



Clinical trial results:

A Phase 3B/4, Multicenter, Randomized, Assessor Blinded, Vehicle and Active (Topical Corticosteroid and Calcineurin Inhibitor) Controlled, Parallel Group Study of the Efficacy, Safety, and Local Tolerability of Crisaborole Ointment, 2% in Pediatric and Adult Subjects (Ages 2 Years and Older) With Mild to Moderate Atopic Dermatitis

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2018-001043-31 |
| Trial protocol | SE GB DE BE PL IT |
| Global end of trial date | 11 December 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 25 June 2021 |
| First version publication date | 25 June 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | C3291037 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03539601 |
| 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 ClinicalTrials.gov Call Center, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 December 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of crisaborole ointment, 2 percent (%) applied twice daily (BID) versus vehicle in pediatric and adult subjects, aged 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 trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 14 May 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Germany: 38 |
| Country: Number of subjects enrolled | Italy: 18 |
| Country: Number of subjects enrolled | Poland: 14 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | Switzerland: 9 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 151 |
| Worldwide total number of subjects | 237 |
| EEA total number of subjects | 76 |

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) | 96 |

| | |
|---------------------------|----|
| Adolescents (12-17 years) | 48 |
| Adults (18-64 years) | 87 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Number of subjects enrolled at study termination was insufficient to allow meaningful inference and robust statistical analyses. As a result all safety data were summarized with Cohort 1 and Cohort 2 combined for crisaborole and vehicle groups. PIP (EMA-002065-PIP01-16-M03) was discontinued in Oct 2020 for business reasons after study termination.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vehicle |

Arm description:

Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

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

Dosage and administration details:

Vehicle matched to Crisaborole ointment 2% was applied topically BID at Baseline (Day 1) through Day 28.

| | |
|------------------|-----------------------------|
| Arm title | Crisaborole Ointment 2% BID |
|------------------|-----------------------------|

Arm description:

Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Crisaborole |
| Investigational medicinal product code | |
| Other name | PF-06930164, AN2728 |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Crisaborole ointment 2% was applied topically BID at Baseline (Day 1) through Day 28.

| | |
|------------------|--|
| Arm title | Hydrocortisone Butyrate Cream 0.1% BID |
|------------------|--|

Arm description:

Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

| | |
|--|-------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Hydrocortisone Butyrate |
| Investigational medicinal product code | |
| Other name | Locoid |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Hydrocortisone Butyrate cream 0.1% was applied topically BID at Baseline (Day 1) through Day 28.

| | |
|------------------|---------------------------|
| Arm title | Pimecrolimus Cream 1% BID |
|------------------|---------------------------|

Arm description:

Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Pimecrolimus |
| Investigational medicinal product code | |
| Other name | Elidel |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Pimecrolimus cream 1% was applied topically BID at Baseline (Day 1) through Day 28.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Subject, assessor and carer were blind in the study

| Number of subjects in period 1 ^[2] | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID |
|---|---------|-----------------------------|--|
| | | | |
| Started | 59 | 58 | 71 |
| Completed | 54 | 52 | 65 |
| Not completed | 5 | 6 | 6 |
| Consent withdrawn by subject | 2 | - | - |
| Adverse event, non-fatal | - | 2 | - |
| Withdraw by parent/guardian | 1 | - | 1 |
| Lost to follow-up | 2 | 4 | 5 |

| Number of subjects in period 1 ^[2] | Pimecrolimus Cream 1% BID |
|---|---------------------------|
| | |
| Started | 47 |
| Completed | 46 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | - |
| Withdraw by parent/guardian | - |
| Lost to follow-up | - |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline analysis was performed on Safety Analysis Set (SAF) which included all subjects

who received at least one dose of the investigational product according to actual treatment received.

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Vehicle |
| Reporting group description: | |
| Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Crisaborole Ointment 2% BID |
| Reporting group description: | |
| Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Hydrocortisone Butyrate Cream 0.1% BID |
| Reporting group description: | |
| Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Pimecrolimus Cream 1% BID |
| Reporting group description: | |
| Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |

| Reporting group values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID |
|--|---------|-----------------------------|--|
| Number of subjects | 59 | 58 | 71 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 26 | 25 | 26 |
| Adolescents (12-17 years) | 12 | 12 | 13 |
| Adults (18-64 years) | 20 | 18 | 31 |
| From 65-84 years | 1 | 3 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 35 | 35 | 43 |
| Male | 24 | 23 | 28 |
| Race | | | |
| Units: Subjects | | | |
| White | 38 | 38 | 44 |
| Black or African American | 17 | 14 | 23 |
| Asian | 2 | 3 | 1 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |

| | | | |
|------------------------------|----|----|----|
| Multiracial | 1 | 3 | 1 |
| Not Reported | 0 | 0 | 2 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 6 | 1 | 11 |
| Not Hispanic or Latino | 53 | 57 | 60 |

| Reporting group values | Pimecrolimus Cream 1% BID | Total | |
|---|------------------------------|-------|--|
| Number of subjects | 47 | 235 | |
| 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) | 19 | 96 | |
| Adolescents (12-17 years) | 11 | 48 | |
| Adults (18-64 years) | 16 | 85 | |
| From 65-84 years | 1 | 6 | |
| 85 years and over | 0 | 0 | |
| Gender Categorical Units: Subjects | | | |
| Female | 26 | 139 | |
| Male | 21 | 96 | |
| Race Units: Subjects | | | |
| White | 37 | 157 | |
| Black or African American | 6 | 60 | |
| Asian | 3 | 9 | |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | |
| Multiracial | 0 | 5 | |
| Not Reported | 1 | 3 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 4 | 22 | |
| Not Hispanic or Latino | 43 | 213 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Vehicle |
| Reporting group description: Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Crisaborole Ointment 2% BID |
| Reporting group description: Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Hydrocortisone Butyrate Cream 0.1% BID |
| Reporting group description: Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Reporting group title | Pimecrolimus Cream 1% BID |
| Reporting group description: Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Subject analysis set title | Vehicle: Subjects 2-17 Years |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Subject analysis set title | Crisaborole Ointment 2% BID: Subjects 2-17 Years |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Subject analysis set title | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Subject analysis set title | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60. | |
| Subject analysis set title | Vehicle: Subjects >=18 Years |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to | |

Day 60.

| | |
|----------------------------|--|
| Subject analysis set title | Crisaborole Ointment 2% BID: Subjects >=18 Years |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

| | |
|----------------------------|---|
| Subject analysis set title | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

| | |
|----------------------------|--|
| Subject analysis set title | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up for at least 28 days after last dose, maximum up to Day 60.

Primary: Percent Change From Baseline in the Eczema Area and Severity Index (EASI) Total Score at Day 29

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in the Eczema Area and Severity Index (EASI) Total Score at Day 29 ^[1] |
|-----------------|--|

End point description:

EASI quantifies severity of AD (excluded scalp) based on lesion severity and percent (%) body surface area (%BSA) affected. Lesion severity included erythema(E), induration/papulation(I), excoriation(Ex), lichenification(L) scored for 4 regions (head, neck [h], upper limbs [u], trunk [t] [including axillae, groin], lower limbs [l] [including buttocks]) on 4-point scale: 0=absent;1=mild;2=moderate;3=severe. EASI area score(A) based upon %BSA with AD in body region:0(0%),1(>0to<10%),2(10to<30%),3(30to<50%),4(50to<70%),5(70to<90%),6(90to100%). Total EASI score (aged>=8 years)=0.1*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+Exu+Lu)+0.3*At*(Et+It+Ext+Lt)+0.4*Al*(El+Il+Exl+Ll); for aged 2to<8 years=0.2*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+Exu+Lu)+0.3*At*(Et+It+Ext+Lt)+0.3*Al*(El+Il+Exl+Ll). Total score range=0.0-72.0, higher scores=greater AD severity. Full analysis set: randomized

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Day 29

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 | Vehicle: Subjects 2-17 Years | Crisaborole Ointment 2% BID: Subjects 2-17 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
|--------------------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 31 | 36 | 29 |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -26.62 (± 46.283) | -49.47 (± 34.195) | -75.50 (± 30.305) | -60.08 (± 31.877) |

| End point values | Vehicle: Subjects >=18 Years | Crisaborole Ointment 2% BID: Subjects >=18 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
|--------------------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 17 | 19 | 29 | 14 |
| Units: Percent change | | | | |
| arithmetic mean (standard deviation) | -44.67 (± 49.267) | -57.14 (± 48.345) | -70.29 (± 32.097) | -62.59 (± 28.317) |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Adverse Events (AEs), Serious Adverse Events (SAEs) and Discontinuations due to AEs and SAEs

| | |
|-----------------|---|
| End point title | Number of Subjects with Adverse Events (AEs), Serious Adverse Events (SAEs) and Discontinuations due to AEs and SAEs ^[2] |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. A SAE is any untoward medical occurrence at any dose that: results in death; is life-threatening (immediate risk of death); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); results in congenital anomaly/birth defect; or that is considered to be an important medical event. Safety analysis set (SAF) included all subjects who received at least one dose of the investigational product according to actual treatment received.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline up to 28 days after last dose of study treatment (up to 60 Days)

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 | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 71 | 47 |
| Units: subjects | | | | |
| AEs | 18 | 25 | 12 | 24 |
| SAEs | 0 | 0 | 0 | 0 |
| Discontinuation due to AEs | 0 | 3 | 0 | 0 |
| Discontinuation due to SAEs | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Local Tolerability Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Number of Subjects with Local Tolerability Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[3] |
|-----------------|--|

End point description:

Local tolerability adverse events included application and instillation site reactions, application site discharge, application site erythema, application site exfoliation, application site pain, application site pruritus, application site swelling, dermatitis and eczema, dermatitis atopic, dermatitis contact, eczema, skin irritation, telangiectasia and related conditions, and urticarias. SAF included all subjects who received at least one dose of the investigational product according to actual treatment received.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline up to 28 days after last dose of study treatment (up to 60 Days)

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 | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 71 | 47 |
| Units: subjects | | | | |
| AEs | 12 | 13 | 2 | 8 |
| SAEs | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Signs

| | |
|-----------------|--|
| End point title | Number of Subjects With Clinically Significant Changes in Vital Signs ^[4] |
|-----------------|--|

End point description:

Vital sign measurements included temperature, respiratory rate, pulse rate, and blood pressure. Temperature, respiratory rate, pulse rate, and blood pressure was taken in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes (when possible for younger children). Position of recording was consistent within subject through-out the study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening up to Day 29

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 analyzed for this endpoint.

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 71 | 47 |
| Units: subjects | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Clinically Significant Abnormal Laboratory Parameters

| | |
|-----------------|--|
| End point title | Number of Subjects with Clinically Significant Abnormal Laboratory Parameters ^[5] |
|-----------------|--|

End point description:

Hematology parameters included with criteria greater than (>) 1.2*upper limit of normal (ULN): leukocytes (10³ per cubic millimeter [10³/mm³]), lymphocytes (10³/mm³), lymphocytes/leukocytes (%), neutrophils (10³/mm³), neutrophils/leukocytes (%), basophils/leukocytes (%), eosinophils (10³/mm³), eosinophils/leukocytes (%), monocytes (10³/mm³), monocytes/leukocytes (%). Clinical chemistry included parameters: aspartate aminotransferase (units per litre [U/L]) (>3.0* ULN), alanine aminotransferase (U/L) (>3.0* ULN), alkaline phosphatase (U/L) (>3.0* ULN), creatinine (milligram per deciliter [mg/dL]) (>1.3* ULN), potassium (milliequivalent per litre [mEq/L]) (>1.1* ULN), bicarbonate (mEq/L) (>1.1* ULN). SAF included all subjects who received at least 1 dose of investigational product according to actual treatment received.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening up to Day 29

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 analyzed for this endpoint.

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 71 | 47 |
| Units: subjects | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Eczema Area And Severity Index (EASI) Total Score at Days 8, 15 and 22

| | |
|--|--|
| End point title | Percent Change From Baseline in Eczema Area And Severity Index (EASI) Total Score at Days 8, 15 and 22 |
| End point description: | |
| EASI quantifies severity of AD (excluded scalp) based on severity of lesion and %BSA affected. Lesion severity included erythema, induration/papulation, excoriation, lichenification scored for 4 regions (head, neck, upper limbs, trunk [including axillae, groin], lower limbs [including buttocks]) on 4-point scale: 0=absent;1=mild;2=moderate;3=severe. EASI area score(A) based upon %BSA with AD in body region: 0(0%), 1(>0to<10%), 2(10to<30%), 3(30to<50%), 4(50to<70%), 5(70to<90%), 6(90to100%). Total EASI score (aged>=8 years)=0.1*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+ExU+Lu)+0.3*At*(Et+It+Ext+Lt)+0.4*Al*(El+Il+Exl+LI); for aged 2to<8 years=0.2*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+ExU+Lu)+0.3*At*(Et+It+Ext+Lt)+0.3*Al*(El+Il+Exl+LI). Total EASI score range=0.0-72.0, higher scores=greater severity of AD. Analysis was performed on FAS. Number of Subjects Analysed=subjects evaluable for endpoint and 'Number Analysed | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days 8, 15 and 22 | |

| End point values | Vehicle: Subjects 2-17 Years | Crisaborole Ointment 2% BID: Subjects 2-17 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
|--|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 33 | 37 | 30 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 37, 33, 33, 29, 19, 21, 27, 16) | -17.88 (± 36.705) | -26.79 (± 39.280) | -45.59 (± 28.103) | -34.20 (± 25.972) |
| Day 15 (n= 33, 33, 37, 30, 15, 20, 27, 14) | -25.77 (± 35.658) | -36.72 (± 36.625) | -58.96 (± 32.617) | -42.75 (± 31.854) |
| Day 22 (n= 32, 31, 35, 26, 18, 19, 27, 15) | -25.07 (± 49.326) | -38.87 (± 32.624) | -69.09 (± 31.528) | -59.86 (± 24.835) |

| End point values | Vehicle: Subjects >=18 Years | Crisaborole Ointment 2% BID: Subjects >=18 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
|--|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 21 | 27 | 16 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 37, 33, 33, 29, 19, 21, 27, 16) | -14.77 (± 26.308) | -29.83 (± 44.599) | -42.48 (± 27.843) | -18.75 (± 39.016) |
| Day 15 (n= 33, 33, 37, 30, 15, 20, 27, 14) | -25.93 (± 31.690) | -48.42 (± 33.458) | -56.29 (± 32.186) | -37.18 (± 50.487) |
| Day 22 (n= 32, 31, 35, 26, 18, 19, 27, 15) | -34.43 (± 30.587) | -56.05 (± 38.934) | -61.82 (± 27.894) | -42.25 (± 40.192) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Success in the Investigator's Static Global Assessment (ISGA) (ISGA Score of Clear [0] or Almost Clear [1] With at Least a 2-Grade Improvement From Baseline) at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Number of Subjects who Achieved Success in the Investigator's Static Global Assessment (ISGA) (ISGA Score of Clear [0] or Almost Clear [1] With at Least a 2-Grade Improvement From Baseline) at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

ISGA is a five point global assessment scale of AD severity, was used to characterize subjects' overall disease severity across all treatable AD lesions (excluding the scalp). ISGA score ranged from 0 to 4: where 0 = clear (minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting), 1= almost clear (trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting), 2= mild (faint pink erythema with mild induration/papulation and no oozing/crusting), 3= moderate (pink-red erythema with moderate induration/papulation with or without oozing/crusting), 4= severe (deep or bright red erythema with severe induration/papulation and with oozing/crusting). Higher scores indicated greater severity of AD. Full analysis set (FAS) included all randomized subjects who received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle: Subjects 2-17 Years | Crisaborole Ointment 2% BID: Subjects 2-17 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
|-----------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 38 | 27 | 39 | 30 |
| Units: subjects | | | | |
| Day 8 | 2 | 0 | 2 | 0 |
| Day 15 | 1 | 3 | 8 | 2 |
| Day 22 | 2 | 2 | 11 | 5 |
| Day 29 | 2 | 5 | 20 | 7 |

| End point values | Vehicle: Subjects >=18 Years | Crisaborole Ointment 2% BID: Subjects >=18 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
|-----------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 21 | 21 | 32 | 17 |

| | | | | |
|-----------------|---|---|----|---|
| Units: subjects | | | | |
| Day 8 | 0 | 0 | 0 | 0 |
| Day 15 | 0 | 0 | 6 | 1 |
| Day 22 | 1 | 3 | 9 | 1 |
| Day 29 | 3 | 6 | 13 | 2 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Investigator's Static Global Assessment (ISGA) Score of Clear (0) or Almost Clear (1) at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Number of Subjects who Achieved Investigator's Static Global Assessment (ISGA) Score of Clear (0) or Almost Clear (1) at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

ISGA is a five point global assessment scale of AD severity, was used to characterize subjects' overall disease severity across all treatable AD lesions (excluding the scalp). ISGA score ranged from 0 to 4: where 0 = clear (minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting), 1= almost clear (trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting), 2= mild (faint pink erythema with mild induration/papulation and no oozing/crusting), 3= moderate (pink-red erythema with moderate induration/papulation with or without oozing/crusting), 4= severe (deep or bright red erythema with severe induration/papulation and with oozing/crusting). Higher scores indicated greater severity of AD. FAS included all randomized subjects who received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle: Subjects 2-17 Years | Crisaborole Ointment 2% BID: Subjects 2-17 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
|-----------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 38 | 37 | 39 | 30 |
| Units: subjects | | | | |
| Day 8 | 6 | 3 | 12 | 5 |
| Day 15 | 6 | 7 | 19 | 9 |
| Day 22 | 6 | 8 | 19 | 9 |
| Day 29 | 6 | 10 | 27 | 13 |

| End point values | Vehicle: Subjects >=18 Years | Crisaborole Ointment 2% BID: Subjects >=18 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
|-----------------------------|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 21 | 21 | 32 | 17 |

| | | | | |
|-----------------|---|---|----|---|
| Units: subjects | | | | |
| Day 8 | 0 | 4 | 4 | 2 |
| Day 15 | 1 | 3 | 11 | 5 |
| Day 22 | 1 | 8 | 13 | 5 |
| Day 29 | 4 | 9 | 20 | 7 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Greater Than or Equal to (\geq) 75 Percent (%) Improvement From Baseline in Eczema Area And Severity Index (EASI) Total Score at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Number of Subjects who Achieved Greater Than or Equal to (\geq) 75 Percent (%) Improvement From Baseline in Eczema Area And Severity Index (EASI) Total Score at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

EASI quantifies severity of subject's AD (excluded scalp) based on severity of lesion clinical signs and %BSA affected. Lesion severity by clinical signs included erythema, induration/papulation, excoriation, lichenification scored for each of 4 body regions (head and neck, upper limbs, trunk [including axillae and groin], lower limbs [including buttocks]) on 4-point scale: 0=absent; 1=mild; 2=moderate; 3=severe. EASI area score was based upon % BSA with AD in body region: 0 (0%), 1 (>0 to <10%), 2 (10 to <30%), 3 (30 to <50%), 4 (50 to <70%), 5 (70 to <90%), 6 (90 to 100%). Total EASI score (aged \geq 8 years) = $0.1 \times Ah \times (Eh + Ih + Exh + Lh) + 0.2 \times Au \times (Eu + Iu + Exu + Lu) + 0.3 \times At \times (Et + It + Ext + Lt) + 0.4 \times Al \times (El + Il + Exl + Ll)$; Total EASI score (aged 2 to <8 years) = $0.2 \times Ah \times (Eh + Ih + Exh + Lh) + 0.2 \times Au \times (Eu + Iu + Exu + Lu) + 0.3 \times At \times (Et + It + Ext + Lt) + 0.3 \times Al \times (El + Il + Exl + Ll)$. Total EASI score range = 0.0 to 72.0, higher scores = greater severity of AD. Analysis was

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 70 | 47 |
| Units: subjects | | | | |
| Day 8 | 2 | 7 | 9 | 2 |
| Day 15 | 4 | 10 | 25 | 8 |
| Day 22 | 8 | 13 | 29 | 11 |
| Day 29 | 9 | 17 | 40 | 17 |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Greater Than or Equal to (\geq) 75% Improvement From Baseline in Eczema Area And Severity Index (EASI) Total Score

| | |
|---|--|
| End point title | Time to First Greater Than or Equal to (\geq) 75% Improvement From Baseline in Eczema Area And Severity Index (EASI) Total Score |
| End point description: | |
| EASI quantifies severity of AD (excluded scalp) based on severity of lesion and %BSA affected. Lesion severity included erythema, induration/papulation, excoriation, lichenification scored for 4 regions (head, neck, upper limbs, trunk [including axillae, groin], lower limbs [including buttocks]) on 4-point scale: 0=absent;1=mild;2=moderate;3=severe. EASI area score based upon %BSA with AD in body region: 0(0%), 1(>0to<10%), 2(10to<30%), 3(30to<50%), 4(50to<70%), 5(70to<90%), 6(90to100%). Total EASI score (aged \geq 8years)=0.1*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+Exu+Lu)+0.3*At*(Et+It+Ext+Lt)+0.4*Al*(El+Il+Exl+Ll); for aged 2to<8years=0.2*Ah*(Eh+Ih+Exh+Lh)+0.2*Au*(Eu+Iu+Exu+Lu)+0.3*At*(Et+It+Ext+Lt)+0.3*Al*(El+Il+Exl+Ll). Total EASI score range=0.0-72.0, higher scores=greater severity of AD. FAS. Number of Subjects Analysed=subjects evaluable for endpoint; 'Number Analysed'=subjects evaluable for each | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Day 43 | |

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|----------------------------------|------------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 | 58 | 70 | 47 |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 43.0 (28.0 to 99999) | 23.0 (16.0 to 34.0) | 32.0 (27.0 to 99999) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Body Surface Area (%BSA) at Days 8, 15, 22 and 29

| | |
|--|---|
| End point title | Change From Baseline in Percent Body Surface Area (%BSA) at Days 8, 15, 22 and 29 |
| End point description: | |
| 4 body regions were evaluated: head and neck, upper limbs, trunk (including axillae) and lower limbs (including buttocks) excluding scalp. BSA was calculated using handprint method. Number of handprints (size of subject's full palmer hand) fitting in affected area of a body region was estimated. Maximum number of handprints were: 10 for head, neck (20 for <8 years age), 20 for upper limbs, 30 for trunk, 40 for lower limbs (30 for <8 years age). Surface area (SA) of body region equivalent to 1 handprint: 1 handprint=10% for head, neck (5% for <8 years age), 5% for upper limbs, 3.33% for trunk, 2.5% for lower limbs (3.33% for <8 years age). %BSA for a body region =total number of handprints in a body region * % SA equivalent to 1 handprint. % BSA for an individual: mean of % BSA of all 4 body regions, range=0-100%, higher values=greater AD severity. FAS. Number of Subjects Analysed=subjects evaluable for endpoint; 'Number Analysed (n)'=subjects evaluable for each specified timepoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days, 8, 15, 22 and 29 | |

| End point values | Vehicle: Subjects 2-17 Years | Crisaborole Ointment 2% BID: Subjects 2-17 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects 2-17 Years | Pimecrolimus Cream 1% BID: Subjects 2-17 Years |
|--|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 37 | 33 | 37 | 30 |
| Units: %BSA | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 37, 33, 33, 29, 19, 21, 27, 16) | -2.04 (± 7.533) | -2.63 (± 11.920) | -5.25 (± 8.346) | -2.84 (± 5.296) |
| Day 15 (n= 33, 33, 37, 30, 15, 20, 27, 14) | -2.38 (± 8.566) | -4.32 (± 12.620) | -7.40 (± 9.515) | -3.72 (± 4.401) |
| Day 22 (n= 32, 31, 35, 26, 18, 19, 27, 15) | -2.23 (± 12.321) | -7.14 (± 10.123) | -8.54 (± 11.226) | -6.52 (± 9.883) |
| Day 29 (n= 31, 31, 36, 29, 17, 19, 29, 14) | -3.38 (± 9.974) | -9.95 (± 11.324) | -9.63 (± 12.309) | -7.30 (± 10.774) |

| End point values | Vehicle: Subjects >=18 Years | Crisaborole Ointment 2% BID: Subjects >=18 Years | Hydrocortisone Butyrate Cream 0.1% BID: Subjects >=18 Years | Pimecrolimus Cream 1% BID: Subjects >=18 Years |
|--|------------------------------------|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 19 | 21 | 29 | 16 |
| Units: %BSA | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 37, 33, 33, 29, 19, 21, 27, 16) | -1.39 (± 4.417) | -4.09 (± 6.397) | -2.74 (± 2.718) | -1.44 (± 5.600) |
| Day 15 (n= 33, 33, 37, 30, 15, 20, 27, 14) | -3.73 (± 5.895) | -4.63 (± 7.211) | -5.00 (± 5.189) | -3.56 (± 5.750) |
| Day 22 (n= 32, 31, 35, 26, 18, 19, 27, 15) | -4.19 (± 5.464) | -5.98 (± 7.852) | -4.91 (± 5.190) | -4.17 (± 5.588) |
| Day 29 (n= 31, 31, 36, 29, 17, 19, 29, 14) | -6.76 (± 8.089) | -7.18 (± 8.183) | -7.18 (± 5.971) | -6.86 (± 8.172) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Peak Pruritus Numerical Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (>=) 12 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Change From Baseline in Peak Pruritus Numerical Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (>=) 12 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to AD was assessed using the Peak Pruritus Numerical Rating Scale (NRS). Subjects at specified time points were asked the following question: "how would you rate your itch at the worst moment during the previous 24 hours?" The scale ranged from 0 to 10, where 0= no

itch and 10= worst itch imaginable. Higher scores indicated worse itch. Analysis was performed on all subjects aged ≥ 12 years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'Number Analysed (n)' signifies number of subjects evaluable for each specified timepoint.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days 8, 15, 22 and 29 | |

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|----------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 30 | 32 | 43 | 26 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 30, 30, 43, 26) | -0.67 (\pm 1.254) | -1.01 (\pm 1.145) | -2.24 (\pm 2.065) | -0.29 (\pm 1.225) |
| Day 15 (n= 29, 32, 43, 25) | -0.97 (\pm 1.778) | -1.08 (\pm 1.419) | -3.21 (\pm 2.598) | -1.35 (\pm 1.707) |
| Day 22 (n= 27, 30, 42, 24) | -0.98 (\pm 1.887) | -1.28 (\pm 1.642) | -3.83 (\pm 2.554) | -1.66 (\pm 1.759) |
| Day 29 (n= 27, 29, 42, 24) | -1.30 (\pm 2.157) | -1.65 (\pm 1.996) | -4.02 (\pm 2.734) | -1.67 (\pm 1.952) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Itch Severity Scale in Subjects Aged 6-11 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Change From Baseline in Patient Reported Itch Severity Scale in Subjects Aged 6-11 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the five-category Patient Reported Itch Severity Scale for subjects aged 6-11 years. Subjects at specified time points were asked to "Circle the face that shows how itchy your skin has been today". The scale ranged from no itchy to very itchy.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days 8, 15, 22 and 29 | |

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | 0 ^[8] | 0 ^[9] |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[6] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[7] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[8] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[9] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than (<) 6 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Change From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than (<) 6 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the Patient Reported Itch Severity Scale for subjects age <6 years. Subject's caregivers at specified time points were asked the following question "how would you rate your observation of your child's itch (scratching, rubbing) at the worst moment during the previous 24 hours?". The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | 0 ^[12] | 0 ^[13] |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[10] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[11] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[12] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[13] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Greater Than or Equal to (≥ 2) Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than ($>$) 12 Years

| | |
|-----------------|--|
| End point title | Time to Greater Than or Equal to (≥ 2) Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than ($>$) 12 Years |
|-----------------|--|

End point description:

The severity of itch (pruritus) due to AD was assessed using the Peak Pruritus NRS. Subjects at specified time points were asked the following question: "how would you rate your itch at the worst moment during the previous 24 hours?" The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|----------------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | 0 ^[16] | 0 ^[17] |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | (to) |

Notes:

[14] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[15] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[16] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[17] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ≥ 3 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than ($>$) 12 Years

| | |
|-----------------|---|
| End point title | Time to ≥ 3 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than ($>$) 12 Years |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to AD was assessed using the Peak Pruritus NRS. Subjects at specified time points were asked the following question: "how would you rate your itch at the worst moment during the previous 24 hours?" The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|----------------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | 0 ^[20] | 0 ^[21] |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | (to) |

Notes:

[18] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[19] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[20] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[21] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time ≥ 2 Point to Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years

| | |
|-----------------|--|
| End point title | Time ≥ 2 Point to Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years |
|-----------------|--|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the Patient Reported Itch Severity Scale for subjects aged <6 years. Subject's caregivers at specified time points were asked the following question "how would you rate your observation of your child's itch (scratching, rubbing) at the worst moment during the previous 24 hours?". The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|----------------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[22] | 0 ^[23] | 0 ^[24] | 0 ^[25] |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | (to) |

Notes:

[22] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[23] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[24] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

termination.

[25] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to ≥ 3 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years

| | |
|-----------------|--|
| End point title | Time to ≥ 3 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years |
|-----------------|--|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the Patient Reported Itch Severity Scale for subjects aged <6 years. Subject's caregivers at specified time points were asked the following question "how would you rate your observation of your child's itch (scratching, rubbing) at the worst moment during the previous 24 hours?". The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|----------------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[26] | 0 ^[27] | 0 ^[28] | 0 ^[29] |
| Units: days | | | | |
| median (confidence interval 95%) | (to) | (to) | (to) | (to) |

Notes:

[26] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[27] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[28] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[29] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved ≥ 2 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (\geq) 12 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Number of Subjects who Achieved ≥ 2 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (\geq) 12 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to AD was assessed using the Peak Pruritus NRS. Subjects at specified time points were asked the following question: "how would you rate your itch at the worst moment during the previous 24 hours?" The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch. Analysis was performed on all subjects aged ≥ 12 Years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 31 | 32 | 42 | 26 |
| Units: subjects | | | | |
| Day 8 | 3 | 7 | 21 | 1 |
| Day 15 | 9 | 8 | 31 | 7 |
| Day 22 | 9 | 7 | 32 | 9 |
| Day 29 | 10 | 9 | 32 | 9 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved ≥ 3 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (\geq) 12 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Number of Subjects who Achieved ≥ 3 Point Improvement From Baseline in Peak Pruritus Numeric Rating Scale (NRS) in Subjects Aged Greater Than or Equal to (\geq) 12 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The severity of itch (pruritus) due to AD was assessed using the Peak Pruritus NRS. Subjects at specified time points were asked the following question: "how would you rate your itch at the worst moment during the previous 24 hours?" The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch. Analysis was performed on all subjects aged ≥ 12 Years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 29 | 29 | 40 | 26 |
| Units: subjects | | | | |
| Day 8 | 2 | 1 | 11 | 0 |
| Day 15 | 5 | 5 | 21 | 3 |
| Day 22 | 4 | 4 | 25 | 4 |
| Day 29 | 6 | 6 | 24 | 6 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Achieved Greater Than or Equal to (\geq) 2 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Number of Subjects who Achieved Greater Than or Equal to (\geq) 2 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the Patient Reported Itch Severity Scale for subjects age <6 years. Subject's caregivers at specified time points were asked the following question "how would you rate your observation of your child's itch (scratching, rubbing) at the worst moment during the previous 24 hours?". The scale ranged from 0 to 10, where 0= no itch and 10= worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[30] | 0 ^[31] | 0 ^[32] | 0 ^[33] |
| Units: subjects | | | | |

Notes:

[30] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[31] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[32] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[33] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

Secondary: Number of Subjects who Achieved Greater Than or Equal to (\geq) 3 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Number of Subjects who Achieved Greater Than or Equal to (\geq) 3 Point Improvement From Baseline in Observer Reported Itch Severity Scale in Subjects Aged Less Than ($<$) 6 Years at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

The severity of itch (pruritus) due to atopic dermatitis was assessed using the Patient Reported Itch Severity Scale for subjects age <6 years. Subject's caregivers at specified time points were asked the following question "how would you rate your observation of your child's itch (scratching, rubbing) at the worst moment during the previous 24 hours?". The scale ranged from 0 to 10, where 0 = no itch and 10 = worst itch imaginable. Higher scores indicated worse itch.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|-----------------------------|-------------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[34] | 0 ^[35] | 0 ^[36] | 0 ^[37] |
| Units: subjects | | | | |

Notes:

[34] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[35] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[36] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

[37] - Data for this endpoint was not collected and summarised due to low enrollment at study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatology Life Quality Index (DLQI) in Subjects Greater Than or Equal to (\geq) 16 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Change From Baseline in Dermatology Life Quality Index (DLQI) in Subjects Greater Than or Equal to (\geq) 16 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

DLQI is a 10-item questionnaire that measures the impact of skin disease. Each question was evaluated on a 4-point scale ranging from 0 (not at all) to 3 (very much); where higher scores indicated more impact on quality of life. Scores from all 10 questions were added up to give DLQI total score range from 0 (not at all) to 30 (very much). Higher scores indicated more impact on quality of life of subject. Analysis was performed on all subjects aged ≥ 16 years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'Number Analysed (n)' signifies number of subjects evaluable for each specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 | 23 | 28 | 19 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 20, 23, 27, 19) | -1.9 (± 5.53) | -3.8 (± 3.45) | -5.1 (± 4.98) | -1.4 (± 2.99) |
| Day 15 (n= 16, 23, 26, 17) | -3.4 (± 3.72) | -3.5 (± 2.92) | -6.8 (± 5.94) | -2.9 (± 2.63) |
| Day 22 (n= 18, 20, 25,18) | -2.8 (± 4.12) | -3.4 (± 4.73) | -6.9 (± 6.37) | -3.4 (± 3.88) |
| Day 29 (n= 18, 19, 28, 17) | -4.9 (± 5.60) | -3.9 (± 4.76) | -7.0 (± 6.69) | -4.1 (± 3.76) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) in Subjects Aged 4-15 Years at Days 8, 15, 22 and 29

| | |
|-----------------|--|
| End point title | Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) in Subjects Aged 4-15 Years at Days 8, 15, 22 and 29 |
|-----------------|--|

End point description:

The CDLQI was a 10-item questionnaire that measures the impact of skin disease on children's (aged 4 to 15 years) 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 CDLQI total score was the sum of individual scores of question 1-10 and ranges from 0 (not at all) to 30 (very much): 0-1 = no effect on the child's life; 2-6 = small effect; 7-12 = moderate effect; 13-18 = very large effect; 19-30 = extremely large effect. Higher scores indicated more impact on quality of life of children. Analysis was performed on all subjects aged 4 to 15 years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'Number Analysed (n)' signifies number of subjects evaluable for each specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 27 | 24 | 29 | 17 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|----------------------------|---------------|---------------|---------------|---------------|
| Day 8 (n= 27, 22, 25, 15) | -0.2 (± 3.42) | -2.1 (± 4.49) | -5.4 (± 6.14) | -1.7 (± 4.03) |
| Day 15 (n= 22, 24, 29, 17) | -2.0 (± 4.49) | -3.1 (± 5.13) | -5.5 (± 6.32) | -1.6 (± 4.66) |
| Day 22 (n= 21, 21, 27, 13) | -2.7 (± 3.04) | -2.6 (± 5.81) | -4.9 (± 7.89) | -2.5 (± 3.15) |
| Day 29 (n= 20, 21, 28, 16) | -3.1 (± 2.73) | -3.4 (± 4.85) | -6.4 (± 5.49) | -3.4 (± 3.52) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatitis Family Impact Questionnaire (DFI) in Subjects Aged 2-17 Years at Days 8, 15, 22 and 29

| | |
|-----------------|---|
| End point title | Change From Baseline in Dermatitis Family Impact Questionnaire (DFI) in Subjects Aged 2-17 Years at Days 8, 15, 22 and 29 |
|-----------------|---|

End point description:

The DFI was a 10-item disease questionnaire that measures the impact of having a child with AD on family quality of life. It was completed by parent/legal guardian of the child (affected by AD), based on recall over the past week. Each question was scored on a 4-point scale ranging from 0 (not at all) to 30 (very much): where higher scores indicated worst quality of life of family. The DFI total score was the sum of individual scores of the 10 questions and ranges from 0 (no impact on life of family) to 30 (maximum effect on life of family), where higher DFI scores indicated maximum effect on life of family. Analysis was performed on all Subjects 2 to 17 years from FAS, and FAS included all randomized subjects who received at least 1 dose of investigational product. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'Number Analysed (n)' signifies number of subjects evaluable for each specified timepoint.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 8, 15, 22 and 29

| End point values | Vehicle | Crisaborole Ointment 2% BID | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|--------------------------------------|-----------------|-----------------------------|--|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 37 | 32 | 37 | 30 |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 (n= 37, 32, 33, 28) | -1.2 (± 6.43) | -2.3 (± 5.16) | -5.6 (± 5.61) | -2.8 (± 6.79) |
| Day 15 (n= 32, 31, 37, 30) | -1.1 (± 6.77) | -2.3 (± 4.71) | -5.5 (± 6.82) | -3.2 (± 5.94) |
| Day 22 (n= 31, 29, 34, 26) | -2.5 (± 4.84) | -3.1 (± 5.24) | -5.3 (± 6.92) | -4.5 (± 5.93) |
| Day 29 (n= 30, 28, 35, 29) | -1.8 (± 5.26) | -3.6 (± 4.40) | -6.4 (± 5.61) | -4.8 (± 5.61) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 28 days after last dose of study treatment (maximum up to 60 days)

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study. AEs and SAEs were analysed for safety analysis set.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Vehicle |
|-----------------------|---------|

Reporting group description:

Vehicle matched to crisaborole 2% ointment was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up by telephone call on Day 60 or at least 28 days after last dose if subject was terminated early from treatment.

| | |
|-----------------------|--|
| Reporting group title | Hydrocortisone Butyrate Cream 0.1% BID |
|-----------------------|--|

Reporting group description:

Hydrocortisone butyrate cream 0.1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up by telephone call on Day 60 or at least 28 days after last dose if subject was terminated early from treatment.

| | |
|-----------------------|---------------------------|
| Reporting group title | Pimecrolimus Cream 1% BID |
|-----------------------|---------------------------|

Reporting group description:

Pimecrolimus cream 1% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up by telephone call on Day 60 or at least 28 days after last dose if subject was terminated early from treatment.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Crisaborole Ointment 2% BID |
|-----------------------|-----------------------------|

Reporting group description:

Crisaborole ointment 2% was applied topically BID to all treatable AD involved areas (excluding the scalp) identified at Baseline (Day 1) through Day 28. End of treatment visit was scheduled on Day 29. Subjects were followed-up by telephone call on Day 60 or at least 28 days after last dose if subject was terminated early from treatment.

| Serious adverse events | Vehicle | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|---|----------------|--|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 71 (0.00%) | 0 / 47 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | Crisaborole Ointment 2% BID | | |
|------------------------|-----------------------------|--|--|
|------------------------|-----------------------------|--|--|

| | | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Vehicle | Hydrocortisone Butyrate Cream 0.1% BID | Pimecrolimus Cream 1% BID |
|---|------------------|--|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 59 (16.95%) | 4 / 71 (5.63%) | 16 / 47 (34.04%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 71 (2.82%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 3 | 2 |
| General disorders and administration site conditions | | | |
| Application site pain | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 71 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 0 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 7 / 59 (11.86%) | 2 / 71 (2.82%) | 7 / 47 (14.89%) |
| occurrences (all) | 7 | 2 | 8 |
| Eczema | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 0 / 71 (0.00%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 0 / 71 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 0 | 3 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 71 (1.41%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 1 | 3 |

| Non-serious adverse events | Crisaborole Ointment 2% BID | | |
|---|-----------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 18 / 58 (31.03%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| General disorders and administration site conditions | | | |
| Application site pain | | | |
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 9 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 5 | | |
| Eczema | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 23 January 2019 | To do the addition of investigational product withdrawal criteria for signs and symptoms of hypersensitivity as requested by the German Federal Institute for Drugs and Medical Devices (BfArM). |

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.

Study terminated early by Sponsor. Decision was not due to safety/efficacy concerns, was related to business, portfolio reprioritization. Sub study planned per Amendment 3 was not initiated, as sub study site setup didn't complete prior termination.

Notes: