Clinical trial results:
A Multicenter, Open-Label Study of the Long-Term Safety of AN2728 Topical Ointment, 2% in the Treatment of Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis

Summary

EudraCT number	2018-000904-40
Trial protocol	Outside EU/EEA
Global end of trial date	27 August 2015

Results information

Result version number	v1 (current)
This version publication date	17 May 2019
First version publication date	17 May 2019

Trial information

Trial identification

Sponsor protocol code	C3291005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, 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)	EMEA-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	24 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of open-label treatment with AN2728 Topical Ointment, 2% in children, adolescents, and adults (ages 2 years and older) with mild to moderate 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 trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 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: 517
Worldwide total number of subjects	517
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)	308
Adolescents (12-17 years)	146
Adults (18-64 years)	61
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 41 investigational sites in the United States from 30 Apr 2014 to 27 Aug 2015. A total of 517 subjects were enrolled.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AN2728 Ointment, 2 percent

Arm description:

AN2728 ointment 2 percent was applied topically to investigator-identified AD-involved areas of the skin (excluding scalp) in subjects with mild to moderate AD, twice daily in each treatment cycle for up to 48 weeks (each cycle 4 weeks).

Arm type	Experimental
Investigational medicinal product name	AN2728 Topical Ointment, 2%
Investigational medicinal product code	
Other name	Crisaborole
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects were applied AN2728 Topical Ointment, 2 percent twice daily for 48 weeks (each cycle 4 weeks).

Number of subjects in period 1	AN2728 Ointment, 2 percent
Started	517
Completed	271
Not completed	246
Consent withdrawn by subject	23
Adverse event	9
Withdrawal by Parent/Guardian	63
Unspecified	115
Lost to follow-up	36

Baseline characteristics

Reporting groups	
Reporting group title	AN2728 Ointment, 2 percent

Reporting group description:

AN2728 ointment 2 percent was applied topically to investigator-identified AD-involved areas of the skin (excluding scalp) in subjects with mild to moderate AD, twice daily in each treatment cycle for up to 48 weeks (each cycle 4 weeks).

Reporting group values	AN2728 Ointment, 2 percent	Total	
Number of subjects	517	517	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	308	308	
Adolescents (12-17 years)	146	146	
Adults (18-64 years)	61	61	
From 65-84 years	2	2	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	11.71		
standard deviation	± 10.39	-	
Gender Categorical Units: Subjects			
Female	306	306	
Male	211	211	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	28	28	
Black or African American	152	152	
Native Hawaiian or Other Pacific Islander	1	1	
White	315	315	
Other	20	20	

End points

End points reporting groups

Reporting group title	AN2728 Ointment, 2 percent

Reporting group description:

AN2728 ointment 2 percent was applied topically to investigator-identified AD-involved areas of the skin (excluding scalp) in subjects with mild to moderate AD, twice daily in each treatment cycle for up to 48 weeks (each cycle 4 weeks).

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]

End point description:

An AE was any untoward medical occurrence in 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 (up to 48 weeks) that were absent before treatment or that worsened relative to pretreatment state. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline up to end of study (up to 48 weeks)

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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: subjects				
AEs	336			
SAEs	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Baseline

End point title	Number of Subjects With Local Tolerability Symptoms at Baseline[2]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated

more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline (Day 1)

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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: subjects				
None	346			
Mild	87			
Moderate	56			
Severe	28			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 4

End point title	Number of Subjects With Local Tolerability Symptoms at Week 4[3]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 4

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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	494			
Units: subjects				
None	306			
Mild	110			
Moderate	52			
Severe	26			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 8

End point title	Number of Subjects With Local Tolerability Symptoms at Week 8[4]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 8

Notes:

[4] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	454			
Units: subjects				
None	294			
Mild	101			
Moderate	47			
Severe	12			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 12

End point title	Number of Subjects With Local Tolerability Symptoms at Week 12[5]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 12

Notes:

[5] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	439			
Units: subjects				
None	308			
Mild	79			
Moderate	39			
Severe	13			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 16

End point title	Number of Subjects With Local Tolerability Symptoms at Week 16[6]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 16

Notes:

[6] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	417			
Units: subjects				
None	296			
Mild	82			
Moderate	33			
Severe	6			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 20

End point title	Number of Subjects With Local Tolerability Symptoms at Week 20[7]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 20

Notes:

[7] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	407			
Units: subjects				
None	291			
Mild	66			
Moderate	40			
Severe	10			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 24

End point title	Number of Subjects With Local Tolerability Symptoms at Week 24[8]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 24

Notes:

[8] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	403			
Units: subjects				
None	282			
Mild	89			
Moderate	28			
Severe	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 28

End point title	Number of Subjects With Local Tolerability Symptoms at Week 28[9]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 28

Notes:

[9] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	384			
Units: subjects				
None	294			
Mild	59			
Moderate	23			
Severe	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 32

End point title	Number of Subjects With Local Tolerability Symptoms at Week 32[10]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 32

Notes:

[10] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	377			
Units: subjects				
None	271			
Mild	77			
Moderate	23			
Severe	6			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 36

End point title	Number of Subjects With Local Tolerability Symptoms at Week 36[11]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 36

Notes:

[11] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	348			
Units: subjects				
None	259			
Mild	63			
Moderate	19			
Severe	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 40

End point title	Number of Subjects With Local Tolerability Symptoms at Week 40[12]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 40

Notes:

[12] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	319			
Units: subjects				
None	228			
Mild	68			
Moderate	14			
Severe	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 44

End point title	Number of Subjects With Local Tolerability Symptoms at Week 44[13]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 44

Notes:

[13] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	291			
Units: subjects				
None	214			
Mild	51			
Moderate	21			
Severe	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Local Tolerability Symptoms at Week 48

End point title	Number of Subjects With Local Tolerability Symptoms at Week 48[14]

End point description:

Local tolerability symptoms were assessed on 4-point scale ranging from 0 to 3, where 0 = none (no stinging/burning), 1 = mild (slight warm, tingling sensation, not really bothersome); 2= moderate (definite warm; tingling or stinging sensation that was somewhat bothersome and severe) and 3= severe (hot, tingling or stinging sensation that had caused definite discomfort). Higher scores indicated more severe symptoms. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Week 48

Notes:

[14] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	273			
Units: subjects				
None	212			
Mild	46			
Moderate	12			
Severe	3			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Investigator's Static Global Assessment (ISGA) Score

End point title	Change From Baseline in Investigator's Static Global Assessment (ISGA) Score[15]

End point description:

Data not reported since disease severity assessments were not evaluated as primary endpoint because this was only to determine need for treatment.

End point type	Primary

End point timeframe:

Baseline up to end of study (up to 48 weeks)

Notes:

[15] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: subjects				

Notes:

[16] - Data not reported.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Concomitant use of Topical Corticosteroid (TCS)

End point title	Number of Subjects With Concomitant use of Topical Corticosteroid (TCS)[17]

End point description:

Concomitant medications administered prior to and during the study were reported across World Health Organization drug dictionary anatomical therapeutic chemical (ATC) categories and were typically indicated for use for pre-existing medical conditions (including AD, dryness of the skin, allergic rhinitis, asthma) or AEs. The most commonly reported medications by ATC Level 2 term were antihistamines for systemic use, drugs for obstructive airway diseases, antibacterials for systemic use, corticosteroids and dermatological preparations. Corticosteroids, dermatological preparations that were used by at least 1% of subjects by preferred name, were triamcinolone, hydrocortisone, desonide, triamcinolone acetonide, and mometasone furoate. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline up to end of study (up to 48 weeks)

Notes:

[17] - 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 reported for this endpoint

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: subjects	121			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Body Temperature at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point title	Change From Baseline in Body Temperature at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point description:

Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment. Here, "n" signifies subjects evaluable for the specific categories at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline; Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: fahrenheit				
arithmetic mean (standard deviation)				

Temperature: At Baseline (n=517)	98.00 (± 0.634)			
Temperature: Change at Week 4 (n=495)	0.04 (± 0.673)			
Temperature: Change at Week 8 (n=460)	0.01 (± 0.742)			
Temperature: Change at Week 12 (n=446)	-0.01 (± 0.711)			
Temperature: Change at Week 16 (n=422)	-0.06 (± 0.761)			
Temperature: Change at Week 20 (n=407)	-0.03 (± 0.734)			
Temperature: Change at Week 24 (n=401)	-0.07 (± 0.694)			
Temperature: Change at Week 28 (n=383)	-0.05 (± 0.745)			
Temperature: Change at Week 32 (n=378)	-0.05 (± 0.748)			
Temperature: Change at Week 36 (n=349)	-0.08 (± 0.735)			
Temperature: Change at Week 40 (n=319)	-0.06 (± 0.733)			
Temperature: Change at Week 44 (n=291)	-0.02 (± 0.729)			
Temperature: Change at Week 48 (n=273)	-0.01 (± 0.714)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point title	Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point description:

Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment. Here, "n" signifies subjects evaluable for the specific categories at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline; Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: millimeters of mercury				
arithmetic mean (standard deviation)				

