



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Of The Safety And Efficacy Of AN2728 Topical Ointment, 2% In children, Adolescents, And Adults (Ages 2 Years And Older) With Atopic Dermatitis

Summary

EudraCT number	2018-000731-27
Trial protocol	Outside EU/EEA
Global end of trial date	29 April 2015

Results information

Result version number	v1 (current)
This version publication date	01 June 2018
First version publication date	01 June 2018

Trial information

Trial identification

Sponsor protocol code	AN2728-AD-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02118766
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrial.gov Call Centers, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002065-PIP01-16
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	23 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of AN2728 topical ointment, 2% in children, adolescents, and adults (ages 2 years and older) with atopic dermatitis (AD).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2014
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	United States: 763
Worldwide total number of subjects	763
EEA total number of subjects	0

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)	472
Adolescents (12-17 years)	188
Adults (18-64 years)	101
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 48 centers in United States between 26 March 2014 and 29 April 2015.

Pre-assignment

Screening details:

This was a multi center, randomized, double-blind, vehicle-controlled study where a total of 763 subjects with mild to moderate AD were randomized to receive either AN2728 ointment, 2 percent or AN2728 ointment matching vehicle, from Day 1 to Day 28.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AN2728 Topical Ointment, 2 Percent

Arm description:

Subjects with mild to moderate AD applied AN2728 ointment, 2 percent to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

Arm type	Experimental
Investigational medicinal product name	Crisaborole Topical Ointment, 2%
Investigational medicinal product code	
Other name	Crisaborole
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

AN2728 topical ointment, 2 percent to treatment targeted lesions, twice daily from Day 1 to Day 28.

Arm title	AN2728 Topical Ointment, Vehicle
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Arm description:

Subjects with mild to moderate AD applied AN2728 ointment matching vehicle to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

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

Dosage and administration details:

AN2728 topical ointment, Vehicle to treatment targeted lesions, twice daily from Day 1 to Day 28.

Number of subjects in period 1	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle
Started	507	256
Treated	503	256
Completed	477	225
Not completed	30	31
Consent withdrawn by subject	3	6
Unspecified	3	1
Adverse Events	7	2
Lost to follow-up	5	4
Withdrawal by parent/guardian	12	18

Baseline characteristics

Reporting groups

Reporting group title	AN2728 Topical Ointment, 2 Percent
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Reporting group description:

Subjects with mild to moderate AD applied AN2728 ointment, 2 percent to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

Reporting group title	AN2728 Topical Ointment, Vehicle
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Reporting group description:

Subjects with mild to moderate AD applied AN2728 ointment matching vehicle to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

Reporting group values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle	Total
Number of subjects	507	256	763
Age Categorical			
Units: Subjects			
Children (2-11 years)	321	151	472
Adolescents (12-17 years)	121	67	188
Adults (18-64 years)	63	38	101
From 65-84 years	2	0	2
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	12.03	12.36	
standard deviation	± 11.64	± 10.70	-
Gender Categorical			
Units: Subjects			
Female	285	143	428
Male	222	113	335

End points

End points reporting groups

Reporting group title	AN2728 Topical Ointment, 2 Percent
Reporting group description: Subjects with mild to moderate AD applied AN2728 ointment, 2 percent to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.	
Reporting group title	AN2728 Topical Ointment, Vehicle
Reporting group description: Subjects with mild to moderate AD applied AN2728 ointment matching vehicle to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.	

Primary: Percentage of Subjects Who Achieved Treatment Success Based on Investigator's Static Global Assessment (ISGA) at Day 29

End point title	Percentage of Subjects Who Achieved Treatment Success Based on Investigator's Static Global Assessment (ISGA) at Day 29
End point description: ISGA assessed the severity of AD (except scalp and venous access area) on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD. Grades for classification of severity: 0= clear (minor residual hypo/hyper pigmentation, no erythema or induration or papulation, no oozing or crusting), 1= almost clear (trace faint pink erythema, with barely perceptible induration or papulation and no oozing or crusting), 2= mild (faint pink erythema with mild induration or papulation and no oozing or crusting), 3= moderate (pink-red erythema with moderate induration or papulation with or without oozing or crusting) and 4= severe (deep or bright red erythema with severe induration or papulation and with oozing or crusting). Treatment success was defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline. Intent to treat population included all randomized subjects who received the study drug.	
End point type	Primary
End point timeframe: Day 29	

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	256		
Units: percentage of subjects				
number (not applicable)	32.8	25.4		

Statistical analyses

Statistical analysis title	AN2728 Topical Ointment 2 percent Vs. Vehicle
Comparison groups	AN2728 Topical Ointment, 2 Percent v AN2728 Topical Ointment, Vehicle

Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Regression, Logistic

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) And Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) And Serious Adverse Events (SAEs) ^[1]
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End point description:

An AE was any untoward medical occurrence attributed to a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; Initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent were events between first dose of study drug and up to end of study that were absent before treatment or that worsened relative to pre-treatment state. Safety population included all randomized subjects who received at least 1 confirmed dose of study drug, and had at least 1 post-baseline assessment.

End point type	Primary
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End point timeframe:

AEs: Baseline (Day 1) up to Day 29, SAEs: Baseline (Day 1) up to Day 36

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	252		
Units: subjects				
AEs	147	50		
SAEs	5	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs at Day 29

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs at Day 29 ^[2]
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End point description:

Following parameters were analyzed for examination of vital signs: systolic and diastolic blood pressure, respiratory rate and body temperature. Vital sign measurements were performed with the subject in the seated or supine position. Clinical significance of change from baseline value was determined by investigator. Safety population included all randomized subjects who received at least 1 confirmed dose of study drug, and had at least 1 post-baseline assessment.

End point type	Primary
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End point timeframe:

Baseline, Day 29

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	252		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Change From Baseline in Laboratory Values at Day 29

End point title	Number of Subjects With Clinically Significant Change From Baseline in Laboratory Values at Day 29 ^[3]
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End point description:

Laboratory values included: Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase, Albumin, Blood Urea Nitrogen, Creatinine, Hematocrit, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Platelets, Basophils, Eosinophils, Red blood cell count, White blood cell count, Total bilirubin and Glucose (nonfasting), Potassium, Total Protein, and Sodium. Clinical significance of change from baseline value was determined by investigator. Safety population included all randomized subjects who received at least 1 confirmed dose of study drug, and had at least 1 post-baseline assessment.

End point type	Primary
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End point timeframe:

Baseline, Day 29

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	252		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Investigator's Static Global Assessment (ISGA) Score of Clear (0) or Almost Clear (1) at Day 29

End point title	Percentage of Subjects With an Investigator's Static Global Assessment (ISGA) Score of Clear (0) or Almost Clear (1) at Day 29
End point description: ISGA assessed the severity of AD (except scalp and venous access area) on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD. Grades for classification of severity: 0= clear (minor residual discoloration, no erythema or induration or papulation, no oozing or crusting), 1= almost clear (trace faint pink erythema, with barely perceptible induration or papulation and no oozing or crusting), 2= mild (faint pink erythema with mild induration or papulation and no oozing or crusting), 3= moderate (pink-red erythema with moderate induration or papulation with or without oozing or crusting) and 4= severe (deep or bright red erythema with severe induration or papulation and with oozing or crusting). Percentage of subjects with an ISGA score of 0 or 1 were reported. Intent to treat population included all randomized subjects who received the study drug.	
End point type	Secondary
End point timeframe: Day 29	

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	256		
Units: percentage of subjects				
number (not applicable)	51.7	40.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Achieve Treatment Success Based on Investigator's Static Global Assessment (ISGA)

End point title	Time to Achieve Treatment Success Based on Investigator's Static Global Assessment (ISGA)
End point description: Time to achieve treatment success based on ISGA was defined as the time interval between the administrations of first dose of study drug until first documentation of success in ISGA. Success in ISGA was defined as an ISGA score of clear (0) or almost clear (1) with at least 2-grade improvement from baseline. It was analyzed using Kaplan-Meier method. The median time to achieve success in ISGA and its 95% confidence interval (CI) were not estimable, as fewer subjects (less than 50 percent) reached success in ISGA and has been denoted as 99999. Intent to treat population included all randomized subjects who received the study drug.	
End point type	Secondary
End point timeframe: Baseline (Day 1) up to Day 29	

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	256		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Signs of Atopic Dermatitis (AD) at Day 29

End point title	Change From Baseline in Signs of Atopic Dermatitis (AD) at Day 29
End point description:	
Signs of AD included erythema, induration/papulation, exudation, excoriation and lichenification. Each sign was assessed on a 4- point scale ranges from 0 to 3, where 0= none, 1= mild, 2= moderate to 3= severe. Higher score indicates severe signs and symptoms of AD. Here 'n' signifies those subjects who were evaluable at specified time point for each arm, respectively. Intent to treat population included all randomized subjects who received the study drug.	
End point type	Secondary
End point timeframe:	
Baseline, Day 29	

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	256		
Units: units on a scale				
arithmetic mean (standard deviation)				
Erythema: Baseline (n= 503, 256)	1.7 (± 0.59)	1.6 (± 0.57)		
Erythema: Change at Day 29 (n=478,228)	-0.7 (± 0.79)	-0.4 (± 0.77)		
Induration/Papulation: Baseline (n= 503, 256)	1.8 (± 0.59)	1.9 (± 0.56)		
Induration/Papulation:Change at Day 29 (n=478,228)	-0.7 (± 0.85)	-0.7 (± 0.73)		
Exudation: Baseline (n= 503, 256)	0.8 (± 0.82)	0.8 (± 0.86)		
Exudation: Change at Day 29 (n=478, 228)	-0.5 (± 0.78)	-0.3 (± 0.80)		
Excoriation: Baseline (n= 503, 256)	1.4 (± 0.70)	1.5 (± 0.71)		
Excoriation: Change at Day 29 (n=478, 228)	-0.8 (± 0.81)	-0.7 (± 0.89)		
Lichenification: Baseline (n= 503, 256)	1.5 (± 0.73)	1.5 (± 0.67)		
Lichenification: Change at Day 29 (n=478, 228)	-0.7 (± 0.81)	-0.5 (± 0.77)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Improvement in Pruritus

End point title	Time to Improvement in Pruritus
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End point description:

Time to improvement in pruritus was defined as the time interval between the administration of first dose of study drug till the first documentation of improvement in pruritus. Improvement in pruritus was defined as achieving none (0) or mild (1) score with at least a 1- grade improvement from baseline. Severity of pruritus was assessed on 4-point numeric scale ranges from 0 to 3, where 0= none (no itching), 1= mild (occasional, slight itching/scratching), 2= moderate (constant or intermittent itching/scratching which is not disturbing sleep) and 3= severe (bothersome itching/scratching which is disturbing sleep). Higher scores indicated more severe condition. It was analyzed using Kaplan-Meier method. Intent to treat population included all randomized subjects who received the study drug.

End point type	Other pre-specified
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End point timeframe:

Baseline up to Day 29

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	210		
Units: days				
median (confidence interval 95%)	1.32 (1.19 to 1.60)	1.87 (1.45 to 2.64)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Dermatology Life Quality Index (DLQI) Score at Day 29

End point title	Change From Baseline in Dermatology Life Quality Index (DLQI) Score at Day 29
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End point description:

The DLQI was a 10-item questionnaire that measures the impact of skin disease on subject's quality of life. Each question was evaluated on a 4-point scale ranging from 0 (not at all) to 3 (very much); where higher scores indicate more impact on quality of life. The DLQI total score ranges from 0 (not at all) to 30 (very much): 0-1 = no effect at all on the subject's life; 2-6 = small effect on the subject's life; 7-12 = moderate effect on the subject's life; 13-18 = very large effect on the subject's life; 19-30 = extremely large effect on the subjects's life. Higher scores indicate more impact on quality of life of subjects. Here, 'n' signifies those subjects who were evaluable at specified time point for each arm, respectively. Intent to treat population included all randomized subjects who received the study drug.

End point type	Other pre-specified
End point timeframe:	
Baseline, Day 29	

End point values	AN2728 Topical Ointment, 2 Percent	AN2728 Topical Ointment, Vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	256		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =95, 52)	9.6 (± 6.37)	9.5 (± 6.52)		
Change at Day 29 (n =87, 44)	-5.5 (± 5.45)	-3.6 (± 4.60)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to end of study (Day 36)

Adverse event reporting additional description:

Same event may appear as both an AE and Serious AE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Crisaborole (AN2728) Ointment, 2 percent
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Reporting group description:

Subjects with mild to moderate AD applied AN2728 ointment, 2 percent to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

Reporting group title	Crisaborole (AN2728) Ointment Vehicle
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Reporting group description:

Subjects with mild to moderate AD applied AN2728 ointment matching vehicle to treatment-targeted lesions, twice daily from Day 1 to Day 28. Target lesions were identified at Baseline (Day 1) by investigator.

Serious adverse events	Crisaborole (AN2728) Ointment, 2 percent	Crisaborole (AN2728) Ointment Vehicle	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 502 (1.00%)	1 / 252 (0.40%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Suicide attempt			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Crisaborole (AN2728) Ointment, 2 percent	Crisaborole (AN2728) Ointment Vehicle	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 502 (28.88%)	50 / 252 (19.84%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
Application site acne			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Application site discolouration			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Application site erosion			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Application site erythema			
subjects affected / exposed	2 / 502 (0.40%)	1 / 252 (0.40%)	
occurrences (all)	2	1	
Application site irritation			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Application site pain			
subjects affected / exposed	31 / 502 (6.18%)	3 / 252 (1.19%)	
occurrences (all)	34	3	
Application site pruritus			
subjects affected / exposed	4 / 502 (0.80%)	3 / 252 (1.19%)	
occurrences (all)	4	3	
Application site rash			
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)	
occurrences (all)	0	1	
Application site urticaria			
subjects affected / exposed	2 / 502 (0.40%)	0 / 252 (0.00%)	
occurrences (all)	2	0	
Application site vesicles			
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Medical device pain			

subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Pyrexia subjects affected / exposed occurrences (all)	12 / 502 (2.39%) 14	3 / 252 (1.19%) 3	
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	3 / 502 (0.60%) 4	0 / 252 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	5 / 502 (1.00%) 5	1 / 252 (0.40%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	7 / 502 (1.39%) 7	0 / 252 (0.00%) 0	
Nasal polyps subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 502 (0.80%) 4	0 / 252 (0.00%) 0	
Rhinitis allergic			

subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	1 / 252 (0.40%) 1	
Wheezing subjects affected / exposed occurrences (all)	2 / 502 (0.40%) 2	0 / 252 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Anxiety subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Confusional state subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Listless subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Blood potassium increased subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Blood pressure systolic increased			

subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Eosinophil count increased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Monocyte count increased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Staphylococcus test positive subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Blood urea increased subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Burns first degree subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Fall subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Laceration subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Ligament sprain			

subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Limb injury subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Scratch subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	1 / 252 (0.40%) 1	
Upper limb fracture subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Nervous system disorders Carpal tunnel syndrome subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	5 / 502 (1.00%) 5	0 / 252 (0.00%) 0	
Presyncope subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Blood and lymphatic system disorders Lymphocytosis subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	2 / 252 (0.79%) 2	
Neutropenia subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Ear and labyrinth disorders			

Cerumen impaction subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Eye disorders			
Blepharitis subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Conjunctivitis subjects affected / exposed occurrences (all)	4 / 502 (0.80%) 4	1 / 252 (0.40%) 1	
Myopia subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Xerophthalmia subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 502 (0.40%) 2	0 / 252 (0.00%) 0	
Anal fissure subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Dental discomfort subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	3 / 502 (0.60%) 3	0 / 252 (0.00%) 0	
Nausea			

subjects affected / exposed occurrences (all)	4 / 502 (0.80%) 4	0 / 252 (0.00%) 0	
Tooth disorder subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	8 / 502 (1.59%) 9	3 / 252 (1.19%) 3	
Skin and subcutaneous tissue disorders			
Angioedema subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Dyshidrotic eczema subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Dermatitis atopic subjects affected / exposed occurrences (all)	3 / 502 (0.60%) 3	2 / 252 (0.79%) 2	
Eczema subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Erythema subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Hyperkeratosis subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Ingrowing nail subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Pain of skin subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Pruritus generalised subjects affected / exposed occurrences (all)	2 / 502 (0.40%) 2	0 / 252 (0.00%) 0	

Rash papular subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Skin erosion subjects affected / exposed occurrences (all)	2 / 502 (0.40%) 3	0 / 252 (0.00%) 0	
Miliaria subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all)	0 / 502 (0.00%) 0	1 / 252 (0.40%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Muscle spasms subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Scoliosis subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Growing pains subjects affected / exposed occurrences (all)	1 / 502 (0.20%) 1	0 / 252 (0.00%) 0	
Infections and infestations			

Acarodermatitis		
subjects affected / exposed	1 / 502 (0.20%)	1 / 252 (0.40%)
occurrences (all)	1	1
Application site folliculitis		
subjects affected / exposed	2 / 502 (0.40%)	2 / 252 (0.79%)
occurrences (all)	2	2
Application site infection		
subjects affected / exposed	0 / 502 (0.00%)	2 / 252 (0.79%)
occurrences (all)	0	2
Bronchitis		
subjects affected / exposed	3 / 502 (0.60%)	0 / 252 (0.00%)
occurrences (all)	3	0
Cellulitis		
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)
occurrences (all)	0	1
Croup infectious		
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)
occurrences (all)	0	1
Ear infection		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Eczema infected		
subjects affected / exposed	4 / 502 (0.80%)	0 / 252 (0.00%)
occurrences (all)	4	0
Folliculitis		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Gastroenteritis viral		
subjects affected / exposed	1 / 502 (0.20%)	1 / 252 (0.40%)
occurrences (all)	1	1
Hand-foot-and-mouth disease		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Impetigo		
subjects affected / exposed	5 / 502 (1.00%)	0 / 252 (0.00%)
occurrences (all)	5	0

Influenza		
subjects affected / exposed	1 / 502 (0.20%)	1 / 252 (0.40%)
occurrences (all)	1	1
Molluscum contagiosum		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	9 / 502 (1.79%)	0 / 252 (0.00%)
occurrences (all)	9	0
Oral herpes		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Otitis externa		
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	2 / 502 (0.40%)	2 / 252 (0.79%)
occurrences (all)	2	2
Otitis media acute		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	3 / 502 (0.60%)	0 / 252 (0.00%)
occurrences (all)	3	0
Pharyngitis streptococcal		
subjects affected / exposed	1 / 502 (0.20%)	2 / 252 (0.79%)
occurrences (all)	1	2
Prostate infection		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0
Pyoderma		
subjects affected / exposed	1 / 502 (0.20%)	1 / 252 (0.40%)
occurrences (all)	1	1
Rash pustular		
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)
occurrences (all)	1	0

Rhinitis			
subjects affected / exposed	2 / 502 (0.40%)	0 / 252 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	3 / 502 (0.60%)	0 / 252 (0.00%)	
occurrences (all)	3	0	
Skin infection			
subjects affected / exposed	2 / 502 (0.40%)	1 / 252 (0.40%)	
occurrences (all)	2	1	
Staphylococcal skin infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	14 / 502 (2.79%)	10 / 252 (3.97%)	
occurrences (all)	15	11	
Urinary tract infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 252 (0.40%)	
occurrences (all)	0	1	
Viral infection			
subjects affected / exposed	1 / 502 (0.20%)	1 / 252 (0.40%)	
occurrences (all)	1	1	
Viral rash			
subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 502 (0.40%)	0 / 252 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Iron deficiency			

subjects affected / exposed	1 / 502 (0.20%)	0 / 252 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported