

**Clinical trial results:****A Phase 2, Randomized, Double-Blind, 4-week Crossover Trial to Investigate the Effect of a Once-Daily Combination of 500 g Roflumilast Plus 10 mg Montelukast vs 10 mg Montelukast Alone on Pulmonary Function, Asthma Symptoms, and Inflammatory Markers in Subjects With Severe Asthma Not Adequately Controlled With a Combination of at Least Medium Dose Inhaled Corticosteroids and Long-Acting Beta Agonists Maintenance Therapy****Summary**

EudraCT number	2012-002064-27
Trial protocol	DE HU
Global end of trial date	24 October 2013

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	05 August 2015

Trial information**Trial identification**

Sponsor protocol code	ROF-ASTHMA_202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01765192
WHO universal trial number (UTN)	U1111-1132-3160

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Europe, Ltd.
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Medical Director , Takeda Development Center Europe, Ltd., +001 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director , Takeda Development Center Europe, Ltd., +001 877-825-3327, 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	24 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2013
Global end of trial reached?	Yes
Global end of trial date	24 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the effect of roflumilast 500 µg once daily (QD) plus montelukast 10 mg QD versus 10 mg montelukast QD alone on predose (trough) prebronchodilator forced expiratory volume in the first second (FEV1).

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	15 February 2013
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	Germany: 20
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	South Africa: 27
Worldwide total number of subjects	64
EEA total number of subjects	37

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)	54
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 12 investigative sites in Germany, Hungary, and South Africa from 15 February 2013 to 24 October 2013.

Pre-assignment

Screening details:

Participants with a historical diagnosis of severe asthma who were inadequately controlled while receiving a combination of at least medium dose inhaled corticosteroids and long-acting beta agonists maintenance therapy were enrolled in 1 of 2 treatment sequences, 500 µg roflumilast plus 10 mg montelukast once daily (QD) or 10 mg montelukast QD.

Period 1

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

Blinding implementation details:

Blinding was maintained using the interactive voice response system (IVRS), which could be accessed by the investigator or designee in an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast

Arm description:

Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	Daxas, Daliresp
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 µg once daily (QD)

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	Singulair, Pluralair
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily (QD)

Arm title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
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Arm description:

Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.

Arm type	Active comparator
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Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	Singulair, Pluralair
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg once daily (QD)	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Placebo once daily (QD)	

Number of subjects in period 1	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Started	32	32
Completed	32	31
Not completed	0	1
Adverse event, non-fatal	-	1

Period 2	
Period 2 title	Washout period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Arm description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Arm description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Started	32	31
Completed	30	30
Not completed	2	1
Reason not specified	1	-
Voluntary withdrawal	1	1

Period 3

Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Blinding was maintained using the interactive voice response system (IVRS), which could be accessed by the investigator or designee in an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast

Arm description:

Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	Singulair, Pluralair
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily (QD)

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

Dosage and administration details:

Placebo once daily (QD)

Arm title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
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Arm description:

Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks

followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	Singulair, Pluralair
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily (QD)

Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	Daxas, Daliresp
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 µg once daily (QD)

Number of subjects in period 3	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Started	30	30
Completed	30	28
Not completed	0	2
Reason not specified	-	2

Period 4

Period 4 title	End of treatment period 2 to final visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast

Arm description:

Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
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Arm description:

Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg

orally once daily for 4 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Started	30	28
Completed	30	27
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
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Reporting group description:

Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.

Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
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Reporting group description:

Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.

Reporting group values	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast	Total
Number of subjects	32	32	64
Age categorical			
Units: Subjects			
< 65 years	27	27	54
≥ 65 years	5	5	10
Age continuous			
Units: years			
arithmetic mean	50.3	50	-
standard deviation	± 13.8	± 14.1	-
Gender categorical			
Units: Subjects			
Female	21	20	41
Male	11	12	23
Country of enrollement			
Units: Subjects			
Germany	8	12	20
South Africa	16	11	27
Hungary	8	9	17
Race/Ethnicity			
Units: Subjects			
White	29	32	61
Black or African American	3	0	3
Smoking Classification			
Units: Subjects			
Participant has never smoked	22	21	43
Participant is a current smoker	0	0	0
Participant is an ex-smoker	10	11	21
Body Mass Index (BMI)			
Units: kilogram/metre ²			
arithmetic mean	29.53	30.06	-
standard deviation	± 7.105	± 5.605	-
Height			
Units: centimetre(s)			

arithmetic mean	163.7	168.3	
standard deviation	± 8.47	± 10.68	-
Weight			
Units: kilograms			
arithmetic mean	79.06	85.16	
standard deviation	± 18.708	± 17.491	-

End points

End points reporting groups

Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Reporting group description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Reporting group description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Reporting group description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Reporting group description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Reporting group description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Reporting group description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Reporting group description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Reporting group description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Roflumilast Plus Montelukast, Then Placebo Plus Montelukast
Reporting group description: Participants in sequence 1 received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received placebo plus montelukast 10 mg orally once daily for 4 weeks.	
Reporting group title	Placebo Plus Montelukast, Then Roflumilast Plus Montelukast
Reporting group description: Participants in sequence 2 received placebo plus montelukast 10 mg orally once daily for 4 weeks followed by a 4-week washout period and then received roflumilast 500 µg plus montelukast 10 mg orally once daily for 4 weeks.	
Subject analysis set title	Roflumilast Plus Montelukast
Subject analysis set type	Full analysis
Subject analysis set description: Participants received roflumilast 500 µg plus montelukast 10 mg once daily for 4 weeks.	
Subject analysis set title	Placebo Plus Montelukast
Subject analysis set type	Full analysis
Subject analysis set description: Participants received placebo plus montelukast 10 mg once daily for 4 weeks.	

Primary: Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)

End point title	Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced Expiratory Volume in 1 Second (FEV1)
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End point description:

FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEV1 will be measured using spirometry in accordance with the American Thoracic Society / European Respiratory Society (ATS/ERS) consensus guidelines. An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline FEV1 measurement as the covariate was used for analysis.

End point type	Primary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	61		
Units: litre(s)				
least squares mean (standard error)	0.18 (± 0.028)	0.08 (± 0.027)		

Statistical analyses

Statistical analysis title	Change from Baseline in FEV1
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Statistical analysis description:

The primary endpoint was analyzed using an analysis of covariance model adapted for the crossover design. The following fixed factors and covariates were included in the model: Treatment, sequence, period, and baseline FEV1 measurement of the respective treatment period. The reported analysis results are for the 2 crossover treatment periods combined.

Comparison groups	Placebo Plus Montelukast v Roflumilast Plus Montelukast
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0219
upper limit	0.1795
Variability estimate	Standard error of the mean
Dispersion value	0.039

Secondary: Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced

Vital Capacity (FVC)

End point title	Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced Vital Capacity (FVC)
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End point description:

FVC is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC will be measured using spirometry in accordance with ATS/ERS consensus guidelines. An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline FVC measurement as the covariate was used for analysis.

End point type	Secondary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	61		
Units: liters				
least squares mean (standard error)	0.12 (\pm 0.029)	0.06 (\pm 0.027)		

Statistical analyses

Statistical analysis title	Change from Baseline to Week 4 in FVC
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Statistical analysis description:

An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline FVC measurement as the covariate was used for analysis.

Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129 ^[1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0185
upper limit	0.1422
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[1] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline pre-bronchodilator FVC measurement as the covariate.

Secondary: Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced Expiratory Flow (FEF) 25-75%

End point title	Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Forced Expiratory Flow (FEF) 25-75%
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End point description:

FEF is a measure of how much air can be exhaled from the lungs. It is an indicator of obstruction of the smaller airways. FEF25-75% is the mid-flow rate or forced expiratory flow occurring in the middle 50% of the patient's exhaled volume, and will be measured using spirometry in accordance with ATS/ERS consensus guidelines. An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline FEF measurement as the covariate was used for analysis.

End point type	Secondary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	55		
Units: liters/second				
least squares mean (standard error)	0.23 (± 0.039)	0.11 (± 0.039)		

Statistical analyses

Statistical analysis title	Change from Baseline in FEF
Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 ^[2]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0113
upper limit	0.2364
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

[2] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline pre-bronchodilator FEF measurement as the covariate.

Secondary: Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Peak Expiratory Flow (PEF)

End point title	Change From Baseline in Pre-dose (Trough) Pre-bronchodilator Peak Expiratory Flow (PEF)
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End point description:

PEF is a person's maximum speed of expiration. It measures the airflow through the bronchi and thus the degree of obstruction in the airways. PEF will be measured using spirometry in accordance with ATS/ERS consensus guidelines. An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline PEF measurement as the covariate was used for analysis.

End point type	Secondary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	58	61		
Units: liters/minute (L/min)				
least squares mean (standard error)	15.05 (\pm 10.616)	7.85 (\pm 10.401)		

Statistical analyses

Statistical analysis title	Change from Baseline in PEF
Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.635 ^[3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	7.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.0531
upper limit	37.466
Variability estimate	Standard error of the mean
Dispersion value	15.105

Notes:

[3] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline pre-bronchodilator PEF measurement as the covariate.

Secondary: Change From Baseline in Morning Peak Expiratory Flow (PEF)

End point title	Change From Baseline in Morning Peak Expiratory Flow (PEF)
End point description:	PEF will be measured at home using portable electronic peak flow meter. The participant will record PEF daily in the morning immediately after getting up. An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline PEF measurement as the covariate was used for analysis.
End point type	Secondary
End point timeframe:	Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	61		
Units: L/min				
least squares mean (standard error)	20.85 (\pm 3.708)	7.23 (\pm 3.646)		

Statistical analyses

Statistical analysis title	Change from Baseline in Morning PEF
Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 ^[4]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	13.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1896
upper limit	24.0553
Variability estimate	Standard error of the mean
Dispersion value	5.206

Notes:

[4] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline pre-bronchodilator PEF measurement as the covariate.

Secondary: Change From Baseline in Daytime Asthma Symptoms

End point title	Change From Baseline in Daytime Asthma Symptoms
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End point description:

Patients will assess their daily day-time asthma symptoms according to the following scale:

0: Very well, no symptoms.

1: One episode of wheezing, cough, or breathlessness.

2: More than 1 episode of wheezing, cough, or breathlessness without interference with normal activities.

3: Wheezing, cough, or short of breath most of the day which interfered to some extent with normal activities.

4: Asthma very bad. Unable to carry out daily activities, as usual.

An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline Daytime Asthma Symptoms measurement as the covariate was used for analysis. A negative change from Baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	61		
Units: units on a scale				
least squares mean (standard error)	-0.39 (\pm 0.061)	-0.18 (\pm 0.063)		

Statistical analyses

Statistical analysis title	Change from Baseline in Daytime Asthma Symptoms
Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 ^[5]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.385
upper limit	-0.0271
Variability estimate	Standard error of the mean
Dispersion value	0.089

Notes:

[5] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline Daytime Asthma Symptom Score as the covariate.

Secondary: Change From Baseline in Nighttime Asthma Symptoms

End point title	Change From Baseline in Nighttime Asthma Symptoms
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End point description:

Patients will assess their daily night-time asthma symptoms according to the following scale:

0: No symptoms, slept through the night.

1: Slept well but some complaints in the morning.

2: Woke up once because of asthma (inclusive early awakening).

3: Woke up several times because of asthma (inclusive early awakening).

4: Bad night, awake most of the night because of asthma.

An ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline Nighttime Asthma Symptoms measurement as the covariate was used for analysis. A negative change from Baseline indicates improvement.

End point type	Secondary
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End point timeframe:

Baseline (Days 1 and 56) and after 4 weeks of treatment (Days 28 and 84)

End point values	Roflumilast Plus Montelukast	Placebo Plus Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	61		
Units: units on a scale				
least squares mean (standard error)	-0.27 (\pm 0.053)	-0.17 (\pm 0.052)		

Statistical analyses

Statistical analysis title	Change from Baseline in Nighttime Asthma
Comparison groups	Roflumilast Plus Montelukast v Placebo Plus Montelukast
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.217 ^[6]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2426
upper limit	0.0563
Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

[6] - P-values were obtained using an ANCOVA model with treatment sequence, treatment period, and study treatment as fixed factors with Baseline Nighttime Asthma Symptoms measurement as the covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to the end of the study (Days 1-105)

Adverse event reporting additional description:

Safety analysis set: All randomized participants who received at least 1 dose of study drug.
Adverse events are reported for 61 and 62 participants in the roflumilast + montelukast (R+M) and placebo + montelukast (P+M) treatment groups, respectively, as 3 participants discontinued prior to receiving R+M and 2 participants discontinued prior to rec

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Roflumilast Plus Montelukast
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Reporting group description:

Participants received roflumilast 500 µg plus montelukast 10 mg once daily for 4 weeks.

Reporting group title	Placebo Plus Montelukast
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Reporting group description:

Participants received placebo plus montelukast 10 mg once daily for 4 weeks.

Serious adverse events	Roflumilast Plus Montelukast	Placebo Plus Montelukast	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	0 / 62 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Roflumilast Plus Montelukast	Placebo Plus Montelukast	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 61 (8.20%)	0 / 62 (0.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 61 (8.20%)	0 / 62 (0.00%)	
occurrences (all)	5	0	

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