SBP: At Baseline (n=517)	105.3 (± 13.45)			
SBP: Change at Week 4 (n=493)	-0.3 (± 10.10)			
SBP: Change at Week 8 (n=458)	-0.4 (± 10.84)			
SBP: Change at Week 12 (n=446)	0.2 (± 11.17)			
SBP: Change at Week 16 (n=421)	0.4 (± 10.43)			
SBP: Change at Week 20 (n=404)	1.2 (± 11.38)			
SBP: Change at Week 24 (n=401)	0.6 (± 10.93)			
SBP: Change at Week 28 (n=383)	1.9 (± 11.04)			
SBP: Change at Week 32 (n=377)	1.2 (± 10.92)			
SBP: Change at Week 36 (n=348)	1.4 (± 11.11)			
SBP: Change at Week 40 (n=318)	0.7 (± 11.64)			
SBP: Change at Week 44 (n=290)	0.2 (± 11.91)			
SBP: Change at Week 48 (n=272)	2.0 (± 11.06)			
DBP: At Baseline (n=517)	66.1 (± 9.04)			
DBP: At Week 4 (n=493)	0.2 (± 8.98)			
DBP: At Week 8 (n=457)	-0.2 (± 9.00)			
DBP: At Week 12 (n=446)	0.2 (± 8.87)			
DBP: At Week 16 (n=421)	0.6 (± 8.85)			
DBP: At Week 20 (n=404)	0.7 (± 9.04)			
DBP: At Week 24 (n=401)	0.5 (± 9.63)			
DBP: At Week 28 (n=383)	0.6 (± 9.40)			
DBP: At Week 32 (n=377)	0.9 (± 9.89)			
DBP: At Week 36 (n=348)	0.9 (± 9.96)			
DBP: At Week 40 (n=318)	0.1 (± 9.60)			
DBP: At Week 44 (n=290)	0.4 (± 10.33)			
DBP: At Week 48 (n=272)	0.8 (± 9.71)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Pulse Rate at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point title	Change From Baseline in Pulse Rate at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point description:

Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment. Here, "n" signifies subjects evaluable for the specific categories at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline; Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: beats per minute				
arithmetic mean (standard deviation)				
Pulse Rate: At Baseline (n=517)	85.3 (± 14.05)			
Pulse Rate: Change at Week 4 (n=493)	-0.4 (± 12.58)			
Pulse Rate: Change at Week 8 (n=457)	-1.3 (± 12.03)			
Pulse Rate: Change at Week 12 (n=446)	-0.4 (± 13.75)			
Pulse Rate: Change at Week 16 (n=421)	-0.5 (± 12.90)			
Pulse Rate: Change at Week 20 (n=406)	0.1 (± 13.11)			
Pulse Rate: Change at Week 24 (n=401)	0.0 (± 13.54)			
Pulse Rate: Change at Week 28 (n=383)	0.2 (± 13.65)			
Pulse Rate: Change at Week 32 (n=377)	0.4 (± 12.66)			
Pulse Rate: Change at Week 36 (n=348)	0.2 (± 12.34)			
Pulse Rate: Change at Week 40 (n=318)	0.1 (± 12.58)			
Pulse Rate: Change at Week 44 (n=290)	-1.4 (± 12.08)			
Pulse Rate: Change at Week 48 (n=272)	-0.7 (± 12.36)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Respiratory Rate at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point title	Change From Baseline in Respiratory Rate at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point description:

Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment. Here, "n" signifies subjects evaluable for the specific categories at specified time point.

End point type	Other pre-specified

End point timeframe:

Baseline; Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: breaths per minute				
arithmetic mean (standard deviation)				
Respiratory Rate: At Baseline (n=517)	18.9 (± 3.33)			
Respiratory Rate: Change at Week 4 (n=494)	0.2 (± 2.74)			
Respiratory Rate: Change at Week 8 (n=459)	0.1 (± 2.85)			
Respiratory Rate: Change at Week 12 (n=445)	0.1 (± 2.91)			
Respiratory Rate: Change at Week 16 (n=421)	0.1 (± 2.91)			
Respiratory Rate: Change at Week 20 (n=407)	0.3 (± 3.13)			
Respiratory Rate: Change at Week 24 (n=401)	0.3 (± 2.71)			
Respiratory Rate: Change at Week 28 (n=384)	0.2 (± 2.96)			
Respiratory Rate: Change at Week 32 (n=378)	0.1 (± 2.94)			
Respiratory Rate: Change at Week 36 (n=349)	0.2 (± 2.73)			
Respiratory Rate: Change at Week 40 (n=318)	0.4 (± 2.88)			
Respiratory Rate: Change at Week 44 (n=291)	0.1 (± 3.06)			
Respiratory Rate: Change at Week 48 (n=273)	0.2 (± 2.78)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Abnormalities

End point title	Number of Subjects With Laboratory Abnormalities

End point description:

Laboratory parameters included: hematology (hemoglobin, hematocrit, red blood cell, platelet and white blood cell count, neutrophils, eosinophils, monocytes, basophils and lymphocytes), chemistry (blood urea nitrogen, creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, albumin, total protein and urine (urine pregnancy test [for all female subjects of childbearing potential only]). Clinical significance of laboratory parameters was determined at the investigator's discretion. Safety analysis set included all subjects who received at least one confirmed dose of study drug and had at least one post-baseline assessment. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Other pre-specified

End point timeframe:

Baseline up to end of study (up to 48 weeks)

End point values	AN2728 Ointment, 2 percent			
Subject group type	Reporting group			
Number of subjects analysed	517			
Units: subjects	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (up to 48 weeks)

Adverse event reporting additional description:

Same event may appear as both an adverse event (AE) and serious adverse event (SAE). 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	AN2728 Ointment, 2 percent

Reporting group description:

AN2728 ointment 2 percent was applied topically to treatment-targeted lesions in subjects with mild to moderate AD, twice daily for up to 28 days. Lesions were identified at Baseline (Day 1) by investigator.

Serious adverse events	AN2728 Ointment, 2 percent		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 517 (1.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CNS ventriculitis			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Application site infection			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 517 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AN2728 Ointment, 2 percent		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	243 / 517 (47.00%)		
Nervous system disorders			

Headache			
subjects affected / exposed	11 / 517 (2.13%)		
occurrences (all)	14		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	12 / 517 (2.32%)		
occurrences (all)	14		
Pyrexia			
subjects affected / exposed	29 / 517 (5.61%)		
occurrences (all)	40		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	11 / 517 (2.13%)		
occurrences (all)	12		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 517 (2.32%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	15 / 517 (2.90%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	15 / 517 (2.90%)		
occurrences (all)	18		
Cough			
subjects affected / exposed	35 / 517 (6.77%)		
occurrences (all)	42		
Oropharyngeal pain			
subjects affected / exposed	19 / 517 (3.68%)		
occurrences (all)	19		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	58 / 517 (11.22%)		
occurrences (all)	72		
Dermatitis contact			

subjects affected / exposed	16 / 517 (3.09%)		
occurrences (all)	17		
Eczema			
subjects affected / exposed	13 / 517 (2.51%)		
occurrences (all)	17		
Infections and infestations			
Application site infection			
subjects affected / exposed	18 / 517 (3.48%)		
occurrences (all)	20		
Ear infection			
subjects affected / exposed	12 / 517 (2.32%)		
occurrences (all)	12		
Influenza			
subjects affected / exposed	12 / 517 (2.32%)		
occurrences (all)	13		
Nasopharyngitis			
subjects affected / exposed	40 / 517 (7.74%)		
occurrences (all)	46		
Otitis media			
subjects affected / exposed	11 / 517 (2.13%)		
occurrences (all)	12		
Pharyngitis			
subjects affected / exposed	12 / 517 (2.32%)		
occurrences (all)	17		
Pharyngitis streptococcal			
subjects affected / exposed	20 / 517 (3.87%)		
occurrences (all)	22		
Sinusitis			
subjects affected / exposed	25 / 517 (4.84%)		
occurrences (all)	29		
Upper respiratory tract infection			
subjects affected / exposed	52 / 517 (10.06%)		
occurrences (all)	69		
Viral infection			
subjects affected / exposed	11 / 517 (2.13%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2014	1) Grading of local tolerability safety assessment included at scheduled in-clinic visits of each On- and Off-Treatment Period for safety assessment. 2) Description revised for subjects requiring pregnancy test from "postmenarchal females" to "females of childbearing potential".
25 July 2014	1) A complete physical examination was added at Study Day 337 (End-of-Study) and the early discontinuation visit to collect more comprehensive safety data. 2) Added requirement for women who become of childbearing potential during the study who were previously considered of nonchildbearing potential (ie, menses begins), a urine pregnancy test should be performed at the next study visit to clarify the birth control requirements. 3) Additional procedures visits added to the study Day 85 (Week 12) and study Day 253 (Week 36) to the schedule of events table in order to obtain additional clinical laboratory test results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data not reported since disease severity assessments were not evaluated as primary endpoint because this was only to determine need for treatment.

Notes: