



Clinical trial results:

Protocol 271-12-205: A Phase 2 Multi-center, Randomized, Double-blind, Vehicle-controlled, Three-arm, Parallel Group Study to Assess the Safety, Tolerability, and Efficacy of Topical OPA-15406 Ointment, in Subjects With Mild/Moderate Atopic Dermatitis

Summary

EudraCT number	2013-003899-12
Trial protocol	PL
Global end of trial date	28 January 2015

Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016

Trial information

Trial identification

Sponsor protocol code	271-12-205
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02068352
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
Public contact	Angela Smith, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 301-956-2790, angela.smith@otsuka-us.com
Scientific contact	Agnes Elekes, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609-720-8453, agnes.elekes@otsuka-us.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	22 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2015
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 2 concentrations of OPA-15406 ointment (0.3% weight to weight [w/w] and 1% w/w) compared to vehicle, when administered topically twice daily (BID) in participants with mild to moderate atopic dermatitis.

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research participants, no trial procedures were performed on trial participants until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Poland: 12
Worldwide total number of subjects	121
EEA total number of subjects	12

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)	7
Adolescents (12-17 years)	17
Adults (18-64 years)	96
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 121 participants at 30 trial sites in 3 countries.

Pre-assignment

Screening details:

Participants had screening evaluations between 30 and 2 days before entering the 8-week treatment phase.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

During the trial, the treatment assignment code list was available only to an independent biostatistician and the clinical supply operations group. Except in cases of emergency unblinding, participants, investigational site personnel, sponsor employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every participant had completed the trial and the database had been locked.

Arms

Are arms mutually exclusive?	Yes
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Arm title	OPA-15406 0.3% w/w
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Arm description:

OPA-15406 0.3% w/w ointment was applied topically BID

Arm type	Experimental
Investigational medicinal product name	OPA-15406 0.3% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

OPA-15406 0.3% w/w was applied topically BID for 8 weeks

Arm title	OPA-15406 1% w/w
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Arm description:

OPA-15406 1% w/w ointment was applied topically BID

Arm type	Experimental
Investigational medicinal product name	OPA-15406 1% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

OPA-15406 1% w/w was applied topically BID for 8 weeks

Arm title	Vehicle ointment
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Arm description:

Vehicle ointment was applied topically BID

Arm type	Vehicle ointment
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Investigational medicinal product name	Vehicle ointment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Vehicle ointment was applied topically BID for 8 weeks

Number of subjects in period 1	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment
Started	41	43	37
Completed	31	35	28
Not completed	10	8	9
Consent withdrawn by subject	6	3	1
Protocol specified withdrawal criteria	-	1	-
Adverse event	4	2	7
Lost to follow-up	-	2	-
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	OPA-15406 0.3% w/w
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Reporting group description:

OPA-15406 0.3% w/w ointment was applied topically BID

Reporting group title	OPA-15406 1% w/w
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Reporting group description:

OPA-15406 1% w/w ointment was applied topically BID

Reporting group title	Vehicle ointment
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Reporting group description:

Vehicle ointment was applied topically BID

Reporting group values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment
Number of subjects	41	43	37
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	1	2	4
Adolescents (12-17 years)	6	7	4
Adults (18-64 years)	34	33	29
From 65-84 years	0	1	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	36.4	34.1	32.2
standard deviation	± 15.2	± 16.5	± 15.6
Gender categorical			
Units: Subjects			
Female	27	22	23
Male	14	21	14

Reporting group values	Total		
Number of subjects	121		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	7		
Adolescents (12-17 years)	17		
Adults (18-64 years)	96		

From 65-84 years	1		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	72		
Male	49		

End points

End points reporting groups

Reporting group title	OPA-15406 0.3% w/w
Reporting group description: OPA-15406 0.3% w/w ointment was applied topically BID	
Reporting group title	OPA-15406 1% w/w
Reporting group description: OPA-15406 1% w/w ointment was applied topically BID	
Reporting group title	Vehicle ointment
Reporting group description: Vehicle ointment was applied topically BID	

Primary: Incidence of success in the Overall Investigator's Global Assessment of Disease Severity (IGA) score at Week 4 (using non-responder imputation or last observation carried forward [LOCF] imputation)

End point title	Incidence of success in the Overall Investigator's Global Assessment of Disease Severity (IGA) score at Week 4 (using non-responder imputation or last observation carried forward [LOCF] imputation)
End point description: IGA evaluation performed by a certified rater. The IGA consists of a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease, and 5 = very severe disease). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. The IGA assessment was performed for the overall selected treatment area(s): overall percentage body surface area to be treated and additionally for the target lesion. Success was defined as a score of 0 or 1 with at least a 2-grade reduction from Baseline. In the primary analysis, participants without IGA score at Week 4 were treated as non-responders. In the sensitivity analysis, missing IGA score at Week 4 was imputed using LOCF method first and the success was defined based on the imputed IGA score.	
End point type	Primary
End point timeframe: Week 4	

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Percentage of participants				
number (not applicable)				
Week 4 (non-responder imputation) n=41, 43, 37	14.63	20.93	2.7	
Week 4 (LOCF) n=40, 43, 37	15	20.93	2.7	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 4
Statistical analysis description:	
Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication. Per the 2-step testing procedure pre-specified in the protocol, the comparison of the success rate for Overall IGA score in OPA-15406 1% versus vehicle at Week 4 was performed first and if significant comparison was made between OPA-15406 0.3% versus vehicle ointment.	
Comparison groups	Vehicle ointment v OPA-15406 0.3% w/w
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	11.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	23.95

Notes:

[1] - P-value was derived using Cochran-Mantel-Haenszel (CMH) test stratified by age group (< 18 or ≥ 18) and region.

Statistical analysis title	Statistical analysis 2 at Week 4
Statistical analysis description:	
Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication. Per the 2-step testing procedure pre-specified in the protocol, the comparison of the success rate for Overall IGA score in OPA-15406 1% versus vehicle at Week 4 was performed first and if significant comparison was made between OPA-15406 0.3% versus vehicle ointment.	
Comparison groups	Vehicle ointment v OPA-15406 1% w/w
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0165 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	18.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.99
upper limit	31.46

Notes:

[2] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Statistical analysis title	Statistical analysis 3 at Week 4 (LOCF)
Statistical analysis description:	
Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication. Per the 2-step testing procedure pre-specified in the protocol, the comparison of the success rate for Overall IGA score in OPA-15406 1% versus vehicle at Week 4 was performed first and if significant comparison was made between OPA-15406 0.3% versus vehicle ointment.	

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0617 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	24.53

Notes:

[3] - Last observation carried forward (LOCF)

[4] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Statistical analysis title	Statistical analysis 4 at Week 4 (LOCF)
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication. Per the 2-step testing procedure pre-specified in the protocol, the comparison of the success rate for Overall IGA score in OPA-15406 1% versus vehicle at Week 4 was performed first and if significant comparison was made between OPA-154060 0.3% versus vehicle ointment.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0165 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	18.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.99
upper limit	31.46

Notes:

[5] - LOCF

[6] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Secondary: Change from Baseline in Overall IGA Score (Using MMRM analysis)

End point title	Change from Baseline in Overall IGA Score (Using MMRM analysis)
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End point description:

The IGA evaluation was performed by a certified rater. The IGA allows for an assessment of overall disease severity at a given time point, and it consists of a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease, and 5 = very severe disease). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. The IGA assessment was performed for the overall selected treatment area(s): overall percentage body surface area to be treated and additionally for the target lesion.

End point type	Secondary
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End point timeframe:

Week 4

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 (n=35, 40, 29)	-0.56 (\pm 0.14)	-0.55 (\pm 0.13)	-0.09 (\pm 0.15)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication.

Comparison groups	Vehicle ointment v OPA-15406 0.3% w/w
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0128 ^[7]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.1

Notes:

[7] - Derived from mixed model repeated measures (MMRM) with fixed effects of treatment, region, visit, age group (< 18 or \geq 18), and interaction of treatment by visit as terms, Baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication.

Comparison groups	Vehicle ointment v OPA-15406 1% w/w
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134 ^[8]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.1

Notes:

[8] - Derived from mixed model repeated measures (MMRM) with fixed effects of treatment, region, visit, age group (< 18 or ≥ 18), and interaction of treatment by visit as terms, Baseline score as a covariate

Secondary: Change From Baseline in Overall IGA Score (Using LOCF Analysis)

End point title	Change From Baseline in Overall IGA Score (Using LOCF Analysis)
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End point description:

The IGA allows for an assessment of overall disease severity at a given time point, and it consists of a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease, and 5 = very severe disease). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. Missing overall IGA scores at Week 4 were imputed using LOCF method.

End point type	Secondary
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End point timeframe:

Week 4

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 4 (n=40, 43, 37)	-0.54 (± 0.15)	-0.54 (± 0.14)	-0.04 (± 0.15)	

Statistical analyses

Statistical analysis title	Statistical analysis at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.0048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.16

Notes:

[9] - Analysis of covariance (ANCOVA) model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.0045
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.16

Notes:

[10] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Secondary: Incidence and Severity of Adverse Events (AEs).

End point title	Incidence and Severity of Adverse Events (AEs).
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End point description:

AEs were captured for all participants from the time the informed consent was signed until end of trial. An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A serious AE (SAE) was defined as any event which resulted in death, was life-threatening, was a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, required in-patient hospitalization or prolonged hospitalization, was a congenital anomaly/birth defect, or was another medically significant event.

End point type	Secondary
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End point timeframe:

From signing of informed consent through Week 8.

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Percentage of participants				
number (not applicable)				
Treatment emergent AEs	58.5	41.9	54.1	
Application site TEAEs	26.8	11.6	18.9	
Serious TEAEs	4.9	4.7	0	

Severe TEAEs	12.2	4.7	8.1	
Severe application site TEAEs	4.9	0	5.4	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of success in the Overall IGA score at Week 8 (using Non-responder imputation or LOCF imputation)

End point title	Incidence of success in the Overall IGA score at Week 8 (using Non-responder imputation or LOCF imputation)
End point description:	
IGA evaluation was performed by a certified rater. The IGA consists of a 6-point severity scale from clear to very severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease, and 5 = very severe disease). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. The IGA assessment was performed for the overall selected treatment area(s): overall percentage body surface area to be treated and additionally for the target lesion. Success was defined as a score of 0 or 1 with at least a 2-grade reduction from Baseline. In the primary analysis, participants without IGA score available at Week 4 were treated as non-responders. In the sensitivity analysis, the missing IGA score at Week 4 was imputed using LOCF method first and the success was defined based on the imputed IGA score.	
End point type	Other pre-specified
End point timeframe:	
Week 8	

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Percentage of patients				
number (not applicable)				
Week 8 (non responder imputation N=41, 43, 37)	17.07	16.28	10.81	
Week 8 (LOCF N=40, 43, 37)	20	20.93	10.81	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 8
Statistical analysis description:	
Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.	
Comparison groups	Vehicle ointment v OPA-15406 0.3% w/w

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4173 ^[11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	6.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.99
upper limit	21.52

Notes:

[11] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Statistical analysis title	Statistical analysis 2 at Week 8
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4895 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	5.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.43
upper limit	20.36

Notes:

[12] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Statistical analysis title	Statistical analysis 3 at Week 8 (LOCF)
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomised participants who received at least one dose of study medication.

Comparison groups	Vehicle ointment v OPA-15406 0.3% w/w
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.2677 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.74
upper limit	25.12

Notes:

[13] - LOCF

[14] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Statistical analysis title	Statistical analysis 4 at Week 8 (LOCF)
Statistical analysis description:	
Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication	
Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.2319 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	10.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.63
upper limit	25.87

Notes:

[15] - LOCF

[16] - P-value was derived using CMH test stratified by age group (< 18 or ≥ 18) and region

Other pre-specified: Change From Baseline in Eczema Area and Severity Index (EASI) (Using MMRM Analysis)

End point title	Change From Baseline in Eczema Area and Severity Index (EASI) (Using MMRM Analysis)
End point description:	
The EASI evaluation assesses the extent of disease at 4 body sites and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale from 0 (no disease) to 3 (very severe). The EASI scale allows for a maximum score of 72. The EASI assessment was performed on the overall body.	
End point type	Other pre-specified
End point timeframe:	
Weeks 1, 2, 4 ,6 and 8.	

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (n=38, 41, 36)	-1.47 (± 0.64)	-2.39 (± 0.6)	-0.31 (± 0.64)	
Week 2 (n=39, 41, 21)	-2.24 (± 0.71)	-3.21 (± 0.68)	-0.61 (± 0.74)	
Week 4 (n=35, 40, 29)	-2.21 (± 0.85)	-3.19 (± 0.8)	-1.1 (± 0.9)	
Week 6 (n=32, 35, 27)	-2.33 (± 0.87)	-3.36 (± 0.83)	-1.99 (± 0.93)	
Week 8 (n=31, 35, 28)	-2.6 (± 0.9)	-3.47 (± 0.86)	-1.57 (± 0.95)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 1
Statistical analysis description: Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.	
Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.1221
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	0.32

Notes:

[17] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 1
Statistical analysis description: Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.	
Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.0056
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.54
upper limit	-0.62

Notes:

[18] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received

at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0687
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.38
upper limit	0.13

Notes:

[19] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.0035
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.33
upper limit	-0.87

Notes:

[20] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.3213
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	1.11

Notes:

[21] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.0594
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.09

Confidence interval

level	95 %
sides	2-sided
lower limit	-4.27
upper limit	0.08

Notes:

[22] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 6
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.7706
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.34

Confidence interval

level	95 %
sides	2-sided
lower limit	-2.66
upper limit	1.98

Notes:

[23] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 6
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	= 0.2379
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.65
upper limit	0.92

Notes:

[24] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 8
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.396
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	1.37

Notes:

[25] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 8
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.1135
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.26
upper limit	0.46

Notes:

[26] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Other pre-specified: Change From Baseline in EASI (Using LOCF Analysis)

End point title	Change From Baseline in EASI (Using LOCF Analysis)
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End point description:

The EASI evaluation assesses the extent of disease at 4 body sites and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale from 0 (no disease) to 3 (very severe). The EASI scale allows for a maximum score of 72. The EASI assessment was performed on the overall body.

End point type	Other pre-specified
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End point timeframe:

Week 1, 2, 4, 6 and 8

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (n=38, 41, 36)	-1.35 (± 0.58)	-2.37 (± 0.58)	-0.58 (± 0.58)	
Week 2 (n=40, 43, 37)	-2.27 (± 0.73)	-3.25 (± 0.69)	-0.54 (± 0.73)	
Week 4 (n=40, 43, 37)	-2 (± 0.91)	-3.07 (± 0.87)	-0.51 (± 0.92)	
Week 6 (n=40, 43, 37)	-1.88 (± 0.98)	-3.09 (± 0.93)	-0.89 (± 0.99)	
Week 8 (n=40, 43, 37)	-2.42 (± 1.01)	-3.36 (± 0.96)	-1 (± 1.02)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 1
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.2676
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	0.6

Notes:

[27] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 1
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.0098
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.78

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.13
upper limit	-0.44

Notes:

[28] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.0463
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.73

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.43
upper limit	-0.03

Notes:

[29] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.0017
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	-1.04

Notes:

[30] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 4
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.1703
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.63
upper limit	0.65

Notes:

[31] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 4
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.0176
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	-0.45

Notes:

[32] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline

Statistical analysis title	Statistical analysis 1 at Week 6
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.3996
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.98

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.29
upper limit	1.32

Notes:

[33] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 6
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.3996
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.98

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.29
upper limit	1.32

Notes:

[34] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 6
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.0573
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.46
upper limit	0.07

Notes:

[35] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 8
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.2381
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	0.95

Notes:

[36] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 8
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	= 0.047
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.68
upper limit	-0.03

Notes:

[37] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Other pre-specified: Change from Baseline in Visual Analog Scale (VAS) for pruritus (Using MMRM analysis)

End point title	Change from Baseline in Visual Analog Scale (VAS) for pruritus (Using MMRM analysis)
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End point description:

At each evaluation, the participants were asked to record their current pruritus intensity over their body overall, not just within the selected treatment areas[s] (ie, intensity over the last 24 hours) on a horizontal 100-mm line marked as "No itch" on the left end and "Worst imaginable itch" on the right end. The VAS assessment was performed on the overall impression of itch on the body and not just for the selected treatment area(s) or for the target lesion.

End point type	Other pre-specified
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End point timeframe:

Weeks 1, 2, 4, 6 and 8

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (n=38, 41, 36)	-9.02 (± 3.91)	-17.58 (± 3.7)	-0.25 (± 3.95)	
Week 2 (n=39, 41, 33)	-8.94 (± 4.27)	-21.14 (± 4.08)	-6.11 (± 4.41)	
Week 4 (n=35, 40, 29)	-6.27 (± 4.67)	-16.71 (± 4.4)	-4.87 (± 4.96)	
Week 6 (n=32, 35, 27)	-9.44 (± 5.07)	-18.68 (± 4.83)	-8.61 (± 5.4)	
Week 8 (n=31, 35, 28)	-10.98 (± 5.12)	-20.71 (± 4.85)	-7.3 (± 5.44)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 1
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	Vehicle ointment v OPA-15406 0.3% w/w
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Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[38]
P-value	= 0.0639
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.07
upper limit	0.52

Notes:

[38] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 1
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-17.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.47
upper limit	-8.18

Notes:

[39] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[40]
P-value	= 0.597
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.45
upper limit	7.77

Notes:

[40] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	= 0.0053
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.03

Confidence interval

level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-4.56

Notes:

[41] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 4
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	= 0.8196
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.4

Confidence interval

level	95 %
sides	2-sided
lower limit	-13.5
upper limit	10.7

Notes:

[42] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 4
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[43]
P-value	= 0.0503
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.69
upper limit	0.02

Notes:

[43] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 6
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[44]
P-value	= 0.9028
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.23
upper limit	12.58

Notes:

[44] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 6
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	= 0.1338
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.29
upper limit	3.15

Notes:

[45] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 1 at Week 8
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[46]
P-value	= 0.5902
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.68

Confidence interval

level	95 %
sides	2-sided
lower limit	-17.22
upper limit	9.85

Notes:

[46] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Statistical analysis title	Statistical analysis 2 at Week 8
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[47]
P-value	= 0.0482
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-13.42

Confidence interval

level	95 %
sides	2-sided
lower limit	-26.73
upper limit	-0.11

Notes:

[47] - MMRM with fixed effects of treatment, region, visit, age group, interaction of treatment by visit, baseline score as a covariate.

Other pre-specified: Change from Baseline in VAS for pruritus (Using LOCF analysis)

End point title	Change from Baseline in VAS for pruritus (Using LOCF analysis)
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End point description:

At each evaluation, the participants were asked to record their current pruritus intensity over their body overall, not just within the selected treatment areas[s] (ie, intensity over the last 24 hours) on a horizontal 100-mm line marked as "No itch" on the left end and "Worst imaginable itch" on the right end. The VAS assessment was performed on the overall impression of itch on the body and not just for the selected treatment area(s) or for the target lesion

End point type	Other pre-specified
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End point timeframe:

Weeks 1, 2, 4, 6 and 8

End point values	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	43	37	
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (n=38, 41, 26)	-9.3 (± 4.01)	-18.36 (± 3.8)	-1.1 (± 4.07)	
Week 2 (n=40, 43, 37)	-9.96 (± 4.5)	-22.15 (± 4.24)	-6.26 (± 4.54)	
Week 4 (n=40, 43, 37)	-4.05 (± 4.92)	-14.59 (± 4.64)	-3.05 (± 4.96)	
Week 6 (n=40, 43, 37)	-10.69 (± 5.31)	-20.31 (± 5)	-9.29 (± 5.35)	
Week 8 (n=40, 43, 37)	-10.01 (± 5.51)	-20.33 (± 5.2)	-7.28 (± 5.56)	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 1
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	= 0.089
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.66
upper limit	1.27

Notes:

[48] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 1
-----------------------------------	----------------------------------

Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[49]
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-17.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.57
upper limit	-7.94

Notes:

[49] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[50]
P-value	= 0.4853
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.21
upper limit	6.79

Notes:

[50] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 2
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[51]
P-value	= 0.0029
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.22
upper limit	-5.57

Notes:

[51] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 6
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[52]
P-value	= 0.8633
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1

Confidence interval

level	95 %
sides	2-sided
lower limit	-12.48
upper limit	10.48

Notes:

[52] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline

Statistical analysis title	Statistical analysis 1 at Week 6
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Statistical analysis description:

ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8227
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.4

Confidence interval

level	95 %
sides	2-sided
lower limit	-13.78
upper limit	10.97

Statistical analysis title	Statistical analysis 2 at Week 6
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[53]
P-value	= 0.0754
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-11.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.2
upper limit	1.15

Notes:

[53] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 1 at Week 8
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication

Comparison groups	OPA-15406 0.3% w/w v Vehicle ointment
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority ^[54]
P-value	= 0.6746
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.58
upper limit	10.12

Notes:

[54] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Statistical analysis title	Statistical analysis 2 at Week 8
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Statistical analysis description:

Analysis was performed on the Efficacy Sample which include all randomized participants who received at least one dose of study medication.

Comparison groups	OPA-15406 1% w/w v Vehicle ointment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	= 0.0432
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-13.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.69
upper limit	-0.4

Notes:

[55] - ANCOVA model with treatment, region, age group as terms, and baseline score as a covariate for change from baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were captured from the time the informed consent was signed until the end of the 8-week treatment period.

Adverse event reporting additional description:

Treatment-related AEs were followed up until resolution or until physician assesses that resolution will not be achieved. For SAEs, physician continued to report any significant follow-up information until event resolved.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	OPA-15406 0.3% w/w
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Reporting group description:

OPA-15406 0.3% w/w ointment was applied topically BID

Reporting group title	OPA-15406 1% w/w
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Reporting group description:

OPA-15406 1% w/w ointment was applied topically BID

Reporting group title	Vehicle ointment
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Reporting group description:

Vehicle ointment was applied topically BID

Serious adverse events	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)	2 / 43 (4.65%)	0 / 37 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Giardiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	OPA-15406 0.3% w/w	OPA-15406 1% w/w	Vehicle ointment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 41 (58.54%)	16 / 43 (37.21%)	20 / 37 (54.05%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Thermal burn			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)	3 / 43 (6.98%)	0 / 37 (0.00%)
occurrences (all)	2	3	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Application site irritation			

subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 43 (0.00%) 0	1 / 37 (2.70%) 1
Induration subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 43 (0.00%) 0	1 / 37 (2.70%) 1
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 43 (0.00%) 0	0 / 37 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 43 (0.00%) 0	1 / 37 (2.70%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 43 (0.00%) 0	0 / 37 (0.00%) 0
Dental caries subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 43 (0.00%) 0	0 / 37 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	2 / 43 (4.65%) 4	0 / 37 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 43 (2.33%) 1	2 / 37 (5.41%) 2
Mouth haemorrhage subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 43 (0.00%) 0	1 / 37 (2.70%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	2 / 43 (4.65%) 2	1 / 37 (2.70%) 1
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 43 (2.33%) 1	0 / 37 (0.00%) 0
Rhinitis allergic			

subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 43 (2.33%) 1	0 / 37 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acanthosis nigricans			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	11 / 41 (26.83%)	7 / 43 (16.28%)	8 / 37 (21.62%)
occurrences (all)	12	7	8
Erythema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Papule			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Post inflammatory pigmentation change			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	3 / 41 (7.32%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1
Rash vesicular			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Tendonitis			

subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	0 / 43 (0.00%) 0	0 / 37 (0.00%) 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Folliculitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Klebsiella infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 43 (2.33%)	3 / 37 (8.11%)
occurrences (all)	5	1	3
Oral candidiasis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

Staphylococcal infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 41 (7.32%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2014	The main purpose of the amendment was to incorporate the results of the phase 1b trial and to adjust the number and concentrations based on the phase 1b results. This amendment also added more information regarding use in the pediatric population, language regarding additional safety review by Data Monitoring Committee, skin sensitization monitoring, and patch testing. In addition, minor changes were made to correct typographical errors.
01 October 2014	The main purpose of the amendment was to mandate discontinuation of any enrolled participant who experienced atopic dermatitis disease worsening beyond 40% body surface area. In addition, minor changes were made to correct typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported