



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double Blind, Vehicle Controlled Study of the Efficacy and Safety of Crisaborole Ointment, 2% in Chinese and Japanese Pediatric and Adult Subjects (Ages 2 Years and Older) With Mild to Moderate Atopic Dermatitis

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2021-006538-38 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 08 September 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 March 2022 |
| First version publication date | 01 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | C3291032 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04360187 |
| 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., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 September 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 September 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of crisaborole ointment, 2% in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate atopic dermatitis involving at least 5% treatable body surface area (BSA).

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 Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed. The external data monitoring committee (E-DMC) was responsible for ongoing monitoring of the safety of subjects in the study according to the charter.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 27 July 2020 |
| 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 | China: 237 |
| Country: Number of subjects enrolled | Japan: 154 |
| Worldwide total number of subjects | 391 |
| 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) | 192 |
| Adolescents (12-17 years) | 40 |
| Adults (18-64 years) | 154 |
| From 65 to 84 years | 5 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

418 subjects were screened, 391 of whom were randomized and treated.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Double-Blind Treatment |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------------------|
| Arm title | Vehicle Twice a Day (BID) |
|------------------|---------------------------|

Arm description:

Vehicle was applied BID for 28 days to the Treatable body surface area (BSA) identified at Baseline/Day 1 and new atopic dermatitis (AD) lesions that appear after the Baseline/Day 1.

| | |
|--|-------------|
| 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 was applied BID to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28

| | |
|------------------|----------------------------------|
| Arm title | Crisaborole 2% Twice a Day (BID) |
|------------------|----------------------------------|

Arm description:

Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Crisaborole 2% |
| Investigational medicinal product code | PF-06930164 |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Crisaborole 2% was applied BID to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28

| Number of subjects in period 1 | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) |
|--------------------------------|---------------------------|----------------------------------|
| Started | 131 | 260 |
| Completed | 108 | 245 |
| Not completed | 23 | 15 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 4 | 2 |
| Adverse event, non-fatal | 9 | 11 |
| Withdrawal By Parent/Guardian | 2 | - |
| Lack of efficacy | 7 | 2 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Follow-Up |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vehicle Twice a Day (BID) |

Arm description:

Vehicle was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1.

| | |
|--|-------------|
| 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 was applied BID to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28

| | |
|------------------|----------------------------------|
| Arm title | Crisaborole 2% Twice a Day (BID) |
|------------------|----------------------------------|

Arm description:

Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Crisaborole 2% |
| Investigational medicinal product code | PF-06930164 |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Crisaborole 2% was applied BID to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28

| Number of subjects in period 2^[1] | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) |
|---|---------------------------|----------------------------------|
| Started | 114 | 232 |
| Completed | 113 | 232 |
| Not completed | 1 | 0 |
| Lost to follow-up | 1 | - |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All subjects from double-blind treatment period did not enter into follow-up period.

Baseline characteristics

Reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Vehicle Twice a Day (BID) |
| Reporting group description: | |
| Vehicle was applied BID for 28 days to the Treatable body surface area (BSA) identified at Baseline/Day 1 and new atopic dermatitis (AD) lesions that appear after the Baseline/Day 1. | |
| Reporting group title | Crisaborole 2% Twice a Day (BID) |
| Reporting group description: | |
| Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1. | |

| Reporting group values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | Total |
|---|---------------------------|----------------------------------|-------|
| Number of subjects | 131 | 260 | 391 |
| Age Categorical | | | |
| Units: Subjects | | | |
| 2-11 Years | 69 | 123 | 192 |
| 12-17 Years | 15 | 25 | 40 |
| >=18 Years | 47 | 112 | 159 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 16.0 | 19.4 | |
| standard deviation | ± 13.58 | ± 15.80 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 64 | 122 | 186 |
| Male | 67 | 138 | 205 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 131 | 260 | 391 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 0 | 0 | 0 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 131 | 260 | 391 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Vehicle Twice a Day (BID) |
| Reporting group description: Vehicle was applied BID for 28 days to the Treatable body surface area (BSA) identified at Baseline/Day 1 and new atopic dermatitis (AD) lesions that appear after the Baseline/Day 1. | |
| Reporting group title | Crisaborole 2% Twice a Day (BID) |
| Reporting group description: Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1. | |
| Reporting group title | Vehicle Twice a Day (BID) |
| Reporting group description: Vehicle was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1. | |
| Reporting group title | Crisaborole 2% Twice a Day (BID) |
| Reporting group description: Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1. | |

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

| | |
|--|---|
| End point title | Percent Change From Baseline in Eczema Area and Severity Index (EASI) Total Score at Day 29 |
| End point description: The EASI quantifies the severity of a subject's atopic dermatitis (AD) based on both severity of lesion clinical signs and the percent of body surface area (BSA) affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body. Total EASI score ranged from 0.0 to 72.0, higher scores = greater severity of AD. Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received. | |
| End point type | Primary |
| End point timeframe: Baseline, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 256 | | |
| Units: Percent Change | | | | |
| least squares mean (confidence interval 95%) | -42.79 (-50.14 to -35.44) | -59.92 (-64.86 to -54.98) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Crisaborole versus Vehicle |
| Comparison groups | Crisaborole 2% Twice a Day (BID) v Vehicle Twice a Day (BID) |
| Number of subjects included in analysis | 380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Mixed effect Model for Repeated Measures |
| Parameter estimate | LS mean of difference |
| Point estimate | -17.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.98 |
| upper limit | -8.27 |

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs) ^[1] |
|-----------------|---|

End point description:

An adverse event was considered as a treatment-emergent adverse event (TEAE) if the event started after the first dose of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period. 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. AEs are classified according to the severity in 3 categories a) mild – AEs does not interfere with subject's usual function b) moderate – AEs interferes to some extent with subject's usual function c) severe – AEs interferes significantly with subject's usual function. Overall number of subjects analyzed included all subjects who were randomized and received at least 1 confirmed dose of investigational product.

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

End point timeframe:

Baseline up to Day 60

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 Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| With Adverse Events (AEs) | 44.3 | 46.2 | | |
| With Serious AEs | 0.8 | 0.4 | | |
| With Severe AEs | 1.5 | 0 | | |
| Discontinued (D/C) From Study due to AEs | 0.8 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Clinically Significant Changes From Baseline in Clinical Laboratory Parameters

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Clinically Significant Changes From Baseline in Clinical Laboratory Parameters ^[2] |
|-----------------|---|

End point description:

Laboratory parameters included: hematology and chemistry. Clinically significant laboratory abnormalities are defined as abnormal values that have clinical manifestations or require medical intervention. Clinically significant laboratory criteria included Hemoglobin $<0.8 \times$ lower limit of normal (LLN), Leukocytes $>1.5 \times$ upper limit of normal (ULN), Lymphocytes $<0.8 \times$ LLN, Lymphocytes/Leukocytes $>1.2 \times$ ULN, Neutrophils $<0.8 \times$ LLN, Neutrophils $>1.2 \times$ ULN, Neutrophils/Leukocytes $<0.8 \times$ LLN, Basophils/Leukocytes $>1.2 \times$ ULN, Eosinophils $>1.2 \times$ ULN, Eosinophils/Leukocytes $>1.2 \times$ ULN, Monocytes $>1.2 \times$ ULN, Monocytes/Leukocytes (%) $>1.2 \times$ ULN, Bicarbonate $<0.9 \times$ LLN, and Glucose $>1.5 \times$ ULN.

Overall number of subjects analyzed included all subjects who were randomized and received at least 1 confirmed dose of investigational product.

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

End point timeframe:

Baseline up to Day 29

Notes:

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

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

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 126 | 258 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Hemoglobin $<0.8 \times$ lower limit of normal (LLN) | 1.6 | 0 | | |
| Leukocytes $>1.5 \times$ upper limit of normal (ULN) | 0 | 0.4 | | |
| Lymphocytes $<0.8 \times$ LLN | 0.8 | 0 | | |
| Lymphocytes/Leukocytes $>1.2 \times$ ULN | 3.2 | 1.9 | | |
| Neutrophils $<0.8 \times$ LLN | 0 | 0.4 | | |
| Neutrophils $>1.2 \times$ ULN | 0 | 0.4 | | |
| Neutrophils/Leukocytes $<0.8 \times$ LLN | 3.2 | 2.7 | | |
| Basophils/Leukocytes $>1.2 \times$ ULN | 4.8 | 3.1 | | |
| Eosinophils $>1.2 \times$ ULN | 33.1 | 31.1 | | |
| Eosinophils/Leukocytes $>1.2 \times$ ULN | 29.8 | 33.1 | | |
| Monocytes $>1.2 \times$ ULN | 0 | 0.4 | | |
| Monocytes/Leukocytes $>1.2 \times$ ULN | 1.6 | 1.6 | | |
| Bicarbonate $<0.9 \times$ LLN | 0.8 | 0.8 | | |
| Glucose $>1.5 \times$ ULN | 0 | 0.8 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Clinically Significant Changes From Baseline in Vital Signs

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Clinically Significant Changes From Baseline in Vital Signs ^[3] |
|-----------------|--|

End point description:

Vital signs (temperature, respiratory rate, pulse, systolic and diastolic blood pressure) were obtained with subjects in the seated position, after having sat/lie calmly for at least 5 minutes. Clinically significant vital signs criteria included Diastolic Blood Pressure (DBP) Value <50 mmHg, DBP Change ≥20 mmHg increase, DBP Change ≥20 mmHg decrease, Pulse Rate Value >120 beats per minute (bpm), Systolic Blood Pressure (SBP) Value <90 mmHg, SBP Change ≥30 mmHg increase, SBP Change ≥30mmHg decrease.

Overall number of subjects analyzed included all subjects who were randomized and received at least 1 confirmed dose of investigational product.

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

End point timeframe:

Baseline up to Day 29

Notes:

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

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

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|---|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 259 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Diastolic Blood Pressure (DBP) Value <50 mmHg | 7.8 | 7.3 | | |
| DBP Change ≥20mmHg increase | 2.3 | 3.5 | | |
| DBP Change ≥20mmHg decrease | 3.9 | 3.1 | | |
| Pulse Rate Value >120 beats per minute (bpm) | 2.3 | 1.9 | | |
| Systolic Blood Pressure (SBP) Value <90mmHg | 23.3 | 26.3 | | |
| SBP Change ≥30mmHg increase | 0 | 2.3 | | |
| SBP Change ≥30mmHg decrease | 3.1 | 0.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Improvement in Investigator's Static Global Assessment (ISGA) at Day 29

| | |
|--|--|
| End point title | Percentage of Subjects Achieving Improvement in Investigator's Static Global Assessment (ISGA) at Day 29 |
| End point description: ISGA assessed the severity of AD on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD. Grades for classification of severity: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. Improvement in ISGA is defined as ISGA score of 0 or 1. Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received. | |
| End point type | Secondary |
| End point timeframe: Baseline, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 28.5 (20.4 to 36.6) | 41.4 (35.4 to 47.5) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Crisaborole versus Vehicle |
| Comparison groups | Vehicle Twice a Day (BID) v Crisaborole 2% Twice a Day (BID) |
| Number of subjects included in analysis | 391 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0124 |
| Method | normal approximation to response rates |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 12.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.8 |
| upper limit | 23.1 |

Secondary: Percentage of Subjects Achieving Success in ISGA at Day 29

| | |
|---|--|
| End point title | Percentage of Subjects Achieving Success in ISGA at Day 29 |
| End point description: ISGA assessed the severity of AD on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD. Grades for classification of severity: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. Success in ISGA is defined as an ISGA score of | |

Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline.
Overall number of subjects analyzed included all subjects randomized and dispensed study drug.
Subjects were assigned to the randomized treatment regardless of what treatment was received.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 15.9 (9.4 to 22.5) | 27.6 (22.1 to 33.1) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Crisaborole versus Vehicle |
| Comparison groups | Vehicle Twice a Day (BID) v Crisaborole 2% Twice a Day (BID) |
| Number of subjects included in analysis | 391 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0078 |
| Method | normal approximation to response rates |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 11.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.1 |
| upper limit | 20.3 |

Secondary: Change From Baseline in Peak Pruritus Numeric Rating Scale (NRS) at Week 4-for Subjects ≥12 years

| | |
|--|---|
| End point title | Change From Baseline in Peak Pruritus Numeric Rating Scale (NRS) at Week 4-for Subjects ≥12 years |
| End point description: | |
| Subject-rated pruritus score of lesions rated the severity of pruritus suffered in the past 24 hours on an 11-point NRS where 0 is no pruritus and 10 is worst itch imaginable. Change: score at Week 4 minus score at baseline. | |
| Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 131 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | -0.79 (-1.18 to -0.40) | -1.58 (-1.84 to -1.33) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Crisaborole versus Vehicle |
| Comparison groups | Vehicle Twice a Day (BID) v Crisaborole 2% Twice a Day (BID) |
| Number of subjects included in analysis | 191 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 |
| Method | Mixed effect Model for Repeated Measures |
| Parameter estimate | LS mean of difference |
| Point estimate | -0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.26 |
| upper limit | -0.33 |

Secondary: Percentage of Subjects Achieving Success in ISGA Over Time

| | |
|--|--|
| End point title | Percentage of Subjects Achieving Success in ISGA Over Time |
| End point description: | |
| ISGA assessed the severity of AD on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD. Grades for classification of severity: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. | |
| Success in ISGA is defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline. | |
| Overall number of subjects analyzed included all subjects randomized and dispensed study drug. | |
| Subjects were assigned to the randomized treatment regardless of what treatment was received. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 8, Day 15, Day 22, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 8 | 0.0 (-0.2 to 0.2) | 4.8 (2.2 to 7.4) | | |
| Day 15 | 4.9 (1.1 to 8.7) | 11.6 (7.6 to 15.6) | | |
| Day 22 | 10.8 (5.2 to 16.3) | 18.1 (13.4 to 22.8) | | |
| Day 29 | 15.9 (9.4 to 22.5) | 27.6 (22.1 to 33.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Improvement in ISGA Over Time

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving Improvement in ISGA Over Time |
|-----------------|--|

End point description:

ISGA assessed the severity of AD on a 5-point scale ranged from 0 (clear) to 4 (maximum severe), where higher scores indicate higher degree of AD.

Improvement in ISGA is defined as an ISGA score of Clear (0) or Almost Clear (1).

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 8, Day 15, Day 22, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 8 | 7.8 (3.2 to 12.4) | 16.8 (12.3 to 21.4) | | |
| Day 15 | 18.3 (11.6 to 25.1) | 25.6 (20.2 to 31.0) | | |
| Day 22 | 25.1 (17.4 to 32.7) | 32.3 (26.6 to 38.1) | | |
| Day 29 | 28.5 (20.4 to 36.6) | 41.4 (35.4 to 47.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in EASI Total Score Over Time

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in EASI Total Score Over Time |
|-----------------|--|

End point description:

The EASI quantifies the severity of a subject's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body. Total EASI score ranged from 0.0 to 72.0, higher scores = greater severity of AD. Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 8, Day 15, Day 22, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 256 | | |
| Units: Percent Change | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Day 8 | -21.43 (-28.43 to -14.44) | -36.65 (-41.52 to -31.78) | | |
| Day 15 | -37.15 (-44.24 to -30.05) | -49.65 (-54.53 to -44.76) | | |
| Day 22 | -42.92 (-50.16 to -35.69) | -55.05 (-59.96 to -50.13) | | |
| Day 29 | -42.79 (-50.14 to -35.44) | -59.92 (-64.86 to -54.98) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percent Body Surface Area (%BSA) Over Time

| | |
|-----------------|--|
| End point title | Change from Baseline in Percent Body Surface Area (%BSA) Over Time |
|-----------------|--|

End point description:

4 body regions were evaluated: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Scalp was excluded. BSA was calculated using handprint method. Number of handprints (size of subject's hand with fingers in a closed position) fitting in the affected area of a body region was estimated.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 8, Day 15, Day 22, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 259 | | |
| Units: Percentage BSA | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Day 8 | -1.75 (-3.37 to -0.13) | -5.12 (-6.26 to -3.98) | | |
| Day 15 | -3.31 (-4.94 to -1.68) | -7.60 (-8.75 to -6.46) | | |
| Day 22 | -4.38 (-6.04 to -2.71) | -8.72 (-9.87 to -7.57) | | |
| Day 29 | -4.81 (-6.50 to -3.11) | -9.89 (-11.05 to -8.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving EASI-50 Over Time

| | |
|---|--|
| End point title | Percentage of Subjects Achieving EASI-50 Over Time |
| End point description: | |
| The EASI quantifies the severity of a subject's AD based on both severity of lesion clinical signs and the percent of BSA affected. The EASI score can vary in increments of range from 0.0 to 72.0, with higher scores representing greater severity of atopic dermatitis. | |
| EASI-50 is defined as EASI score has $\geq 50\%$ improvement from baseline. | |
| Overall number of subjects analyzed included all subjects randomized and dispensed study drug. | |
| Subjects were assigned to the randomized treatment regardless of what treatment was received. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 8, Day 15, Day 22, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 8 | 18.5 (11.8 to 25.1) | 37.1 (31.2 to 43.0) | | |
| Day 15 | 32.7 (24.5 to 40.8) | 58.9 (52.9 to 65.0) | | |
| Day 22 | 42.2 (33.5 to 50.9) | 66.4 (60.7 to 72.2) | | |

| | | | | |
|--------|---------------------|---------------------|--|--|
| Day 29 | 49.4 (40.5 to 58.2) | 72.7 (67.3 to 78.2) | | |
|--------|---------------------|---------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving EASI-75 Over Time

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving EASI-75 Over Time |
|-----------------|--|

End point description:

The EASI quantifies the severity of a subject's AD based on both severity of lesion clinical signs and the percent of BSA affected. The EASI score can vary in increments of range from 0.0 to 72.0, with higher scores representing greater severity of atopic dermatitis.

EASI-75 is defined as EASI score has $\geq 75\%$ improvement from baseline.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 8, Day 15, Day 22, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|----------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 260 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Day 8 | 6.1 (2.0 to 10.2) | 11.2 (7.4 to 15.0) | | |
| Day 15 | 15.4 (9.2 to 21.6) | 26.3 (20.9 to 31.7) | | |
| Day 22 | 26.3 (18.6 to 34.0) | 38.2 (32.2 to 44.1) | | |
| Day 29 | 27.6 (19.8 to 35.4) | 46.4 (40.3 to 52.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Peak Pruritus NRS Over Time-for Subjects ≥ 12 Years

| | |
|-----------------|--|
| End point title | Change From Baseline in Peak Pruritus NRS Over Time-for Subjects ≥ 12 Years |
|-----------------|--|

End point description:

Peak Pruritus NRS is subjects-rated pruritus score of lesions rated the severity of pruritus suffered in the past 24 hours on an 11-point NRS where 0 is no pruritus and 10 is worst itch imaginable.

Change: score at observation minus score at baseline.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 1, Week 2, Week 3, Week 4 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 131 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 1 | -0.38 (-0.75 to -0.01) | -0.94 (-1.19 to -0.69) | | |
| Week 2 | -0.53 (-0.90 to -0.15) | -1.26 (-1.52 to -1.01) | | |
| Week 3 | -0.64 (-1.02 to -0.26) | -1.41 (-1.66 to -1.16) | | |
| Week 4 | -0.79 (-1.18 to -0.40) | -1.58 (-1.84 to -1.33) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Itch Severity Scale Over Time-for Subjects ≥6 Years and <12 Years

| | |
|-----------------|--|
| End point title | Change From Baseline in Patient Reported Itch Severity Scale Over Time-for Subjects ≥6 Years and <12 Years |
|-----------------|--|

End point description:

Patient Reported Itch Severity Scale is a 5-point scale indicating no itchy to very itchy (ranged from 0 to 4, where 0=no itch to 4=worst itch imaginable) for subjects ≥6 and <12 years of age.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 1, Week 2, Week 3, Week 4 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 76 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | | | | |

| | | | | |
|--------|------------------------|------------------------|--|--|
| Week 1 | -0.26 (-0.47 to -0.05) | -0.51 (-0.66 to -0.36) | | |
| Week 2 | -0.22 (-0.43 to -0.01) | -0.70 (-0.85 to -0.55) | | |
| Week 3 | -0.37 (-0.59 to -0.16) | -0.78 (-0.92 to -0.63) | | |
| Week 4 | -0.52 (-0.74 to -0.30) | -0.86 (-1.00 to -0.71) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Observer Reported Itch Severity Scale Over Time-for Subjects <6 Years

| | |
|-----------------|---|
| End point title | Change From Baseline in Observer Reported Itch Severity Scale Over Time-for Subjects <6 Years |
|-----------------|---|

End point description:

Observer Reported Itch Severity Scale is an 11-point (ranged from 0 to 10, where 0=no itch to 10=worst itch imaginable) scale and must be completed by the observer (caregivers of subjects) for subjects <6 years of age.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 41 | | |
| Units: Units on a Scale | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 1 | -0.31 (-0.80 to 0.17) | -1.03 (-1.44 to -0.62) | | |
| Week 2 | -0.73 (-1.22 to -0.24) | -1.68 (-2.10 to -1.27) | | |
| Week 3 | -0.96 (-1.46 to -0.47) | -1.79 (-2.21 to -1.38) | | |
| Week 4 | -1.25 (-1.75 to -0.75) | -1.95 (-2.37 to -1.53) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatology Life Quality Index (DLQI) Total

Score Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in Dermatology Life Quality Index (DLQI) Total Score Over Time |
|-----------------|---|

End point description:

The DLQI was a 10-item questionnaire that measures the impact of skin disease on subject's quality of life. The questionnaire will be completed by all subjects aged 16 years and older, based on the age at Screening Visit/time of informed consent/assent. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49 | 117 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -1.1 (± 4.02) | -1.7 (± 3.57) | | |
| Day 29 | -1.5 (± 4.67) | -1.8 (± 4.11) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) Score Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in Children's Dermatology Life Quality Index (CDLQI) Score Over Time |
|-----------------|---|

End point description:

The CDLQI was a 10-item questionnaire that measures the impact of skin disease on children's (aged 4-15 years) quality of life. The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 127 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -1.3 (± 5.18) | -3.6 (± 4.64) | | |
| Day 29 | -1.8 (± 6.00) | -3.9 (± 5.37) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Infants' Dermatitis Quality of Life Index (IDQOL) Total Score Over Time

| | |
|-----------------|---|
| End point title | Change From Infants' Dermatitis Quality of Life Index (IDQOL) Total Score Over Time |
|-----------------|---|

End point description:

The IDQOL was completed by observer for subjects aged 2-3 years, based on the age at the Screening Visit/time of informed consent/assent. The IDQOL is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score the more quality of life is impaired.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 16 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -1.3 (± 3.34) | -3.0 (± 3.30) | | |
| Day 29 | -0.7 (± 3.86) | -4.3 (± 4.44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dermatitis Family Impact Questionnaire (DFI) Score Over Time

| | |
|-----------------|--|
| End point title | Change From Baseline in Dermatitis Family Impact Questionnaire (DFI) Score Over Time |
|-----------------|--|

End point description:

The DFI was completed by all observer for subjects aged 2-17 years, based on the age at Screening Visit/time of informed consent/assent. The minimum DFI score is 0; the maximum DFI score is 30. The higher score means worse outcome.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 148 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -0.5 (± 3.87) | -2.4 (± 4.66) | | |
| Day 29 | -2.1 (± 4.86) | -3.0 (± 5.22) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient-Oriented Eczema Measure (POEM) Over Time in Subjects ≥12 Years

| | |
|-----------------|--|
| End point title | Change From Baseline in Patient-Oriented Eczema Measure (POEM) Over Time in Subjects ≥12 Years |
|-----------------|--|

End point description:

The POEM is a validated 7-item measure used to assess the impact of AD over the past week. The POEM contains 7 symptom based questions with responses rating number of days each symptom is experienced over the past week, from 0 (no days) to 4 (every day), with a maximum score of 28. Higher score means worse outcome.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 137 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -1.8 (± 5.25) | -5.4 (± 5.19) | | |
| Day 29 | -3.3 (± 5.38) | -5.7 (± 6.32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POEM Over Time in Subjects ≥ 2 Years and < 12 Years

| | |
|-----------------|--|
| End point title | Change From Baseline in POEM Over Time in Subjects ≥ 2 Years and < 12 Years |
|-----------------|--|

End point description:

The POEM is a validated 7-item measure used to assess the impact of AD over the past week. The POEM contains 7 symptom based questions with responses rating number of days each symptom is experienced over the past week, from 0 (no days) to 4 (every day), with a maximum score of 28. Higher score means worse outcome.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 123 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 | -2.5 (\pm 5.17) | -6.7 (\pm 6.09) | | |
| Day 29 | -3.8 (\pm 5.33) | -7.7 (\pm 5.41) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average of Patient Global Impression of Severity (PGIS) Score

| | |
|-----------------|--|
| End point title | Change From Baseline in Weekly Average of Patient Global Impression of Severity (PGIS) Score |
|-----------------|--|

End point description:

The PGIS (for subjects 12 years and older) is a single item patient-rated measure of the subject's AD condition severity at a given point in time.

This single item instrument uses a 7-point rating scale, which range from 1 to 7, where 1=Not present to 7=Extremely severe.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 1, Week 2, Week 3, Week 4 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 133 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 | -0.24 (± 0.511) | -0.43 (± 0.649) | | |
| Week 2 | -0.26 (± 0.692) | -0.60 (± 0.836) | | |
| Week 3 | -0.38 (± 0.871) | -0.66 (± 0.913) | | |
| Week 4 | -0.44 (± 0.965) | -0.71 (± 1.028) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) Score

| | |
|---|--|
| End point title | Patient Global Impression of Change (PGIC) Score |
| End point description: | |
| <p>The PGIC (for subjects 12 years and older) was used to determine global improvement as assessed by the patient. It was used as an anchor to define a responder definition for the peak pruritus scales for 'clinically important responder' and as a sensitivity analysis for defining a 'clinical important difference' on the peak pruritus scales.</p> <p>This single item instrument is a 7-point rating scale, anchored by (1) 'very much improved' to (7) 'very much worse'.</p> <p>Overall number of subjects analyzed included all subjects randomized and dispensed study drug. Subjects were assigned to the randomized treatment regardless of what treatment was received.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Day 8, Day 15, Day 22, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 137 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 | 3.3 (± 1.05) | 2.6 (± 1.10) | | |
| Day 15 | 3.2 (± 1.10) | 2.6 (± 1.07) | | |

| | | | | |
|--------|-------------------|-------------------|--|--|
| Day 22 | 3.0 (\pm 1.19) | 2.6 (\pm 1.04) | | |
| Day 29 | 2.9 (\pm 1.21) | 2.5 (\pm 1.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average of Observer Reported Global Impression of Severity (OGIS) Score

| | |
|-----------------|--|
| End point title | Change From Baseline in Weekly Average of Observer Reported Global Impression of Severity (OGIS) Score |
|-----------------|--|

End point description:

The OGIS (for subjects ≥ 2 and < 12 years) is a single item observer-rated measure of the subject's AD condition severity at a given point in time.

This single item instrument uses a 7-point rating scale, which ranged from 1 to 7, where 1=Not present to 7=Extremely severe.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

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

End point timeframe:

Baseline, Week 1, Week 2, Week 3, Week 4

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 67 | 119 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 | -0.12 (\pm 0.593) | -0.62 (\pm 0.667) | | |
| Week 2 | -0.27 (\pm 0.617) | -0.93 (\pm 0.794) | | |
| Week 3 | -0.41 (\pm 0.770) | -1.03 (\pm 0.822) | | |
| Week 4 | -0.54 (\pm 0.854) | -1.14 (\pm 0.893) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Observer Reported Global Impression of Change (OGIC) Score

| | |
|-----------------|--|
| End point title | Observer Reported Global Impression of Change (OGIC) Score |
|-----------------|--|

End point description:

The OGIC (for subjects ≥ 2 and < 12 years) was used to determine global improvement as assessed by the observer. It was used as an anchor to define a responder definition for the peak pruritus scales for

'clinically important responder' and as a sensitivity analysis for defining a 'clinical important difference' on the peak pruritus scales.

This single item instrument is a 7-point rating scale, anchored by (1) 'very much improved' to (7) 'very much worse'.

Overall number of subjects analyzed included all subjects randomized and dispensed study drug.

Subjects were assigned to the randomized treatment regardless of what treatment was received.

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 8, Day 15, Day 22, Day 29 | |

| End point values | Vehicle Twice a Day (BID) | Crisaborole 2% Twice a Day (BID) | | |
|--------------------------------------|---------------------------|----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 69 | 123 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 8 | 3.0 (± 1.08) | 2.3 (± 0.81) | | |
| Day 15 | 3.0 (± 1.10) | 2.3 (± 0.92) | | |
| Day 22 | 2.9 (± 1.16) | 2.4 (± 0.99) | | |
| Day 29 | 2.8 (± 1.07) | 2.2 (± 1.05) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 60

Adverse event reporting additional description:

Same event may appear as AE and serious AE, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. Safety analysis set analyzed.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
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| Dictionary version | 24.0 |
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Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Crisaborole 2% Twice a Day (BID) |
|-----------------------|----------------------------------|

Reporting group description:

Crisaborole 2% was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1.

| | |
|-----------------------|---------------------------|
| Reporting group title | Vehicle Twice a Day (BID) |
|-----------------------|---------------------------|

Reporting group description:

Vehicle was applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1.

| Serious adverse events | Crisaborole 2% Twice a Day (BID) | Vehicle Twice a Day (BID) | |
|---|-------------------------------------|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 1 / 131 (0.76%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Myocardial necrosis marker increased | | | |
| subjects affected / exposed | 0 / 260 (0.00%) | 1 / 131 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 260 (0.38%) | 0 / 131 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| Non-serious adverse events | Crisaborole 2% Twice a Day (BID) | Vehicle Twice a Day (BID) | |
|---|---|--------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 101 / 260 (38.85%) | 43 / 131 (32.82%) | |
| General disorders and administration site conditions | | | |
| Application site discolouration | | | |
| subjects affected / exposed | 9 / 260 (3.46%) | 1 / 131 (0.76%) | |
| occurrences (all) | 9 | 1 | |
| Application site pain | | | |
| subjects affected / exposed | 34 / 260 (13.08%) | 5 / 131 (3.82%) | |
| occurrences (all) | 41 | 6 | |
| Application site paraesthesia | | | |
| subjects affected / exposed | 7 / 260 (2.69%) | 1 / 131 (0.76%) | |
| occurrences (all) | 8 | 1 | |
| Application site irritation | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 1 / 131 (0.76%) | |
| occurrences (all) | 3 | 1 | |
| Application site urticaria | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 131 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 260 (2.31%) | 1 / 131 (0.76%) | |
| occurrences (all) | 6 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 260 (1.15%) | 0 / 131 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 4 / 260 (1.54%) | 3 / 131 (2.29%) | |
| occurrences (all) | 5 | 4 | |
| Dermatitis atopic | | | |
| subjects affected / exposed | 20 / 260 (7.69%) | 15 / 131 (11.45%) | |
| occurrences (all) | 22 | 15 | |
| Pruritus | | | |

| | | | |
|--|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 260 (0.00%) 0 | 3 / 131 (2.29%) 3 | |
| Miliaria | | | |
| subjects affected / exposed occurrences (all) | 0 / 260 (0.00%) 0 | 2 / 131 (1.53%) 3 | |
| Dermatitis contact | | | |
| subjects affected / exposed occurrences (all) | 6 / 260 (2.31%) 6 | 1 / 131 (0.76%) 1 | |
| Urticaria | | | |
| subjects affected / exposed occurrences (all) | 3 / 260 (1.15%) 3 | 1 / 131 (0.76%) 1 | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed occurrences (all) | 3 / 260 (1.15%) 3 | 2 / 131 (1.53%) 2 | |
| Folliculitis | | | |
| subjects affected / exposed occurrences (all) | 8 / 260 (3.08%) 8 | 6 / 131 (4.58%) 6 | |
| Gastroenteritis | | | |
| subjects affected / exposed occurrences (all) | 3 / 260 (1.15%) 3 | 0 / 131 (0.00%) 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed occurrences (all) | 9 / 260 (3.46%) 9 | 4 / 131 (3.05%) 6 | |
| Otitis media acute | | | |
| subjects affected / exposed occurrences (all) | 1 / 260 (0.38%) 1 | 2 / 131 (1.53%) 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed occurrences (all) | 9 / 260 (3.46%) 10 | 4 / 131 (3.05%) 4 | |
| Tonsillitis | | | |
| subjects affected / exposed occurrences (all) | 3 / 260 (1.15%) 3 | 0 / 131 (0.00%) 0 | |
| Pharyngitis | | | |
| subjects affected / exposed occurrences (all) | 3 / 260 (1.15%) 3 | 2 / 131 (1.53%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 15 November 2019 | Updated the primary and key secondary efficacy endpoints to align with global clinical development program, including: Change of primary endpoint from ISGA (Investigator's Static Global Assessment) to EASI (Eczema Area and Severity Index). Addition of ISGA as a key secondary endpoint. Addition of age specification for Pruritus assessments. Addition of tertiary endpoints pertaining to pruritus assessment. |
| 28 August 2020 | (1) Only for Japan: Japan subjects who completed the study intervention period in Study C3291032 were offered participation in the long-term safety extension study C3291027 if eligibility criteria were met. The subjects who rolled over into study C3291027 without a Post Treatment Follow Up period were considered completers in this study. (2) All female subjects who were of childbearing potential as applicable to the study who were, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must have agreed to use an appropriate method of contraception consistently and correctly for the screening period, the duration of the active treatment period and for at least 28 days after the last dose of investigational product. |
| 18 December 2020 | Updated the sample size and power: The total sample size of 384 subjects in this study with a 2:1 randomization ratio (256:128) provided approximately 90% power to detect a 12% difference of percent change from baseline in EASI total score at Day 29 between crisaborole arm and vehicle arm at the 0.05 (2-sided) significance level, assuming the common standard deviation of percent change from baseline in EASI total score at Day 29 is 34%. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported