Clinical trial results:
A Phase 2a, 15-Day, Randomized, Parallel Group, Double-Blind, Multi-Centre, Vehicle Controlled Trial to Assess the Efficacy and Local Safety of a Cream Containing 0.5% Roflumilast - a Phosphodiesterase Type 4 Inhibitor (PDE4i) Dermal Formulation – on Atopic Dermatitis Patients with Skin Lesions of Moderate Severity

Summary

EudraCT number	2012-003000-12
Trial protocol	DE
Global end of trial date	18 March 2014

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-DERM_203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01856764
WHO universal trial number (UTN)	U1111-1133-6455

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, Illinois, United States, 60015
Public contact	Medical Director, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Takeda, +1 877-825-3327, trialdisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2014
Global end of trial reached?	Yes
Global end of trial date	18 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of dermal 0.5% roflumilast cream formulation compared with vehicle on the reduction of atopic dermatitis (AD) lesions during 15 days of treatment in AD subjects with skin lesions of moderate severity, using the modified local SCORing Atopic Dermatitis (SCORAD) tool.

Protection of trial subjects:

This study was conducted with respect for the study subjects in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance, and all applicable local regulations. All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 3 centers in Germany from 10 June 2013 to 18 March 2014.

Pre-assignment

Screening details:

Participants with an historical diagnosis of Atopic Dermatitis were enrolled in 1 of 2 twice daily (BID) treatment groups.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	0.5% Roflumilast Cream

Arm description:

Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.

Arm type	Experimental
Investigational medicinal product name	0.5% Roflumilast Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.

Arm title	Vehicle Cream

Arm description:

Roflumilast formulation vehicle, cream, topically, twice daily for up to 15 days.

Arm type	Placebo
Investigational medicinal product name	0.5% Roflumilast Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.

Investigational medicinal product name	Vehicle Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Roflumilast formulation vehicle, cream, topically, twice daily for up to 15 days.

Number of subjects in period 1	0.5% Roflumilast Cream	Vehicle Cream
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	0.5% Roflumilast Cream
Reporting group description:	
Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.	
Reporting group title	Vehicle Cream
Reporting group description:	
Roflumilast formulation vehicle, cream, topically, twice daily for up to 15 days.	

Reporting group values	0.5% Roflumilast Cream	Vehicle Cream	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	40
Age continuous Units: years			
arithmetic mean	32.7	36.5	
standard deviation	± 11.5	± 9.65	-
Gender categorical Units: Subjects			
Female	9	11	20
Male	11	9	20
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	20	20	40
Multiracial	0	0	0
Smoking classfication Units: Subjects			
Subject has never smoked	5	8	13
Subject is a current smoker	10	9	19
Subject is an ex-smoker	5	3	8
Female Reproductive Status Units: Subjects			
Postmenopausal	0	0	0
Surgically Sterile	0	0	0
Female of Childbearing Potential	9	11	20
N/A (Subject is Male)	11	9	20
Height Units: Centimeter			
arithmetic mean	177.3	174.9	
standard deviation	± 9.27	± 10.13	-
Weight			

Units: Kilograms			
arithmetic mean	81.72	78.31	
standard deviation	± 21.757	± 12.965	-
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	25.65	25.59	
standard deviation	± 5.007	± 3.477	-
Baseline Modified Local SCORing Atopic Dermatitis (SCORAD)			
Units: Scores on a scale			
arithmetic mean	5.6	5.85	
full range (min-max)	4 to 8	4 to 8	-
Baseline Transepidermal Water Loss (TEWL)			
Units: g/m^2/hr			
arithmetic mean	41.47	41.57	
full range (min-max)	17.8 to 69.8	17.8 to 63.3	-
Baseline Participant Assessment of Pruritis			
Units: Scores on a scale			
arithmetic mean	5.05	5	
full range (min-max)	0 to 9	2 to 10	-

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who received at least one application of any double-blind study medication.

Reporting group values	Full Analysis Set		
Number of subjects	40		
Age categorical			
Units: Subjects			
Adults (18-64 years)	40		
Age continuous			
Units: years			
arithmetic mean	34.6		
standard deviation	± 10.66		
Gender categorical			
Units: Subjects			
Female	20		
Male	20		
Race			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White	40		
Multiracial			

Smoking classfication Units: Subjects			
Subject has never smoked	13		
Subject is a current smoker	19		
Subject is an ex-smoker	8		
Female Reproductive Status Units: Subjects			
Postmenopausal	0		
Surgically Sterile	0		
Female of Childbearing Potential	20		
N/A (Subject is Male)	20		
Height Units: Centimeter			
arithmetic mean	176.1		
standard deviation	± 9.66		
Weight Units: Kilograms			
arithmetic mean	80.02		
standard deviation	± 17.762		
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	25.62		
standard deviation	± 4.255		
Baseline Modified Local SCORing Atopic Dermatitis (SCORAD) Units: Scores on a scale			
arithmetic mean	5.725		
full range (min-max)	4 to 8		
Baseline Transepidermal Water Loss (TEWL) Units: g/m^2/hr			
arithmetic mean	41.52		
full range (min-max)	17.8 to 69.8		
Baseline Participant Assessment of Pruritis Units: Scores on a scale			
arithmetic mean	5.025		
full range (min-max)	0 to 10		

End points

End points reporting groups

Reporting group title	0.5% Roflumilast Cream
Reporting group description:	
Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.	
Reporting group title	Vehicle Cream
Reporting group description:	
Roflumilast formulation vehicle, cream, topically, twice daily for up to 15 days.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects who received at least one application of any double-blind study medication.	

Primary: Change From Baseline to Day 15 in Modified Local SCORing Atopic Dermatitis (SCORAD)

End point title	Change From Baseline to Day 15 in Modified Local SCORing Atopic Dermatitis (SCORAD)
End point description:	
Modified Local SCORAD is the sum of 5 individual indexes; erythema, edema/papulation, oozing/crusts, excoriations and lichenification scored on a 4 point scale, where 0=absent and 3=severe, with a total possible score of 15. Higher scores indicate greater severity.	
End point type	Primary
End point timeframe:	
Baseline and Day 15	

End point values	0.5% Roflumilast Cream	Vehicle Cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[1]	20		
Units: Scores on a scale				
least squares mean (standard error)	-2.3 (± 0.354)	-1.75 (± 0.347)		

Notes:

[1] - One subject in the 0.5% Roflumilast group was missing Day 15 data.

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	0.5% Roflumilast Cream v Vehicle Cream
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.276 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5542
upper limit	0.4574
Variability estimate	Standard error of the mean
Dispersion value	0.496

Notes:

[2] - This was an exploratory study designed to obtain preliminary information on the efficacy and safety of topical roflumilast for the treatment of AD.
[3] - Mixed Model Repeated Measures (MMRM) Model: SCORAD change from baseline = treatment + visit + treatment by visit interaction + baseline SCORAD score.

Secondary: Change From Baseline to Day 15 in Transepidermal Water Loss (TEWL) Values

End point title	Change From Baseline to Day 15 in Transepidermal Water Loss (TEWL) Values

End point description:

Diffusion of water through the skin is measured using a Tewameter. At each visit, 3 measurements are taken per treatment area (at 3 different areas of the target lesion). The TEWL value at each visit is the average of these measurements.

End point type	Secondary

End point timeframe:

Baseline and Day 15

End point values	0.5% Roflumilast Cream	Vehicle Cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: g/m^2/hr				
least squares mean (standard error)	-18.6 (± 2.467)	-12.69 (± 2.417)		

Statistical analyses

Statistical analysis title	Statiscal Analysis
Comparison groups	0.5% Roflumilast Cream v Vehicle Cream
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.095 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9134
upper limit	1.0835

Variability estimate	Standard error of the mean
Dispersion value	3.454

Notes:

[4] - MMRM model: TEWL change from baseline = treatment + visit + treatment by visit interaction + baseline TEWL score.

Secondary: Change From Baseline to Day 15 in Participants' Assessment of Pruritus

End point title	Change From Baseline to Day 15 in Participants' Assessment of Pruritus

End point description:

Severity of pruritus is assessed by the participants and recorded on a numeric scale ranging from 0 to 10, where 0 indicates the absence of the symptoms and 10 indicates the most severe symptoms.

End point type	Secondary

End point timeframe:

Baseline and Day 15

End point values	0.5% Roflumilast Cream	Vehicle Cream		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[5]	20		
Units: Scores on a Scale				
least squares mean (standard error)	-3.05 (± 0.426)	-1.5 (± 0.417)		

Notes:

[5] - One subject in the 0.5% Roflumilast group was missing Day 15 data.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	0.5% Roflumilast Cream v Vehicle Cream
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.013 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7656
upper limit	-0.3492
Variability estimate	Standard error of the mean
Dispersion value	0.596

Notes:

[6] - MMRM model: Assessment of Pruritus change from baseline = treatment + visit + treatment by visit interaction + baseline Assessment of Pruritus score.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time informed consent is signed through 7 days after the last dose of study drug (up to Day 22)

Adverse event reporting additional description:

The population consisted of all randomized participants. At each visit, investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	0.5% Roflumilast Cream

Reporting group description:

Roflumilast 0.5%, cream, topically, twice daily for up to 15 days.

Reporting group title	Vehicle Cream

Reporting group description:

Roflumilast formulation vehicle, cream, topically, twice daily for up to 15 days.

Serious adverse events	0.5% Roflumilast Cream	Vehicle Cream	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (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	0.5% Roflumilast Cream	Vehicle Cream	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	3 / 20 (15.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Red blood cells urine positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application Site Pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2012	Protocol Amendment 1 The following changes were implemented in Protocol Amendment 1: • Changed department name for SAE and pregnancy reporting. • Changed the signatory responsibility for pharmacovigilance and clinical trial management. • Clarified contraception duration. • Clarified that subjects not capable of giving informed consent were not allowed to participate in the study. • Clarified that subjects with a history of regulator antidepressant administration would not be included. • Added language to exclude institutionalized subjects. • Added text to clarify that antidepressant use was excluded during the study. • Lowered the threshold value for withdrawing subjects due to LFT abnormalities. • Increased total volume of blood drawn due to extra clinical laboratory tests at Day 8. • Clarified laboratory analysis and the use of a central laboratory. • Clarified pregnancy and SAE reporting process. • Corrected typographical errors.
15 March 2013	Protocol Amendment 2 The following changes were implemented in Protocol Amendment 2: • Changed the sponsor name.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported