End point title	CD68+ Count in Biopsied Material (submucosa)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
arithmetic mean (standard deviation)	149.1 (± 113.91)	124.4 (± 93.15)		

Statistical analyses

Statistical analysis title	CD68+ Cell count
Statistical analysis description:	
2-sided, 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7145
Method	Poisson regression model

Secondary: CD68+ Cell Count in Biopsied Material (submucosa): Poisson regression (ratio)

End point title	CD68+ Cell Count in Biopsied Material (submucosa): Poisson regression (ratio)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	126.8	121.6		

Statistical analyses

Statistical analysis title	CD68+ Cell count (ratio)
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 7136
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.119

Secondary: Change from V2 to V6 in CD68+ Cell Count in Biopsied Material (submucosa) (ITT)

End point title	Change from V2 to V6 in CD68+ Cell Count in Biopsied Material (submucosa) (ITT)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Cells/mm^2				
least squares mean (standard error)	6.1 (± 10.99)	-5.3 (± 11.05)		

Statistical analyses

Statistical analysis title	Change from V2 to V6 in CD68+ Cell count
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4606
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.2
upper limit	42.1
Variability estimate	Standard error of the mean
Dispersion value	15.45

Secondary: CD4+ Cell Counts in biopsied Material (submucosa)

End point title	CD4+ Cell Counts in biopsied Material (submucosa)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	304.6	255		

Statistical analyses

Statistical analysis title	CD4+ Cell Counts in biopsied Material

Statistical analysis description:

2-sided 5% test

Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2744
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	0.194

Secondary: CD45+ Cell Counts in biopsied Material (submucosa)

End point title	CD45+ Cell Counts in biopsied Material (submucosa)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	818.4	960.3		

Statistical analyses

Statistical analysis title	CD45+ Cell counts in biopsied Material
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1128
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.086

Secondary: Neutrophils Cell Counts in biopsied Material (submucosa)

End point title	Neutrophils Cell Counts in biopsied Material (submucosa)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	118.6	127.7		

Statistical analyses

Statistical analysis title	Nuetrophils cell count in biopsied material
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.31
Variability estimate	Standard error of the mean
Dispersion value	0.164

Secondary: CD8+ Cell Count in biopsied material (Bronchial Epithelium)

End point title	CD8+ Cell Count in biopsied material (Bronchial Epithelium)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	422.1	505.3		

Statistical analyses

Statistical analysis title	CD8+ cell count (bronchial epithelium)
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0677
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.01
Variability estimate	Standard error of the mean
Dispersion value	0.082

Secondary: CD68+ Cell Count in biopsied material (Bronchial Epithelium)

End point title	CD68+ Cell Count in biopsied material (Bronchial Epithelium)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Cells/mm^2				
number (not applicable)	76.3	93.1		

Statistical analyses

Statistical analysis title	CD68+ cell count (bronchial epithelium)
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3566
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.25
Variability estimate	Standard error of the mean
Dispersion value	0.177

Secondary: Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Neutrophils)

End point title	Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Neutrophils)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: 10^6/mL				
least squares mean (standard error)	1.7181 (± 1.64471)	0.0827 (± 1.6122)		

Statistical analyses

Statistical analysis title	V1 to V5 in Absolute cell count (Neutrophils)
Statistical analysis description:	
2 sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4794
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.6354
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9429
upper limit	6.2137

Variability estimate	Standard error of the mean
Dispersion value	2.30185

Secondary: Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Macrophages)

End point title	Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Macrophages)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: 10^6/mL				
least squares mean (standard error)	0.1017 (± 0.23396)	-0.371 (± 0.2297)		

Statistical analyses

Statistical analysis title	V1 to V5 in Absolute Cell count (Macrophages)

Statistical analysis description:

2 sided 5% test

Comparison groups	R500 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1541
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4727
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.181
upper limit	1.1264
Variability estimate	Standard error of the mean
Dispersion value	0.32866

Secondary: Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Eosinophils)

End point title	Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Eosinophils)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: 10^6/mL				
least squares mean (standard error)	-0.0986 (± 0.02639)	-0.036 (± 0.02585)		

Statistical analyses

Statistical analysis title	V1 to V5 in Absolute Cell count (Eosinophils)

Statistical analysis description:

2 sided 5% test

Comparison groups	R500 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0927
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.0626
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1358
upper limit	0.0106
Variability estimate	Standard error of the mean
Dispersion value	0.03681

Secondary: Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Lymphocytes)

End point title	Change from V1 to V5 in Absolute Cell Count inInduced Sputum (10^6/mL): Between-Treatment Difference (Lymphocytes)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: 10^6/mL				
least squares mean (standard error)	-0.0167 (± 0.01167)	0.006 (± 0.01141)		

Statistical analyses

Statistical analysis title	V1 to V5 in Absolute Cell count (Lymphocetes)
Statistical analysis description:	
2 sided 5% test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5175
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.0107
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0435
upper limit	0.022
Variability estimate	Standard error of the mean
Dispersion value	0.01647

Secondary: Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Neutrophils)

End point title	Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Neutrophils)

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: 10^6/mL				
least squares mean (standard error)	2.527 (± 2.3571)	0.382 (± 2.3535)		

Statistical analyses

Statistical analysis title	V1 to V5 in Differential Cell count (Neutrophils)
Statistical analysis description:	
2-sided 5 % test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5205
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.466
upper limit	8.757
Variability estimate	Standard error of the mean
Dispersion value	3.3253

Secondary: Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Macrophages)

End point title	Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Macrophages)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: 10^6/mL				
least squares mean (standard error)	0.315 (± 2.1328)	-0.826 (± 2.1316)		

Statistical analyses

Statistical analysis title	V1 to V5 in Differential Cell count (Macrophages)
Statistical analysis description:	
2-sided 5 % test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7052
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.835
upper limit	7.117
Variability estimate	Standard error of the mean
Dispersion value	3.0057

Secondary: Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Eosinophils)

End point title	Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Eosinophils)
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: 10^6/mL				
least squares mean (standard error)	-1.826 (± 0.5214)	0.041 (± 0.52)		

Statistical analyses

Statistical analysis title	V1 to V5 in Differential Cell count (Eosinophils)
Statistical analysis description: 2-sided 5 % test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.324
upper limit	-0.409
Variability estimate	Standard error of the mean
Dispersion value	0.7331

Secondary: Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Lymphocytes)

End point title	Change from V1 to V5 in Differential Cell Count in Induced Sputum(10^6/mL) (Lymphocytes)
End point description:	
End point type	Secondary
End point timeframe: 16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	44		
Units: 10^6/mL				
least squares mean (standard error)	-0.137 (± 0.1332)	-0.086 (± 1.329)		

Statistical analyses

Statistical analysis title	V1 to V5 in Differential Cell count (Lymphocytes)
Statistical analysis description:	
2-sided 5 % test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7862
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.423
upper limit	0.321
Variability estimate	Standard error of the mean
Dispersion value	0.1871

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (alfa- 2-Macroglobulin (µg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (alfa- 2-Macroglobulin (µg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	57		
Units: µg/mL				
least squares mean (standard error)	-0.32 (± 0.73)	-0.48 (± 0.7)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of alfa-2-Macroglobulin
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8769
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	2.15
Variability estimate	Standard error of the mean
Dispersion value	1.005

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (IL-8 (pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (IL-8 (pg/mL))

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	56		
Units: pg/mL				
least squares mean (standard error)	-827.3 (± 1995.79)	-1538.4 (± 1941.08)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of IL-8

Statistical analysis description:

2-sided 5% test

Comparison groups	R500 v Placebo

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7978
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	711.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4778.3
upper limit	6200.5
Variability estimate	Standard error of the mean
Dispersion value	2768.79

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (MMP type 9 (ng/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (MMP type 9 (ng/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: ng/mL				
least squares mean (standard error)	80.1 (± 57.07)	-8.4 (± 55.44)		

Statistical analyses

Statistical analysis title	Change from Base of conc of MMP type 9
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2669
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	88.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.6
upper limit	245.6
Variability estimate	Standard error of the mean
Dispersion value	79.26

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (MCP-1 (pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (MCP-1 (pg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	57		
Units: pg/mL				
least squares mean (standard error)	-95.2 (± 49.23)	-69.3 (± 46.93)		

Statistical analyses

Statistical analysis title	Change from Base of conc MCP-1
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7033
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-25.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-160.3
upper limit	108.5
Variability estimate	Standard error of the mean
Dispersion value	67.78

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (TIMP-1 (ng/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (TIMP-1 (ng/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	57		
Units: ng/mL				
least squares mean (standard error)	25.87 (± 13.085)	-1.92 (± 12.551)		

Statistical analyses

Statistical analysis title	Change from Base of conc of TIMP-1
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1264
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	27.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.97
upper limit	63.55
Variability estimate	Standard error of the mean
Dispersion value	18.039

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (VEGF (pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Induced Sputum: Primary Parameters of interest (FAS) (VEGF (pg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: pg/mL				
least squares mean (standard error)	253.1 (± 89.46)	-43.7 (± 86.84)		

Statistical analyses

Statistical analysis title	Change from Base of conc. VEGF
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	296.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.9
upper limit	542.7
Variability estimate	Standard error of the mean
Dispersion value	124.07

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (alfa-2-Macroglobulin (µg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (alfa-2-Macroglobulin (µg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: µg/mL				
least squares mean (standard error)	-0.05 (± 0.061)	-0.05 (± 0.062)		

Statistical analyses

Statistical analysis title	Change from Base of conc of alfa-2-Macroglobulin
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9989
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.086

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (IL-8 (pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (IL-8 (pg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: pg/mL				
least squares mean (standard error)	-4.48 (± 0.929)	-3.92 (± 0.945)		

Statistical analyses

Statistical analysis title	Change from Base of conc IL-8
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6701
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.15
upper limit	2.03
Variability estimate	Standard error of the mean
Dispersion value	1.309

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (MMP type 9 (ng/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (MMP type 9 (ng/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: ng/mL				
least squares mean (standard error)	0.8 (± 0.78)	-1 (± 0.79)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of MMP type 9
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1105
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	1.1

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (MCP-1(pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (MCP-1(pg/mL))

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: pg/mL				
least squares mean (standard error)	-24.8 (± 11)	-23.4 (± 11.21)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of MCP-1

Statistical analysis description:

2-sided 5% test

Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9261
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.4
upper limit	29.5
Variability estimate	Standard error of the mean
Dispersion value	15.62

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (TIMP-1(ng/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (TIMP-1(ng/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: ng/mL				
least squares mean (standard error)	2.7 (± 3.19)	-7.5 (± 3.25)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of TIMP-1
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0257
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	19
Variability estimate	Standard error of the mean
Dispersion value	4.49

Secondary: Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (VEGF(pg/mL))

End point title	Change from baseline of Concentration of Inflammatory Biomarkers in Blood Serum: Primary Parameters of interest (FAS) (VEGF(pg/mL))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	66		
Units: pg/mL				
least squares mean (standard error)	11.3 (± 12.8)	-21.5 (± 13.08)		

Statistical analyses

Statistical analysis title	Change from Base of conc. of VEGF
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0728
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	32.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	168.6
Variability estimate	Standard error of the mean
Dispersion value	18.11

Secondary: Change from baseline in lung function variables: Between-Treatment Differences (FAS) (FEV1 (L))

End point title	Change from baseline in lung function variables: Between-Treatment Differences (FAS) (FEV1 (L))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: Litres				
least squares mean (standard error)	0.028 (± 0.0212)	-0.035 (± 0.0212)		

Statistical analyses

Statistical analysis title	Change from base in lung function var (FEV1)
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.122
Variability estimate	Standard error of the mean
Dispersion value	0.03

Secondary: Change from baseline in lung function variables: Between-Treatment Differences (FAS) (FVC (L))

End point title	Change from baseline in lung function variables: Between-Treatment Differences (FAS) (FVC (L))
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: Litres				
least squares mean (standard error)	0.031 (± 0.0391)	-0.033 (± 0.391)		

Statistical analyses

Statistical analysis title	Change from base in lung function var: (FVC)
Statistical analysis description:	
2-sided 5% test	
Comparison groups	R500 v Placebo

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2482
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.173
Variability estimate	Standard error of the mean
Dispersion value	0.0552

Secondary: Wicoxon Signed-rank test for Change from V2 to V6 in FEV1/FVC: Within Treatment Difference

End point title	Wicoxon Signed-rank test for Change from V2 to V6 in FEV1/FVC: Within Treatment Difference
End point description:	
End point type	Secondary
End point timeframe:	
16 weeks	

End point values	R500	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	77		
Units: percentage				
number (confidence interval 95%)	0.5 (0 to 1)	-0.5 (-1 to 0.5)		

Statistical analyses

Statistical analysis title	Mann-Whitney U-test V2 to V6 in FEV1/FVC
Statistical analysis description:	
2 sided 5 % test	
Comparison groups	R500 v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2629
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann point estimate
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
24 weeks	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	R500
Reporting group description:	
Roflumilast 500 µg	

Serious adverse events	Placebo	R500	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 79 (6.33%)	8 / 79 (10.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
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			

Hydrocele			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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			
Incarcerated hernia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Spermatocele			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
COPD			
subjects affected / exposed	1 / 79 (1.27%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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	0 / 79 (0.00%)	1 / 79 (1.27%)	
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			
Synovial cyst			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (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: 2 %

Non-serious adverse events	Placebo	R500	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 79 (72.15%)	66 / 79 (83.54%)	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	3 / 79 (3.80%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
Weight decreased			
subjects affected / exposed	2 / 79 (2.53%)	6 / 79 (7.59%)	
occurrences (all)	2	6	
White blood cell count increased			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			

Laceration			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Procedural pain			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
Haedache			
subjects affected / exposed	3 / 79 (3.80%)	4 / 79 (5.06%)	
occurrences (all)	3	4	
Lethargy			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	4	
Tremor			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 79 (3.80%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 79 (5.06%)	11 / 79 (13.92%)	
occurrences (all)	4	11	
Dry mouth			
subjects affected / exposed	3 / 79 (3.80%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	1 / 79 (1.27%)	6 / 79 (7.59%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	2 / 79 (2.53%)	5 / 79 (6.33%)	
occurrences (all)	2	5	

Respiratory, thoracic and mediastinal disorders			
Bronchial polyp			
subjects affected / exposed	2 / 79 (2.53%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
COPD			
subjects affected / exposed	12 / 79 (15.19%)	9 / 79 (11.39%)	
occurrences (all)	13	10	
Cough			
subjects affected / exposed	12 / 79 (15.19%)	10 / 79 (12.66%)	
occurrences (all)	12	11	
Dyspnoea			
subjects affected / exposed	1 / 79 (1.27%)	3 / 79 (3.80%)	
occurrences (all)	1	3	
Haemoptysis			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	4	
Productive cough			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	3 / 79 (3.80%)	1 / 79 (1.27%)	
occurrences (all)	3	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 79 (2.53%)	7 / 79 (8.86%)	
occurrences (all)	2	7	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 79 (2.53%)	5 / 79 (6.33%)	
occurrences (all)	2	5	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	

Muscle spasms			
subjects affected / exposed	2 / 79 (2.53%)	2 / 79 (2.53%)	
occurrences (all)	2	2	
Myalgia			
subjects affected / exposed	0 / 79 (0.00%)	3 / 79 (3.80%)	
occurrences (all)	0	5	
Pain in extremity			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Synovial cyst			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Infections and infestations			
Eye infection			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	12 / 79 (15.19%)	13 / 79 (16.46%)	
occurrences (all)	15	14	
Rhinitis			
subjects affected / exposed	3 / 79 (3.80%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	0 / 79 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			

Decreased appetite		
subjects affected / exposed	1 / 79 (1.27%)	2 / 79 (2.53%)
occurrences (all)	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2012	Incl AM 5
06 November 2012	9
30 November 2012	Incl Am 5, 9
23 May 2013	Incl Am 5, 9, 10
06 October 2014	Incl all amendments
21 May 2015	Incl. all amendments AM 12

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported