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
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

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

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

Arm description:

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

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
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 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.	
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.	