



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	v2 (current)
This version publication date	01 March 2022
First version publication date	25 June 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	C3291037
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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:

At time of early termination, <40% of planned subjects were treated across treatment groups. Number of subjects enrolled up to early termination of study were insufficient to allow meaningful inference and robust statistical analyses of data. As a result, all safety data was summarized with Cohort 1 and 2 combined for crisaborole and vehicle groups.

Pre-assignment

Screening details:

This study was originally plan to conduct in 2 different cohorts for crisaborole and vehicle groups. Cohort 1 was planned for eligible for TCS therapy (hydrocortisone butyrate cream 0.1%), and Cohort 2 was planned for subjects not eligible for TCS therapy but eligible for topical calcineurin inhibitor (TCI) therapy (pimecrolimus cream 1%).

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
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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
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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
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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: Treatment was clinical assessor blinded for all treatment groups and double blinded for crisaborole ointment, 2% and vehicle treatment groups.

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: The endpoint was planned to be analysed in specified arms only. Only descriptive summary was performed due to study early termination.

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]
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End point description:

EASI quantifies severity of subjects's 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) = $0.1 \cdot Ah \cdot (Eh + Ih + Exh + Lh) + 0.2 \cdot Au \cdot (Eu + Iu + Exu + Lu) + 0.3 \cdot At \cdot (Et + It + Ext + Lt) + 0.4 \cdot Al \cdot (El + Il + Exl + Ll)$; for aged 2to<8 years = $0.2 \cdot Ah \cdot (Eh + Ih + Exh + Lh) + 0.2 \cdot Au \cdot (Eu + Iu + Exu + Lu) + 0.3 \cdot At \cdot (Et + It + Ext + Lt) + 0.3 \cdot Al \cdot (El + Il + Exl + Ll)$. Total score range = 0.0-72.0, higher scores = greater AD severity. Full analysis set: randomised

End point type	Primary
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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 reported 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 (\pm 46.283)	-49.47 (\pm 34.195)	-75.50 (\pm 30.305)	-60.08 (\pm 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 Treatment Discontinuations due to AEs and SAEs

End point title	Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs) and Treatment Discontinuations due to AEs and SAEs ^[2]
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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. TEAEs are events between the first dose of study drug up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. A SAE is any untoward medical occurrence at any dose that: results in death; is life-threatening (immediate risk of death); requires inpatient hospitalisation or prolongation of existing hospitalisation; 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
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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 reported 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)

End point title	Number of Subjects With Local Tolerability Adverse Events (AEs) ^[3]
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End point description:

Local tolerability AEs 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
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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 reported 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	12	13	2	8

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]
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End point description:

Vital sign measurements included temperature, respiratory rate, pulse rate, and blood pressure. Temperature, respiratory rate, pulse rate, and blood pressure were 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. SAF included all subjects who received at least one dose of the investigational product according to actual treatment received.

End point type	Primary
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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 reported 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	1	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]
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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
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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 reported 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	1	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 Day 8, 15 and 22

End point title	Percent Change From Baseline in Eczema Area and Severity Index (EASI) Total Score at Day 8, 15 and 22
End point description:	
EASI quantifies severity of subjects's AD (excluded scalp) based on lesion severity and %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 EASI score range=0.0-72.0, higher scores=greater severity of AD. Analysis was performed	
End point type	Secondary
End point timeframe:	
Baseline, Day 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)				
Percent Change at 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)
Percent Change at Day15(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)
Percent Change at Day22(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)				
Percent Change at 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)
Percent Change at Day15(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)
Percent Change at Day22(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 Day 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 Day 8, 15, 22 and 29
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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 randomised subjects who received at least 1 dose of investigational product.

End point type	Secondary
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End point timeframe:

Day 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 Day 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 Day 8, 15, 22 and 29
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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 randomised subjects who received at least 1 dose of investigational product.

End point type	Secondary
End point timeframe:	
Day 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 Day 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 Day 8, 15, 22 and 29
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End point description:

EASI quantifies severity of subjects's AD (excluded scalp) based on lesion severity and % 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 \geq 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. FAS included all randomised subjects who received at least 1 dose of investigational product. Number of Subjects

End point type	Secondary
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End point timeframe:

Day 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 Improvement From Baseline in Eczema Area and Severity Index (EASI) Total Score of Greater Than or Equal to (\geq) 75%

End point title	Time to First Improvement From Baseline in Eczema Area and Severity Index (EASI) Total Score of Greater Than or Equal to (\geq) 75%
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 Day 8, 15, 22 and 29

End point title	Change From Baseline in Percent Body Surface Area (%BSA) at Day 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, Day, 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)				
Change at 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)
Change at 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)
Change at 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)
Change at 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)				
Change at 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)
Change at 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)
Change at 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)
Change at 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 Day 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 Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD was assessed using the peak pruritus NRS for subjects aged >=12 years. 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 randomised 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, Day 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)				
Change at 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)
Change at 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)
Change at 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)
Change at 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 Subject Reported Itch Severity Scale in Subjects Aged 6-11 Years at Day 8, 15, 22 and 29

End point title	Change From Baseline in Subject Reported Itch Severity Scale in Subjects Aged 6-11 Years at Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD was assessed using the five-category subject 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 0 to 4, where 0= no itch and 4= very itch. Higher scores indicated worse itch. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

End point type	Secondary
End point timeframe:	
Baseline, Day 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 is not reported because of low enrolment.

[7] - Data is not reported because of low enrolment.

[8] - Data is not reported because of low enrolment.

[9] - Data is not reported because of low enrolment.

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 Day 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 Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD was assessed using the subject 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

End point type	Secondary
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End point timeframe:

Baseline, Day 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 is not reported because of low enrolment.

[11] - Data is not reported because of low enrolment.

[12] - Data is not reported because of low enrolment.

[13] - Data is not reported because of low enrolment.

Statistical analyses

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
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End point description:

The severity of itch (pruritus) due to AD was assessed using the peak pruritus NRS for subjects aged >12 years. 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflected limitations related to reduced sample size (only 39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Summarizing further by Time to >2 Point Improvement will not provide additional useful information due to smaller than planned sample size as a result of study early termination.

End point type	Secondary
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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 is not reported because of low enrolment.

[15] - Data is not reported because of low enrolment.

[16] - Data is not reported because of low enrolment.

[17] - Data is not reported because of low enrolment.

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
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End point description:

The severity of itch (pruritus) due to AD was assessed using the peak pruritus NRS for subjects aged >12 years. 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflected limitations related to reduced sample size (only 39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Summarizing further by Time to >3 Point Improvement will not provide additional useful information due to smaller than planned sample size as a result of study early termination.

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 is not reported because of low enrolment.

[19] - Data is not reported because of low enrolment.

[20] - Data is not reported because of low enrolment.

[21] - Data is not reported because of low enrolment.

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
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End point description:

The severity of itch (pruritus) due to AD was assessed using the subject 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

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 is not reported because of low enrolment.

[23] - Data is not reported because of low enrolment.

[24] - Data is not reported because of low enrolment.

[25] - Data is not reported because of low enrolment.

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
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End point description:

The severity of itch (pruritus) due to AD was assessed using the subject 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

End point type	Secondary
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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 is not reported because of low enrolment.

[27] - Data is not reported because of low enrolment.

[28] - Data is not reported because of low enrolment.

[29] - Data is not reported because of low enrolment.

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 Day 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
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End point description:

The severity of itch (pruritus) due to AD was assessed using the peak pruritus NRS for subjects aged ≥ 12 years. 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 randomised 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
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End point timeframe:

Day 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 Day 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 Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD was assessed using the peak pruritus NRS for subjects aged ≥ 12 years. 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 randomised 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
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End point timeframe:

Day 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 Day 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 Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

End point type	Secondary
End point timeframe:	
Day 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 is not reported because of low enrolment.

[31] - Data is not reported because of low enrolment.

[32] - Data is not reported because of low enrolment.

[33] - Data is not reported because of low enrolment.

Statistical analyses

No statistical analyses for this end point

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 Day 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 Day 8, 15, 22 and 29
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End point description:

The severity of itch (pruritus) due to AD was assessed using the subject 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. Data was not summarized as per SAP which was revised prior to the analyses and which reflect limitations related to reduced sample size (39% enrollment) of early terminated study. Smaller than originally planned sample size was insufficient to allow robust statistical analyses. Pruritus related PRO endpoints used different instruments in each of 3 age groups. As a result, subdividing population based on age group renders smaller sample size in pediatric groups, therefore data was not summarized.

End point type	Secondary
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End point timeframe:

Day 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 is not reported because of low enrolment.

[35] - Data is not reported because of low enrolment.

[36] - Data is not reported because of low enrolment.

[37] - Data is not reported because of low enrolment.

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 Day 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 Day 8, 15, 22 and 29
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End point description:

DLQI is a 10-item questionnaire that measures the impact of skin disease on subjects aged ≥ 16 years. 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 randomised 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, Day 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)				
Change at Day 8 (n= 20,23,27,19)	-1.9 (± 5.53)	-3.8 (± 3.45)	-5.1 (± 4.98)	-1.4 (± 2.99)
Change at Day 15 (n=16,23,26,17)	-3.4 (± 3.72)	-3.5 (± 2.92)	-6.8 (± 5.94)	-2.9 (± 2.63)
Change at Day 22 (n=18,20,25,18)	-2.8 (± 4.12)	-3.4 (± 4.73)	-6.9 (± 6.37)	-3.4 (± 3.88)
Change at 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 Day 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 Day 8, 15, 22 and 29
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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 ranged 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 randomised 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, Day 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)				
Change at Day 8 (n= 27,22,25,15)	-0.2 (± 3.42)	-2.1 (± 4.49)	-5.4 (± 6.14)	-1.7 (± 4.03)
Change at Day 15 (n=22,24,29,17)	-2.0 (± 4.49)	-3.1 (± 5.13)	-5.5 (± 6.32)	-1.6 (± 4.66)
Change at Day 22 (n=21,21,27,13)	-2.7 (± 3.04)	-2.6 (± 5.81)	-4.9 (± 7.89)	-2.5 (± 3.15)
Change at 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 Day 8, 15, 22 and 29

End point title	Change From Baseline in Dermatitis Family Impact Questionnaire (DFI) in Subjects Aged 2-17 Years at Day 8, 15, 22 and 29
End point description:	
<p>The DFI was a 10-item disease questionnaire that measures the impact of having a child (aged 2-17 years) 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 randomised 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.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Day 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)				
Change at Day 8 (n= 37,32,33,28)	-1.2 (± 6.43)	-2.3 (± 5.16)	-5.6 (± 5.61)	-2.8 (± 6.79)
Change at Day 15 (n=32,31,37,30)	-1.1 (± 6.77)	-2.3 (± 4.71)	-5.5 (± 6.82)	-3.2 (± 5.94)
Change at Day 22 (n=31,29,34,26)	-2.5 (± 4.84)	-3.1 (± 5.24)	-5.3 (± 6.92)	-4.5 (± 5.93)
Change at 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Vehicle
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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	Pimecrolimus Cream 1% BID
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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	Hydrocortisone Butyrate Cream 0.1% BID
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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	Crisaborole Ointment 2% BID
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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	Pimecrolimus Cream 1% BID	Hydrocortisone Butyrate Cream 0.1% BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	0 / 71 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

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: