# 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<br>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<br>Units: years | | | |
| arithmetic mean | 11.71 | | |
| standard deviation | ± 10.39 | - | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 306 | 306 | |
| Male | 211 | 211 | |
| Race/Ethnicity, Customized<br>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.<br>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.<br>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.<br>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: