Clinical trial results:
A Randomized, Single-Center, Observer-Blind, Vehicle- and Active Comparator-Controlled Phase 1b Study to Assess the Effect and Local Safety and Tolerability of Roflumilast and BYK321084 – Phosphodiesterase Type 4 Inhibitors (PDE4i) Dermal Formulations in Patients with Chronic Plaque Psoriasis using a Psoriasis Plaque Test

Summary

EudraCT number	2012-002998-62
Trial protocol	DE
Global end of trial date	30 October 2013

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	ROF-PSOR_104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1168-0955

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway, Deerfield, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Clinical Science, 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	19 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2013
Global end of trial reached?	Yes
Global end of trial date	30 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A single-center 3-week proof of mechanism/exploratory study to assess the effect and safety of topical roflumilast (0.5% dermal cream) and BYK321084 (5% and 0.5% dermal creams) compared to a vehicle (to roflumilast) formulation and 2 active comparators (betamethasone valerate 0.1% cream and calcipotriol 0.005% cream).

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	13 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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	14
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 1 investigative site in Germany from 13 June 2013 to 30 October 2013.

Pre-assignment

Screening details:

Participants with a diagnosis of Chronic Plaque Psoriasis were randomized to determine the placement order of six treatments: roflumilast 0.5%, TAK-084 5%, TAK-084 0.5%, vehicle to roflumilast, betamethasone valerate 0.1%, cream and calcipotriol 0.005% creams.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

The study was conducted observer-blind, ie, only the investigator performing the measurements and assessments was blinded to treatment.

Arms

Arm title	All Randomized Participants

Arm description:

Roflumilast 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 5%, dermal cream, 100 µL applied topically under Finn skin chambers, Vehicle to roflumilast, dermal cream, 100 µL applied topically under Finn skin chambers, betamethasone valerate 0.1%, dermal cream, 100 µL applied topically under Finn skin chambers, and calcipotriol 0.005%, dermal cream, 100 µL applied under Finn skin chambers, once daily for 21 days.

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

Dosage and administration details:

Roflumilast 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.

Investigational medicinal product name	TAK-084 0.5% Cream
Investigational medicinal product code	
Other name	BYK321084
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

TAK-084 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.

Investigational medicinal product name	TAK-084 5% Cream
Investigational medicinal product code	
Other name	BYK321084
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:	
TAK-084 5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Investigational medicinal product name	Vehicle to Roflumilast Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use
Dosage and administration details:	
Vehicle to roflumilast, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Investigational medicinal product name	Betamethasone Valerate 0.1% Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use
Dosage and administration details:	
Betamethasone valerate 0.1%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Investigational medicinal product name	Calcipotriol 0.005% Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use
Dosage and administration details:	
Calcipotriol 0.005%, dermal cream, 100 µL applied under Finn skin chambers, once daily for 21 days.	

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was conducted observer-blind, ie, only the investigator performing the measurements and assessments was blinded to treatment.

Number of subjects in period 1	All Randomized Participants
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Adults (18-64 years)	14	14	
From 65-84 years	1	1	
Age continuous Units: years			
arithmetic mean	49.1		
standard deviation	± 12.41	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	12	12	
Race Units: Subjects			
White	15	15	
Smoking Classification Units: Subjects			
Never Smoked	3	3	
Current Smoker	6	6	
Ex-smoker	6	6	
Female Reproductive Status Units: Subjects			
Postmenopausal	0	0	
Surgically Sterile	1	1	
Female of Childbearing Potential	2	2	
N/A (Subject is Male)	12	12	
Height Units: cm			
arithmetic mean	178.2		
standard deviation	± 7.84	-	
Weight Units: kg			
arithmetic mean	88.07		
standard deviation	± 14.28	-	
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	27.61		
standard deviation	± 3.316	-	

End points

End points reporting groups

Reporting group title	All Randomized Participants
Reporting group description:	
Roflumilast 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 5%, dermal cream, 100 µL applied topically under Finn skin chambers, Vehicle to roflumilast, dermal cream, 100 µL applied topically under Finn skin chambers, betamethasone valerate 0.1%, dermal cream, 100 µL applied topically under Finn skin chambers, and calcipotriol 0.005%, dermal cream, 100 µL applied under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	Vehicle to Roflumilast Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
Vehicle to roflumilast, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	Roflumilast 0.5% Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
Roflumilast 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	TAK-084 0.5% Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
TAK-084 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	TAK-084 5% Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
TAK-084 5%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	Betamethasone Valerate 0.1% Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
Betamethasone valerate 0.1%, dermal cream, 100 µL applied topically under Finn skin chambers, once daily for 21 days.	
Subject analysis set title	Calcipotriol 0.005% Cream
Subject analysis set type	Full analysis
Subject analysis set description:	
Calcipotriol 0.005%, dermal cream, 100 µL applied under Finn skin chambers, once daily for 21 days.	

Primary: Change from Baseline in Thickness of the Psoriatic Skin Infiltrate on Day 22

End point title	Change from Baseline in Thickness of the Psoriatic Skin Infiltrate on Day 22
End point description:	
Thickness of psoriatic skin infiltrate was assessed using 20 MHz sonographic measurement. A negative change from Baseline indicated improved skin condition. Full Analysis Set included all randomized participants who received at least 1 application of study medication analyzed according to randomized treatment.	
End point type	Primary
End point timeframe:	
Baseline and Day 22	

End point values	Vehicle to Roflumilast Cream	Roflumilast 0.5% Cream	TAK-084 0.5% Cream	TAK-084 5% Cream
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: µm				
arithmetic mean (standard deviation)	-70.3 (± 96.84)	-307.4 (± 150.17)	-223.9 (± 88.96)	-287.1 (± 157.37)

End point values	Betamethasone Valerate 0.1% Cream	Calcipotriol 0.005% Cream		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: µm				
arithmetic mean (standard deviation)	-357.3 (± 130.64)	-258 (± 107.65)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Roflumilast 0.5% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v Roflumilast 0.5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-237.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-320
upper limit	-154.1

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: TAK-084 0.5% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 0.5% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-153.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-224.1
upper limit	-83.1

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: TAK-084 5% cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-216.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-298.7
upper limit	-134.7

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Betamethasone Valerate 0.1% Cream versus Vehicle Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v Betamethasone Valerate 0.1% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-286.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-362
upper limit	-211.9

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Calcipotriol 0.005% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-187.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-256.8
upper limit	-118.5

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Roflumilast 0.5% Cream versus Betamethasone Valerate 0.1% Cream.	
Comparison groups	Roflumilast 0.5% Cream v Betamethasone Valerate 0.1% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	49.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	96.2

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: TAK-084 0.5% Cream versus Betamethasone Valerate 0.1% Cream.	
Comparison groups	TAK-084 0.5% Cream v Betamethasone Valerate 0.1% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	133.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.2
upper limit	196.5

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: TAK-084 5% Cream versus Betamethasone Valerate 0.1% Cream.	
Comparison groups	Betamethasone Valerate 0.1% Cream v TAK-084 5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	70.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.2
upper limit	118.2

Statistical analysis title	Statistical Analysis 9
Statistical analysis description: Calcipotriol 0.005% Cream versus Betamethasone Valerate 0.1% Cream.	
Comparison groups	Betamethasone Valerate 0.1% Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	99.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.3
upper limit	135.3

Statistical analysis title	Statistical Analysis 10
Statistical analysis description: Roflumilast 0.5% Cream versus Calcipotriol 0.005% Cream.	
Comparison groups	Roflumilast 0.5% Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-49.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-111.6
upper limit	12.8

Statistical analysis title	Statistical Analysis 11
Statistical analysis description: TAK-084 0.5% Cream versus Calcipotriol 0.005% Cream.	
Comparison groups	TAK-084 0.5% Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	34.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	85.7

Statistical analysis title	Statistical Analysis 12
Statistical analysis description: TAK-084 5% Cream versus Calcipotriol 0.005% Cream.	
Comparison groups	Calcipotriol 0.005% Cream v TAK-084 5% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-92
upper limit	33.9

Secondary: Change from Baseline in Thickness of the Psoriatic Skin Infiltrate on Days 8 and 15

End point title	Change from Baseline in Thickness of the Psoriatic Skin Infiltrate on Days 8 and 15

End point description:

Thickness of psoriatic skin infiltrate was assessed using 20 MHz sonographic measurement. A negative change from Baseline indicated improved skin condition.
Full Analysis Set included all randomized participants who received at least 1 application of study medication analyzed according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline and Days 8 and 15

End point values	Vehicle to Roflumilast Cream	Roflumilast 0.5% Cream	TAK-084 0.5% Cream	TAK-084 5% Cream
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: µm				
arithmetic mean (standard deviation)				
Day 8	3.3 (± 44.88)	-222.9 (± 136.2)	-90.6 (± 76.72)	-204.1 (± 144.53)
Day 15	-45.3 (± 89.01)	-277.7 (± 153.38)	-154.5 (± 88.85)	-239.1 (± 146.55)

End point values	Betamethasone Valerate 0.1% Cream	Calcipotriol 0.005% Cream		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: µm				
arithmetic mean (standard deviation)				
Day 8	-253.6 (± 104.6)	-184.1 (± 104.52)		

Day 15	-311.8 (± 113.41)	-182.3 (± 153.02)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: 0.5% Roflumilast Cream versus Vehicle to Roflumilast Cream at Day 8.	
Comparison groups	Vehicle to Roflumilast Cream v Roflumilast 0.5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-226.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-302.7
upper limit	-149.6

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: TAK-084 0.5% Cream versus Vehicle to Roflumilast Cream at Day 8.	
Comparison groups	TAK-084 0.5% Cream v Vehicle to Roflumilast Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-93.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-138.9
upper limit	-48.8

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: TAK-084 5% Cream versus Vehicle to Roflumilast Cream at Day 8.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 5% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-207.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-291.3
upper limit	-123.5

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Betamethasone Valerate Cream 0.1% versus Vehicle to Roflumilast Cream at Day 8.	
Comparison groups	Vehicle to Roflumilast Cream v Betamethasone Valerate 0.1% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-256.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-327
upper limit	-186.7

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Calcipotriol 0.005% Cream versus Vehicle to Roflumilast at Day 8.	
Comparison groups	Vehicle to Roflumilast Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-187.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-252.6
upper limit	-122.1

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Roflumilast 0.5% Cream versus Vehicle to Roflumilast Cream at Day 15.	
Comparison groups	Vehicle to Roflumilast Cream v Roflumilast 0.5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-232.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-311.6
upper limit	-153.2

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Tak-084 0.5% Cream versus Vehicle to Roflumilast Cream on Day 15.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 0.5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-109.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-171.2
upper limit	-47.3

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Tak-084 5% Cream versus Vehicle to Roflumilast Cream on Day 15.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 5% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-193.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-268.4
upper limit	-119.3

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Betamethasone Valerate 0.1% Cream versus Vehicle to Roflumilast Cream on Day 15.	
Comparison groups	Vehicle to Roflumilast Cream v Betamethasone Valerate 0.1% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-266.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-334.8
upper limit	-198.2

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Calcipotriol 0.005% Cream versus Vehicle to Roflumilast at Day 15.	
Comparison groups	Vehicle to Roflumilast Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-137
Confidence interval	
level	95 %
sides	2-sided
lower limit	-258.3
upper limit	-15.7

Secondary: Area Under the Curve (AUC) of the Baseline-Corrected Thickness of the Psoriatic Skin Infiltrate

End point title	Area Under the Curve (AUC) of the Baseline-Corrected Thickness of the Psoriatic Skin Infiltrate

End point description:

Thickness of psoriatic skin infiltrate was assessed using 20 MHz sonographic measurement at Baseline and Days 8, 15 and 22. Baseline corrected AUC values were calculated using the linear trapezoidal rule.

Full Analysis Set included all randomized participants who received at least 1 application of study medication analyzed according to randomized treatment. If Baseline measurement was missing AUC was set to missing. If 1 Post-Baseline measurement was missing Last Observation Carried Forward was used. If 2 or more post-Baseline measurements were missing AUC was set to missing.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 8, 15 and 22

End point values	Vehicle to Roflumilast Cream	Roflumilast 0.5% Cream	TAK-084 0.5% Cream	TAK-084 5% Cream
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: µm·day				
arithmetic mean (standard deviation)	-540.17 (± 1162.715)	-4579.63 (± 2495.896)	-2499.7 (± 1300.153)	-4107.6 (± 2564.958)

End point values	Betamethasone Valerate 0.1% Cream	Calcipotriol 0.005% Cream		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: µm·day				
arithmetic mean (standard deviation)	-5208.23 (± 1950.179)	-3467.33 (± 1455.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Roflumilast 0.5% Cream versus Vehicle to Roflumilast Cream.

Comparison groups	Vehicle to Roflumilast Cream v Roflumilast 0.5% Cream

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-4039.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5351.01
upper limit	-2727.93

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: TAK-084 0.5% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 0.5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1959.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2779.91
upper limit	-1139.15

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: TAK-084 5% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v TAK-084 5% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-3567.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4900.71
upper limit	-2234.15

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Betamethasone Valerate 0.1% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v Betamethasone Valerate 0.1% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-4668.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5858.76
upper limit	-3477.37

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Calcipotriol 0.005% Cream versus Vehicle to Roflumilast Cream.	
Comparison groups	Vehicle to Roflumilast Cream v Calcipotriol 0.005% Cream
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-2927.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4082.44
upper limit	-1771.89

Secondary: Change from Baseline in Clinical Severity of the Psoriatic Lesions

End point title	Change from Baseline in Clinical Severity of the Psoriatic Lesions

End point description:

The investigator assessed the clinical severity of the treated psoriatic lesions compared to Baseline as part of the skin examination procedure, including photography, using a 5-Point Scale: -1=worsened to 3=completely healed. A higher number change from Baseline is the best.
Full Analysis Set included all randomized participants who received at least 1 application of study medication analyzed according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline and Days, 8, 15 and 22

End point values	Vehicle to Roflumilast Cream	Roflumilast 0.5% Cream	TAK-084 0.5% Cream	TAK-084 5% Cream
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	15	15
Units: scores on a scale				
arithmetic mean (standard deviation)				
Day 8	0 (± 0)	1.5 (± 0.52)	0.1 (± 0.26)	0.9 (± 0.46)
Day 15	0.1 (± 0.35)	1.9 (± 0.59)	0.3 (± 0.46)	1 (± 0.53)
Day 22	0.1 (± 0.26)	1.9 (± 0.7)	0.5 (± 0.64)	1.3 (± 0.8)

End point values	Betamethasone Valerate 0.1% Cream	Calcipotriol 0.005% Cream		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Day 8	2 (± 0.53)	1.1 (± 0.46)		
Day 15	2.2 (± 0.41)	1.1 (± 0.7)		
Day 22	2.3 (± 0.49)	1.1 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First treatment to 30 days past last treatment (Up to 36 days)

Adverse event reporting additional description:

At each visit the 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	All Participants

Reporting group description:

Roflumilast 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 0.5%, dermal cream, 100 µL applied topically under Finn skin chambers, TAK-084 5%, dermal cream, 100 µL applied topically under Finn skin chambers, vehicle to roflumilast, dermal cream, 100 µL applied topically under Finn skin chambers, betamethasone valerate 0.1%, dermal cream, 100 µL applied topically under Finn skin chambers, and calcipotriol 0.005%, dermal cream, 100 µL applied under Finn skin chambers, once daily for 21 days.

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	All Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin erosion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2012	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. • Corrected the manufacturer of the hydrocolloid dressing. • Clarified that subjects not capable of giving informed consent would not be allowed to participate in the study. • Added language to exclude subjects with extensive ultraviolet light exposure in the 4 weeks prior to study medication application and institutionalized subjects. • Added specific section for exclusion of known inhibitors of CYP2D6 and CYP1A2 per regulatory request. • Revised laboratory analysis of white blood cell count. • Clarified pregnancy and SAE reporting process. • Corrected storage and shipment conditions of genotyping sample. • Added pharmacogenomic sample to schedule of study procedures. • Corrected typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Note: Due to a EudraCT system error, the number of participants analzyed for the Statistical Analyses is appearing as 30. The actual number of participants analyzed is 15. When the issue is corrected the record will be updated with the proper data.

Notes: