Amsterdam, 17 September 2020
EMA/662601/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Staquis

International non-proprietary name: crisaborole

Procedure no.: EMEA/H/C/004863/P46/002

Marketing authorisation holder (MAH): Pfizer Europe MA EEIG

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Introduction

On 14th April 2020, the MAH submitted a completed paediatric study for Crisaborole ointment 2%, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The Marketing Authorisation Holder (MAH) stated that study C3291002 "A Phase 4, Multicenter, Open-Label Safety Study of Crisaborole Ointment 2% in Children Aged 3 Months to Less Than 24 Months with Mild to Moderate Atopic Dermatitis" is a stand-alone study.

Study C3291002 was conducted to fulfil a post marketing requirement in the US under PREA (21 USC 355c), which mandates that all applications for new ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration contain an assessment of the product for the claimed indication(s) in paediatric patients unless this requirement is waived, deferred, or inapplicable.

2.2. Information on the pharmaceutical formulation used in the study

Crisaborole, also referred to as PF-06930164 or AN2728, is a low molecular weight (251.1 daltons) benzoxaborole anti-inflammatory phosphodiesterase (PDE)-4 inhibitor that penetrates into the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate levels, which suppresses inflammation and secretion of certain cytokines, such as tumor necrosis factor-α, interleukin (IL)-2, IL-4, IL-5, and interferon (IFN)-γ, implicated in the pathogenesis of atopic dermatitis (AD). Crisaborole applied to human skin ex vivo or on AD lesions of patients reduces expression of key drivers of atopic inflammation, including T-cell derived cytokines IL-13, IL-31, and IFN-γ as well as innate markers of inflammation such as matrix metalloproteinase-12. The specific mechanism(s) by which crisaborole exerts its therapeutic action for AD is not well defined.

On 14th December 2016, EUCRISA™ (crisaborole) Ointment 2% was approved by the US Food and Drug Administration (FDA) for topical treatment of mild-to-moderate AD in patients 2 years of age and older.

EUCRISA was also approved by Health Canada for the same indication on 07th June 2018. Crisaborole was approved under the trade name STAQUIS in Israel on 10th February 2019, in Australia on 15th February 2019, Hong Kong (20 April 2020) and China (29 July 2020) for the same indication. The formulation containing the 0.1% BHT antioxidant excipient is the authorised formulation of crisaborole in the US, Canada, Israel, and Australia.

The MAH agreed to remove the antioxidant (0.1% BHT) from the formulation to be marketed in the EU (trade name STAQUIS). STAQUIS was granted an EU Marketing Authorisation via the Centralised Procedure on 27th March 2020 for the topical treatment of mild-to-moderate AD in adults and paediatric patients from 2 years of age with ≤40% BSA affected.

The original marketing authorisation application for STAQUIS in the EU was based on the results of two identically designed randomised, double-blind, vehicle-controlled, Phase 3 registration studies (AN2728-AD-301 and AN2728-AD-302). AN2728-AD-303 was an open-label, 12 months safety study

in patients (2 years and older) with mild to moderate AD who completed Study AN2728-AD-301 or Study AN2728-AD-302. Additional studies have been performed (see "Annex - Line Listings" at the end of this report).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study C3291002: "A Phase 4, Multicenter, Open-Label Safety Study of Crisaborole Ointment 2% in Children Aged 3 Months to Less Than 24 Months With Mild to Moderate Atopic Dermatitis"

2.3.2. Clinical study

Study C3291002: "A Phase 4, Multicenter, Open-Label Safety Study of Crisaborole Ointment 2% in Children Aged 3 Months to Less Than 24 Months With Mild to Moderate Atopic Dermatitis"

Study Period:

Date of First Subject First Visit: Jan 16th, 2018

Date of Last Visit: Apr 12th, 2019

Description

Study C3291002 was a Phase 4, multicenter, open label, safety study to evaluate the safety of crisaborole ointment 2% in approximately 125 participants who were 3 to <24 months of age, with mild-to-moderate AD involving at least 5% treatable BSA (body surface area).

In addition, a cohort of at least 16 of the approximately 125 participants enrolled was included in a subgroup for exploratory pharmacokinetic (PK) assessment. These participants must have had moderate AD with a minimum of 35% treatable % BSA, excluding the scalp, and must have completed all PK assessments to have been included in the PK analysis. Of these participants, at least 3 participants who were less than 9 months of age were to be enrolled.

The primary objective of the study was to study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild-to-moderate atopic dermatitis (AD). The exploratory objectives were to evaluate the efficacy of crisaborole ointment 2% in the treatment of AD as well as to assess the PK profile and extent of systemic exposure of crisaborole and its identified main oxidative metabolites.

Methods

Objective(s)

Primary Objective:

To study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild-to-moderate AD.

Exploratory Objectives:

- To assess efficacy of crisaborole ointment 2%.
- To assess the PK profile and extent of systemic exposure of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment 2% BID on Day 8.

Study design

This was a Phase 4, multicenter, open label, safety study to evaluate the safety of crisaborole ointment 2% in approximately 125 participants who were 3 to <24 months of age, with mild-to-moderate AD involving at least 5% treatable BSA. Treatable % BSA was defined as the percent of a participant's total BSA that was AD-involved, excluding the scalp.

In addition, a cohort of at least 16 of the approximately 125 participants enrolled was included in a subgroup for pharmacokinetic (PK) assessment. These participants must have had moderate AD with a minimum of 35% treatable %BSA, excluding the scalp, and must have completed all PK assessments to have been included in the PK analysis. Of these participants, at least 3 participants who were less than 9 months of age were to be enrolled.

Approximately 30 investigational sites were planned to participate in this study. Only selected study sites participated in the PK assessment.

Study population /Sample size

The sample size was determined by clinical judgment based on Sponsor experience with other clinical studies with the investigational product and was not based on statistical power. To ensure 100 completers, 125 subjects (16 of which for PK analysis) were initially planned to be enrolled assuming a 20% drop out rate.

Key Inclusion Criteria:

Subjects had to meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Was male or female aged at least 3 months at the Screening visit to less than 24 months on Baseline/Day 1.
2. Had a clinical diagnosis of AD according to the criteria of Hanifin and Rajka (1980)
3. Met the appropriate % BSA criterion at Baseline/Day 1:
    - Non-PK cohort: has AD involvement ≥ 5% Treatable %BSA, excluding the scalp
    - PK cohort: had at least 35% Treatable %BSA, excluding the scalp, and had adequate venous access to permit repeated PK sampling.
4. Met the appropriate Investigator's Static Global Assessment (ISGA) Score criterion at Baseline/Day 1:
    - Non-PK cohort: ISGA Score of Mild (2) or Moderate (3)
    - PK cohort: ISGA Score of Moderate (3).

Key Exclusion Criteria:

Subjects with any of the following characteristics/conditions were excluded from the study:

1. Had any clinically significant dermatological condition or disease (including active or potentially recurrent non-AD dermatological conditions and/or known genetic dermatological conditions that overlap with AD such as Netherton Syndrome).
2. Was premature at birth, defined as less than 37 gestational weeks.
3. Had estimated creatinine clearance based on the age appropriate calculation that is below the lower limit of normal (LLN), or serum creatinine greater than the upper limit of normal (ULN).
4. Had received any of the following AD treatment regimens without the required minimum washout:

   28 days prior to Baseline/Day 1:

   • Systemic corticosteroids (use of intranasal/inhaled, and ophthalmic corticosteroids allowed);

   • Systemic immunosuppressive agents (e.g. methotrexate, ciclosporin, azathioprine, hydroxychloroquine, mycophenolate mofetil).

   7 days prior to Baseline/Day 1:

   • Use of high or mid potency topical corticosteroids or calcineurin inhibitors anywhere on the body;

   • Topical antibiotics on treatable AD lesions;

   • Light therapy (ultraviolet light therapy);

   • Use of antibacterial soaps (for bathing), bleach baths, or topical sodium hypochlorite based products on treatable AD lesions.

   3 days prior to Baseline/Day 1:

   • Systemic antihistamines;

   • Use of low potency topical corticosteroid (e.g. hydrocortisone 1%) on treatable AD lesions.

   8 hours prior to Baseline/Day 1:

   - Use of emollients on treatable AD lesions;
   - Use of topical antihistamines on treatable AD lesions;
   - Use of topical hydrocortisone <1% on treatable AD lesions.
5. Had unstable AD or a consistent requirement for high potency topical corticosteroids to manage AD signs and symptoms, or the mother required treatment with high potency topical corticosteroids due to potential for topical corticosteroids to transfer to the child.
6. Child was nursing and the child's mother required high dose systemic steroids or systemic immunotherapy or other medications that might have been transmitted in the breast milk and that might have altered the course of the child's AD.
7. Had a history of hyperactive airway disease requiring systemic corticosteroid therapy.
8. Had a significant active systemic or localized infection, including known actively infected AD, within 2 weeks prior to Baseline/Day 1.

9. Had a history of use of biologic therapy including intravenous immunoglobulin at any time prior to study.
10. Had undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only).
11. PK Cohort Only - Participants with lesions on the extremities (below wrists and below ankles) or within 2 cm of the mouth.

Lifestyle requirements:

- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation.
- The parent(s)/legal guardian will be instructed to dress the subject in loose-fitting clothing and avoid occluding the treated areas (with dry wraps, for example). Wet wraps are not permitted.
- Subjects should not swim, be bathed or have treatment areas washed for at least 4 hours after application.
- Use of sunscreen is permitted, but only on skin areas without AD involvement.
- If there are treated lesions on the hands or feet, subjects should be encouraged, as much as possible, not to put these areas in the mouth to avoid ingestion of investigational product.
- The parent(s)/legal guardian should avoid wiping the investigational product off the skin and investigational product should not be reapplied to wiped areas until the next scheduled dose.
- If there are AD lesions in the diaper area, they should be treated with investigational product; however, following diaper change, any investigational product inadvertently wiped off soiled skin should not be reapplied until the next scheduled dose. Diaper rash creams, lotions, ointments, powders, etc are not permitted where AD lesions are present. In the case of rash in the diaper area without AD involvement, standard treatments may be applied.
- When applying investigational product at home, the parent(s)/legal guardian will not be required to wear gloves. However, they must be instructed to wash their hands with mild soap and water before and after each application.
- Product labels for all topical products applied during the study (including emollients, diaper rash creams, diaper wipes, sunscreen, etc) should be reviewed and recorded on the concomitant treatment CRF; use of topical preparations containing propylene should be avoided whenever possible.

Treatments

Dose selection:

The dose strength and regimen selected for this study has been shown to be safe, well tolerated and efficacious in patients and healthy volunteers 2 years of age and older who participated in previously conducted studies of crisaborole. Crisaborole ointment 2% applied BID was studied in two Phase 3, randomized, double-blind, vehicle-controlled studies, and a Phase 3 open-label long-term safety study. Data from the two controlled studies showed a statistically significant therapeutic effect compared to vehicle with acceptable safety in patients 2 years and older. In the open-label study, crisaborole ointment 2% applied BID, demonstrated that the long-term use was well tolerated. The Phase 1 maximal use absorption study in children and adolescents aged 2 to 17 years old showed that subjects who were administered crisaborole ointment 2% BID (single dose on Days 1 and 8) to 27-92% BSA (a mean BSA of 47%) had overall blood levels of crisaborole that were similar to those previously observed in adults after adjusting for %BSA treated. An analysis of variance (ANOVA) showed no statistically significant differences in PK parameters between the age cohorts represented in the study (Cohort 1, ages 12–17 years; Cohort 2, ages 6–11 years; and Cohort 3, ages 2–5 years).

Based on the results of clinical studies conducted with crisaborole ointment 2% to date, it is anticipated that crisaborole ointment 2% will demonstrate similar efficacy and satisfactory safety and local tolerability in the pediatric population to be enrolled in this study.

Dosing procedure:

Parent(s)/legal guardian(s) were instructed how to dispense and apply the ointment and were provided with a body map documenting the designated treatment areas and a paper dosing diary for recording all investigational product applications applied at home. Crisaborole ointment 2% is for external use on the skin only, and avoidance of contact by participants with mucous membranes (i.e. inside of nostrils, mouth, vagina, urethra, and rectum), and the eyes was included in application instructions. Additionally, for participants in the PK cohort, though AD lesions in the perioral area (within 2 cm of the mouth) or on the extremities (below wrists and below ankles) were exclusionary at baseline, if they occurred following enrolment, crisaborole ointment 2% should not have been applied to those areas during the PK phase (Day 1 AM dose through Day 8 final PK sample collection) in order to reduce the possibility of accidental ingestion that could adversely affect PK results.

For non-PK cohort participants, a thin layer of crisaborole ointment 2% was applied BID to all treatable AD lesions identified at Baseline/Day 1. Investigational product continued to be applied to all treatable AD lesions identified at Baseline/Day 1 regardless of whether they became clinically clear prior to Day 29. Investigational product may also have been applied to any new treatable AD lesions that appeared following Baseline/Day 1 after consultation with the Investigator.

For PK cohort participants (from Day 1 through the AM dose on Day 8), the amount of crisaborole ointment 2% to be applied (i.e. the "per application dose") was calculated individually for each participant by study staff, based upon the treatable %BSA as determined at Baseline/Day 1 (i.e. the percent of the participant's total BSA at Baseline/Day 1 that was AD-involved, excluding the scalp). The per application dose remained fixed throughout the PK Phase and was applied to all treatable AD-involved areas identified at Baseline/Day 1, regardless of whether they became clinically clear and to any new AD lesions that appeared post Baseline/Day 1 through the AM dose on Day 8.

Duration of Treatment and Follow-Up:

Screening procedures were to be completed between 2 and 28 days (inclusive) prior to the Baseline/Day 1 Visit. The duration of the Investigational Product Application Period was 29 days and

included study visits at days 1, 8, 15, 29 (End of Treatment) and telephone contact at day 22. The Post-Treatment Follow-Up period included telephone contact at days 36 and 57 (End of Study).

Outcomes/endpoints

Primary endpoint (safety):

The primary endpoint of the study was the incidence of treatment-emergent adverse events (AEs) (including application site reactions), serious AEs (SAEs), and clinically significant changes in height, weight, vital signs, electrocardiogram (ECG), and clinical laboratory parameters.

Exploratory endpoint (efficacy):

- Change from baseline in percent body surface area (%BSA)
- Achievement of treatment success (defined as a score of Clear or Almost Clear with a 2-grade improvement from baseline) based on Investigator's Static Global Assessment (ISGA)
- % Change from baseline in Eczema Area and Severity Index (EASI) at each scheduled time point
- Change from baseline in Patient-Oriented Eczema Measure (POEM) at each scheduled time point.

Exploratory endpoint (pharmacokinetics):

PK (crisaborole, AN7602, and AN8323):

- Maximum observed plasma concentration (Cmax) (Day 8)
- Time to reach maximum observed plasma concentration (Tmax) (Day 8)
- Area under the plasma concentration time curve from time zero to 12 hours (AUC0-12) (Day 8)

Propylene glycol concentrations:

- Screening (all participants)
- Day 8 (PK cohort predose)
- End of treatment (EOT) (all participants, 12 hours post last dose)

Clinical Safety Assessments

- Medical History
- Height/Length and Weight
- Vital Signs (temperature, respiratory rate, pulse rate, blood pressure)
- Physical Examination
- 12-Lead Electrocardiogram
- AE and SAE recording

Laboratory Safety Assessments

- Hematology: hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count % and absoulte (neutrophils, eosinophils, monocytes, basophils, lymphocytes)
- Chemistry: blood urea nitrogen, glucose (non-fasting), creatinine, sodium, potassium, chloride, bicarbonate, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline, phosphatase, albumin, total protein, lactate, calculation of osmolal gap, calculation of anion gap
- Other bioanalytical laboratory assessment (propylene glycol systemic levels)

Schedule of activities all subjects

All Subjects (Including non-PK and PK Cohorts)

Day		1	8	15	22	29	36	57
Window	**-28 to -2 day(s)**		**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**+3 days**
Visit	**Screening**	**Baseline**			**Telephone Contact**	**End of Treatment/Early Termination**	**Telephone Contact**	**Follow-up Contact[a] (End of Study)**
Informed Consent	X							
Demographics	X							
Review Inclusion/Exclusion Criteria	X	X						
Medical History	X	X						
Confirmation of Diagnosis of AD	X	X						
Height/Length and Weight		X				X		
Vital Signs[b]	X	X	X	X		X		
Full Physical Examination	X[c]					X		
12-Lead Electrocardiogram (ECG)		X	X			X		
Limited Physical Examination		X[d]						
ISGA[e]	X	X	X	X		X		
Eczema Area and Severity Index (EASI) (incl. % BSA total)		X		X		X		
Body Site checklist of AD lesions		X						
Patient-Oriented Eczema Measure (POEM)		X	X	X		X		
Calculate Treatable %BSA for eligibilitly assessment[f]	X	X						
Blood collection for serum chemistry and hematology	X[g]					X		
Blood sampling for assessment of propylene glycol concentration in plasma	X					X[h]		
Record treatable AD areas (excluding scalp) in source and provide parent(s)/legal guardian with documentation of the designated treatment areas		X						
Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use		X	X	X				
Dispense and weigh the investigational product tube(s) and apply first dose. First dose applied in office by study staff		X						
Dispense and weigh new investigational product tube(s) and provide for at-home dosing		X[i]	X	X				
At-home dosing, applied by parent(s)/legal guardian[k,j]		**2nd dose (PM) on Day 1, then BID up to PM dose prior to Day 29 visit**						
Review dosing diary; assess compliance; re-train parent(s)/legal guardian if doses missed			X	X	X	X		
Collect and weigh empty, partially used and unused investigational product tubes			X[i]	X		X		
Review and record prior and concomitant medications	X[k]	X	X	X	X	X	X	X
Assess for AEs (including application site reactions) and SAEs	X	X[l]	X	X	X	X	X	X
Review lifestyle requirements	X	X	X	X	X	X		
Schedule/reconfirm next study visit/contact	X	X	X	X	X	X	X	
Remind parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to the next visit		X	X	X	X			

Abbreviations: AD=atopic dermatitis; BP=blood pressure; %BSA=percent of body surface area; ISGA=investigator's static global assessment; PR=pulse rate; RR=respiratory rate; AE=adverse event; SAE=serious adverse event; PK=pharmacokinetic; BID=twice a day

a. Follow-up contact will be completed 28 +3 calendar days after the last administration of the investigational product to capture any adverse events.
b. Vital signs (temperature, respiratory rate, pulse rate, and BP) taken in seated or supine position after subject has been seated or lying face up for 5 minutes.
c. A full physical examination will be performed at the Screening visit. If the full examination cannot be completed during screening, an unscheduled visit may be performed prior to Baseline/Day 1 to complete the full assessment.
d. A limited physical examination will be performed at Baseline/Day 1.
e. ISGA should be completed prior to assessment of EASI, whenever possible.
f. Treatable percent body surface area (%BSA) is defined as the percent of a subject's total body surface area that is AD-involved, excluding the scalp.
g. Blood draw for clinical labs may be completed any time during the screening period, (Day -28 to Day -2) however the results must be available and reviewed by the PI prior to the Baseline/Day 1 visit and investigational product application. If the laboratory sample cannot be obtained due to an upset child, parent or other collections issues, the subject will not be enrolled into the study. Serum chemistry laboratory assessments include lactate and parameters needed to perform calculation of osmolal gap and anion gap.
h. Sample for propylene glycol concentration should be collected within 12 ±3 hours of the final Day 28 evening application. Investigational product should not be applied before this collection.
i. Not applicable to subjects in PK cohort through Day 8.
j. In the event the scheduled Day 29 visit does not fall exactly on Day 29, instruct parent(s)/legal guardian to keep dosing BID until the evening dose prior to the Day 29 visit.
k. All medications and non-medication therapies used within 30 days prior to Screening.
l. Assess for AEs (including application site reactions) /SAEs before and after in clinic dose at Baseline/Day 1.

Schedule of activities PK cohort

PK Cohort Subjects Only

Day	1[a]	2-7	8b Prior to AM dose (168 hours ±1 hour post time of AM application on Day 1)	8 3 hours ±20 minutes after completion of AM dose	8 12 hours ±1 hour after completion of AM dose	Non-PK Study Schedule (see above)[c]
Visit	PK1	PK2	PK8			
Blood sampling to obtain plasma for crisaborole and metabolites PK[d,e]			X	X	X	
Blood sampling for assessment of propylene glycol concentration in plasma[d]			X			
Blood collection for serum chemistry[d,f]			X			
Apply AM and PM Dose in office[g]	X	X	X			
Review lifestyle requirements	X	X	X			
Assess and record any pre- and/or post-dose AEs (including application site reactions) and SAEs	X	X	X			
Assess and record any changes in concomitant medications	X	X	X			
Weigh amount of investigational product to be applied before each dose application	X	X	X[h]			
Dispense dosing diary and train parent(s)/legal guardian on use			X			
Dispense and weigh investigational product tube(s) and provide for at-home dosing			X			
Review the schedule of upcoming study visits with the parent(s)/legal guardian	X	X	X			
Remind parent(s)/legal guardian to bring all investigational product tubes and the dosing diary to the next visit			X			

Abbreviations: PK=pharmacokinetics

a. Perform Day 1 assessments prior to dosing procedures, as applicable (See All Subjects (Including non-PK and PK Cohorts)).
b. Aside from AM dose application, first PK sample collection, serum chemistry and PG sample collection which must all be performed at the first PK collection time point, all other Day 8 procedures may be performed at any of the 3 PK collection time points.
c. Subject to resume regular study schedule following completion of Day 8/PK 8 final PK sample collection.
d. Use of a peripheral venous catheter may be employed for repeat sample collections on Day 8/PK 8 visit based on site and parent(s)/legal guardian preference. A topical lidocaine-based anesthetic (eg, lidocaine 4% cream) may be used provided the subject has no history of intolerance and the agent **does not contain propylene glycol**.
e. Any 2 of the 3 scheduled PK sample collections may be performed by a visiting health care professional in the subject's home if preferred, however the subject must visit the site for one of the scheduled PK collections in order to perform the remainder of the Day 8 assessments.
f. Serum chemistry laboratory assessments include lactate and parameters needed to perform calculation of osmolal gap and anion gap.
g. Following the Baseline/Day 1 visit and AM dose application at the site, the remainder of investigational product applications for the PK portion of the study may be scheduled to be performed in the home by a qualified visiting health care professional based on site and parent(s)/legal guardian agreement where appropriate. PM dose on Day 8 is to be applied after last PK sample collection and may be applied by the parent(s)/legal guardian at home.
h. Weighing of investigational product on Day 8 applies to the AM dose only.

Statistical Methods

This is an open label safety study. There are no hypotheses and decision rules.

In general, number and percent will be presented for categorical variables. Number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum will be presented for continuous variables.

Binary endpoints will be summarized using number, percentage and 95% CI of percentage.

Continuous endpoints will be descriptively summarized using number, mean, standard deviation (standard error of the mean), minimum, 1st, 2nd and 3rd quartiles and maximum.

Categorical endpoints will be summarized using number and percentage.

Missing values will not be imputed for safety, efficacy and PK endpoints.

Analysis populations:

Full Analysis Set, FAS: any participant who received ⩾1 dose of investigational product.

Safety Analysis Set: any participant who received ⩾1 dose of investigational product.

Pharmacokinetic Analysis Set: subset of participants from the safety population who completed any portion of the procedures and evaluations during the PK Phase; such participants were included in any PK analyses for which they had complete data.

Results

Recruitment/ Number analysed

A total of 209 subjects were screened for eligibility, 71 subjects were screen failure and a total of 137 subjects were enrolled.

The *Full Analysis Set* was the same as the *Safety Analysis Set* (any participant who received ⩾1 dose of investigational product) and had a total of 137 subjects. The Pharmacokinetic (PK) Analysis Set consisted of a subset of 21 participants from the safety population who completed any portion of the procedures and evaluations during the PK Phase. Such participants were included in any PK analyses for which they had complete data. The Non-PK Analysis Set consisted of the remaining 116 patients in the Safety Analysis Set.

Table 6. Subject Evaluation Groups

	Crisaborole 2% BID n (%)
Screened: 209	
Screened Failure: 72	
Not Screen Failure but not Randomized: 0	
Assigned to Treatment	137 (100.0)
Treated	137 (100.0)
Not Treated	0
Full Analysis Set	137 (100.0)
Safety Analysis Set	137 (100.0)
Non-PK Set	116 (84.7)
PK Set	21 (15.3)

Of the 137 patients enrolled, 128 (93.4%) completed the Treatment Phase and 132 (96.4%) completed the Follow-Up phase. A total of 9 participants (6.6%) discontinued during the Treatment Phase. Four participants (2.9%) discontinued due to a treatment-emergent AE (TEAE), but all 4 entered the Follow-Up Phase and completed the study (table below).

Table 5. Disposition Events Summary

Number (%) of Subjects	Crisaborole 2% BID (N=137) n (%)
Disposition Phase: Treatment	
Discontinued	9 (6.6)
ADVERSE EVENT	4 (2.9)
LACK OF EFFICACY	1 (0.7)
LOST TO FOLLOW-UP	1 (0.7)
WITHDRAWAL BY PARENT/GUARDIAN	3 (2.2)
Completed	128 (93.4)
Disposition Phase: Follow-up	
Discontinued	5 (3.6)
LOST TO FOLLOW-UP	3 (2.2)
WITHDRAWAL BY PARENT/GUARDIAN	2 (1.5)
Completed	132 (96.4)

A total of 32 investigational sites in the US (24 sites), Canada (2 sites) and Australia (6 sites) participated in this study.

Protocol deviations

All deviations were reviewed and GCP compliance was maintained. Deviations are summarized below:

- Twelve deviations were reported for *concomitant medications*. Ten participants were administered a prohibited medication by the parent; 2 participants were administered a prohibited medication twice.
- Thirteen deviations were reported for *inclusion/exclusion criteria*. Blood collection supplies initially provided to clinical study sites were difficult for sample collection in the study age group. Five participants (9 deviations) were enrolled without complete screening laboratory results. Study recruitment was placed on hold temporarily until the issue was resolved, and recruitment resumed once sites were re-supplied with redesigned blood collection supplies. Two participants (1 deviation each) were administered a TCS within the washout period. One participant had ISGA score of Severe at Screening. One participant was administered a TCS and systemic antihistamine within the washout period.
- Four deviations were reported for *investigational product*:
  - Two participants received the wrong dose: one participant was administered a total volume of ointment that was greater than required by the protocol algorithm by their parent, and the other participant had an extended treatment period of 7 additional days due to the investigator being unavailable. No AEs were reported as a result of these medication errors.
  - Two participants were not compliant within 80 to 120% of the expected doses administered.
- Fifty-four deviations were related to *clinical laboratory issues*. Forty-one participants did not have laboratory assessments completed, or samples were collected but could not be processed.
- Nine deviations were reported for *procedures/tests*. Limited physical examinations were not assessed for 2 participants. ECGs were not performed for 3 participants (2 participants with 1 deviation each and 1 participant with 3 deviations). The dosing diary was not issued to 2 participants for the parents to complete.
- Six deviations were reported for *visit schedule*. Three participants did not have telephone contact conducted. Two participants (3 deviations) did not complete their scheduled clinic visit.

After the study database was closed, *additional protocol deviations were discovered at 1 site* (Site 1009) following analysis of crisaborole plasma concentrations. Five participants from Site 1009 had crisaborole plasma concentration values that were considered outliers. At this site, phlebotomy sites were not cleaned with soap and water prior to blood sample collection on Day 8 but were cleaned with isopropyl alcohol wipes per the site's standard procedure. The protocol deviations of improper preparation of the phlebotomy sites were not reported during the conduct of the trial but discovered after the database had been closed. Since this was discovered after the database had been closed, the protocol deviations of improper preparation of the phlebotomy sites were not reported during the conduct of the study.

According to the MAH, these deviations did not have any impact on the safety of participants, nor did they lead to any participant meeting criteria for withdrawal from the study.

Baseline data

Overall, demographic characteristics were similar between the cohorts (see table below). Subjects were 3 to < 24 months old with 43/137 (31.4%) between 3 to < 9 months and 94/137 (68.6%) between 9 to < 24 months of age. Most subjects were male (88/137 [64.2%]) and White (84/137 [61.3%]). The non-PK cohort had AD involvement ≥5% Treatable %BSA, (excluding the scalp) and the PK cohort had at least 35% Treatable %BSA (excluding the scalp) and had adequate venous access to permit repeated PK sampling. Participants in the PK cohort had higher baseline ISGA, POEM, and EASI scores and higher treatable %BSA compared to the non-PK cohort, consistent with the eligibility criteria of this study. One participant in the PK cohort had an ISGA score of severe at screening and did not meet inclusion/exclusion criteria but proceeded to complete the study. This was documented as a protocol deviation. The mean (SD) duration since onset of AD was 10.4 (6.4) months for the non-PK cohort and 9.1 (5.5) months for the PK-cohort.

Table 7. Demographic and Baseline Characteristics

	Crisaborole 2% BID		
	Non-PK Set (N=116)	PK Set (N=21)	Total (N=137)
Age (months):			
3 - < 9	36 (31.0%)	7 (33.3%)	43 (31.4%)
9 - < 24	80 (69.0%)	14 (66.7%)	94 (68.6%)
Mean	13.7	12.9	13.6
Std Dev	6.41	6.58	6.42
Median	13.5	13.0	13.0
Range(min,max)	(3, 23)	(3, 23)	(3, 23)
Weight (kg)			
Mean	10.2	9.5	10.1
Std Dev	2.39	1.94	2.25
Median	10.2	9.8	10.1
Range(min,max)	(4.9, 16.0)	(6.2, 12.7)	(4.9, 16.0)
Body Length (cm)/Height (cm)			
Mean	77.0	75.5	76.7
Std Dev	8.39	8.56	8.40
Median	76.2	76.5	76.2
Range(min,max)	(58.0, 96.6)	(59.5, 90.0)	(58.0, 96.6)
BMI (kg/m^2)			
Mean	17.13	16.59	17.05
Std Dev	1.935	2.380	2.010
Median	16.97	15.72	16.79
Range(min,max)	(12.6, 23.3)	(14.2, 24.8)	(12.6, 24.8)
Gender			
Male	75 (64.7%)	13 (61.9%)	88 (64.2%)
Female	41 (35.3%)	8 (38.1%)	49 (35.8%)
Race			
White	71 (61.2%)	13 (61.9%)	84 (61.3%)
Black or African American	9 (7.8%)	2 (9.5%)	11 (8.0%)
Asian	23 (19.8%)	4 (19.0%)	27 (19.7%)
American Indian or Alaska Native	1 (0.9%)	0	1 (0.7%)
Native Hawaiian or Other Pacific Islander	1 (0.9%)	0	1 (0.7%)
Other	0	0	0
Unknown	0	0	0
Multiracial	11 (9.5%)	2 (9.5%)	13 (9.5%)
Ethnicity			
Hispanic or Latino	14 (12.1%)	2 (9.5%)	16 (11.7%)
Not Hispanic or Latino	99 (85.3%)	19 (90.5%)	118 (86.1%)
Unknown	0	0	0

Table 7. Demographic and Baseline Characteristics

	Crisaborole 2% BID		
	Non-PK Set (N=116)	PK Set (N=21)	Total (N=137)
Not Reported	3 (2.6%)	0	3 (2.2%)
Investigator's Static Global Assessment			
(0) CLEAR	0	0	0
(1) ALMOST CLEAR	0	0	0
(2) MILD	52 (44.8%)	0	52 (38.0%)
(3) MODERATE	64 (55.2%)	20 (95.2%)	84 (61.3%)
(4) SEVERE	0	1 (4.8%)	1 (0.7%)
Investigator's Static Global Assessment			
Mean	2.6	3.0	2.6
Std Dev	0.50	0.22	0.50
Median	3.0	3.0	3.0
Range(min,max)	(2, 3)	(3, 4)	(2, 4)
Total Patient-Oriented Eczema Measure Score			
Mean	13.9	19.7	14.8
Std Dev	5.86	5.18	6.12
Median	14.0	20.0	15.0
Range(min,max)	(1, 24)	(9, 27)	(1, 27)
Total Eczema Area and Severity Index (EASI) Score			
Mean	10.39	19.79	11.83
Std Dev	8.155	4.420	8.406
Median	7.80	19.50	8.90
Range(min,max)	(1.6, 38.8)	(12.5, 29.2)	(1.6, 38.8)
Treatable Percent Body Surface Area (%BSA)			
Mean	23.53	53.52	28.12
Std Dev	20.134	12.612	21.996
Median	15.50	56.00	19.00
Range(min,max)	(5.0, 94.0)	(35.0, 79.0)	(5.0, 94.0)

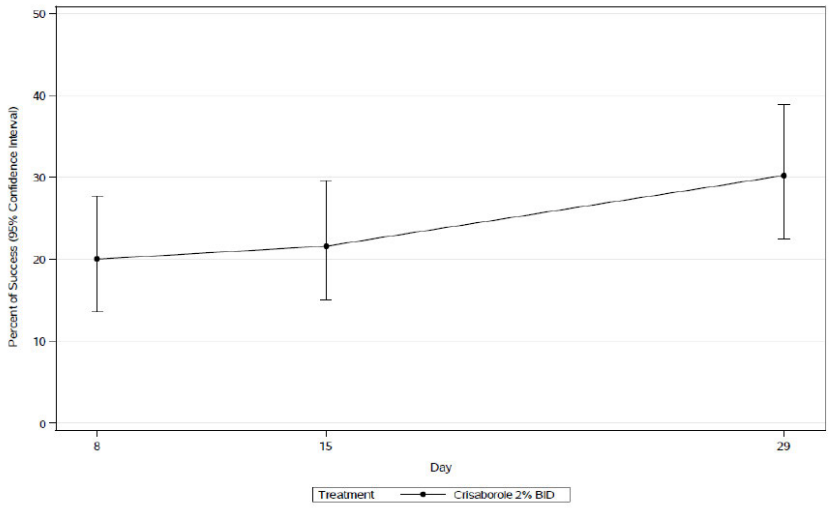
BMI = Body Mass Index.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:34) Source Data: Table 16.2.4.1 Date of Generation: 15MAY2019 (02:03)
Table 14.1.2 is for Pfizer internal use.

Efficacy results

All efficacy endpoints were considered exploratory endpoints in this study.

Investigator's Static Global Assessment (ISGA): Success (defined as a score of clear or almost clear with a 2-grade improvement from baseline) based on ISGA was achieved in 20.0% (95% CI: 13.6; 27.7) of participants at Day 8 and increased to 30.2% (95% CI: 22.5; 38.9) at Day 29. ISGA response of clear or almost clear was achieved by 40.7% (95% CI: 32.4; 49.5) of participants at Day 8 and increased to 47.3% (95% CI: 38.4; 56.3) of participants at Day 29.

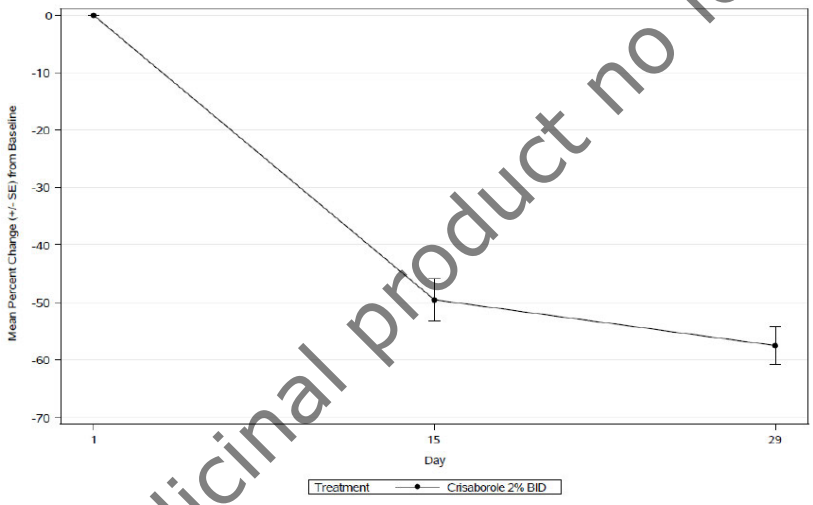
Figure 1. Success in Investigator's Static Global Assessment (ISGA)



Source: Table 14.2.1.1
The FAS included any participant who received ≥1 dose of investigational product.
Bars denote 95% CI.

Eczema Area and Severity Index (EASI): EASI scores improved by a mean (SD) of 49.56% (42.16) at Day 15 and by 57.53% (37.33) at Day 29 compared with baseline.

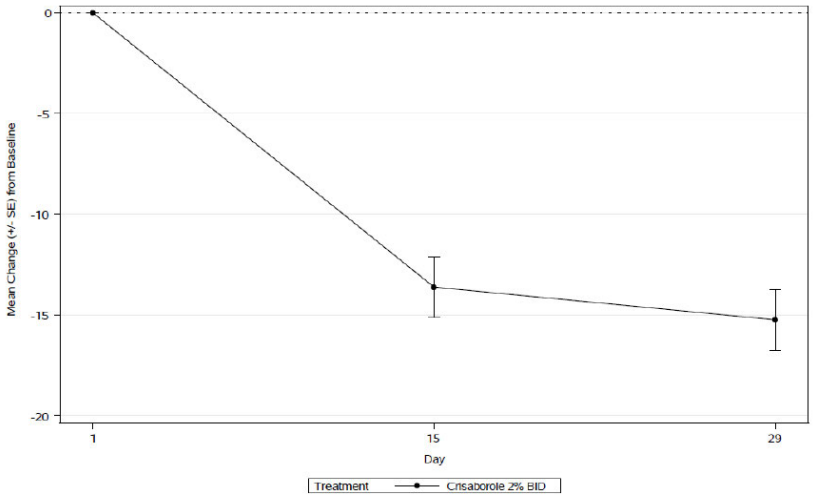
Figure 2. Total Eczema Area and Severity Index (EASI) Score Mean Percent Change (±SE) from Baseline



Source: Table 14.2.2.1
The FAS included any participant who received ≥1 dose of investigational product.
Bars denote standard error.
Day 1 represented Baseline.

Change from Baseline in Treatable %BSA: Mean treatable %BSA decreased by a mean (SD) of 13.61 (17.52) at Day 15 and by 15.24 (17.20) at Day 29 compared with baseline.

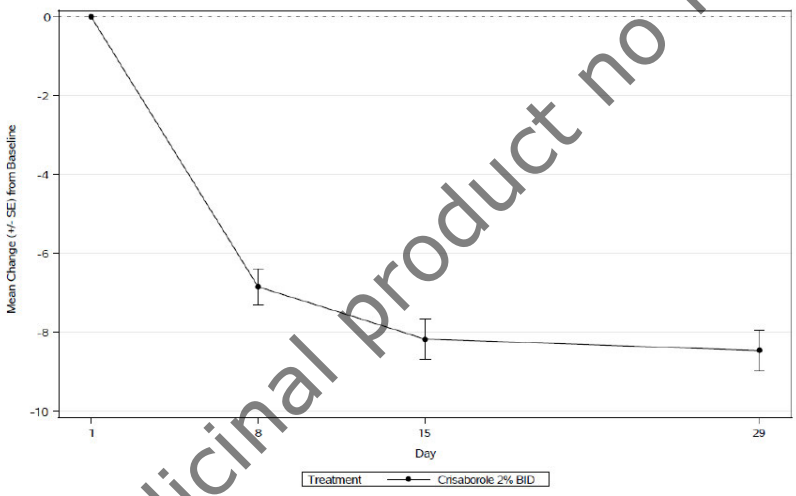
Figure 3. Treatable Percent Body Surface Area (%BSA) Mean Change (±SE) from Baseline



Source: Table 14.2.3.1
The FAS included any participant who received ≥1 dose of investigational product.
Bars denote standard error.
Day 1 represented Baseline.

Patient-Oriented Eczema Measure (POEM): Total mean POEM scores improved (decreased) by a mean (SD) of 6.9 (5.34) at Day 8 and by 8.5 (5.83) at Day 29 compared with baseline. All domains assessed in POEM had mean scores that improved from baseline, including domains related to pruritus and sleep.

Figure 4. Total Patient-Oriented Eczema Measure (POEM) Score Mean Change (±SE) from Baseline



Source: Table 14.2.4.1
The FAS included any participant who received ≥1 dose of investigational product.
Bars denote standard error.
Day 1 represented Baseline.

Pharmacokinetic results

All pharmacokinetic endpoints were considered exploratory endpoints in this study.

Plasma Crisaborole

Systemic exposure (area under the plasma concentration time curve from time zero to time tau [AUC_{tau}] and maximum observed plasma concentration [C_{max}]) was variable. Estimates of the 2-

sided 80% confidence interval (CI; equivalent to 1-sided 90% CI) of the log- transformed AUC_{tau} and C_{max} were calculated using the t-distribution for crisaborole (see below; AN7602 and AN8323 = main metabolites)

Table 14.4.4.2.1
Crisaborole Protocol C3291002
Descriptive Summary of Plasma Crisaborole PK Parameters

		Crisaborole 2% BID (N=18)
Parameter (Unit)		
AUCtau (h*ng/mL)	n	17
	Geometric Mean	2591
	Arithmetic Mean	25080
	Std Dev	66481
	Std Err	16124
	Min	463
	Q1	767
	Median	1440
	Q3	4650
	Max	236000
Cmax (ng/mL)	n	18
	Geometric Mean	379.3
	Arithmetic Mean	3320
	Std Dev	8749.7
	Std Err	2062.3
	Min	45.0
	Q1	130
	Median	248.5
	Q3	640
	Max	28000
Tmax (h)	n	18
	Arithmetic Mean	4.317
	Std Dev	3.2182
	Std Err	0.75853
	Min	2.68
	Q1	2.83
	Median	2.990
Parameter (Unit)		
Tmax (h)	Q3	3.08
	Max	11.7

N = Total number of subjects in the treatment group in the indicated population.
n = Number of subjects contributing to the summary statistics.
PFIZER CONFIDENTIAL SDTM Creation: 30MAY2019 (22:41) Source Data: Table 16.2.5.5.1 Date of Generation: 30MAY2019 (22:52)

Table 3. Descriptive Summary of Plasma Crisaborole PK Parameters (Cmax <500) – Adhoc Analysis

Parameter (Unit)		Crisaborole 2% BID (N=13*)
AUC_{tau} (h*ng/mL)	n	12
	Geometric Mean	1050
	Arithmetic Mean	1164
	Std Dev	549.59
	Std Err	158.65
	Min	463
	Q1	739
	Median	991.0
	Q3	1570
	Max	2230
C_{max} (ng/mL)	n	13
	Geometric Mean	163.0
	Arithmetic Mean	188.0
	Std Dev	99.589
	Std Err	27.621
	Min	45.0
	Q1	122
	Median	164.0
	Q3	250
	Max	398

N = Total number of subjects in the treatment group in the indicated population.
n = Number of subjects contributing to the summary statistics.
Five subjects are excluded from the analysis by the condition of $C_{max} \geq 500$. These subjects were identified as outliers in the nonlinear regression analysis described in PMAR-EQDD-C329a-DP4-965.
PFIZER CONFIDENTIAL SDTM Creation: 20FEB2020 (21:06) Source Data: Table 16.2.5.5.1 Date of Generation: 20FEB2020 (21:07)

Table 14.4.4.2.4
Crisaborole Protocol C3291002
Statistical Summary of Main Oxidative Metabolite AN7602 PK Parameters

	Crisaborole 2% BID	
Parameter (Unit)	Geometric Mean	80% CI for Geometric Mean
AUCtau (h*ng/mL)	401.3	(296.0, 543.9)
Cmax (ng/mL)	55.77	(42.12, 73.83)

Table 14.4.4.2.6
Crisaborole Protocol C3291002
Statistical Summary of Main Oxidative Metabolite AN8323 PK Parameters

	Crisaborole 2% BID	
Parameter (Unit)	**Geometric Mean**	**80% CI for Geometric Mean**
AUCtau (h*ng/mL)	61290	(47610, 78910)
Cmax (ng/mL)	6559	(5054, 8513)

Propylene Glycol

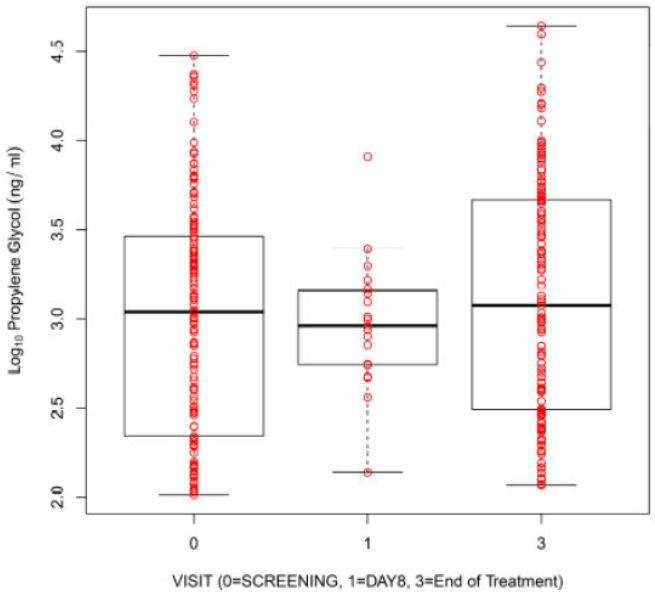
No consistent trend was observed to suggest that Eucrisa contributes to systemic concentrations of propylene glycol (PG) over those observed at screening (see table and figure below).

Table 14.4.4.1.3
Crisaborole Protocol C3291002
Summary of Propylene Glycol Concentration

	Crisaborole 2% BID									
Analysis Visit	**N**	**NALQ**	**Mean**	**Std Dev**	**SE**	**Min**	**Q1**	**Median**	**Q3**	**Max**
BASELINE	135	127	2838.84	5099.611	438.905	0	215.00	1020.00	2890.00	30000
DAY 8	19	19	1380.26	1737.101	398.518	138	553.00	916.00	1470.00	8130
END_OF_TREATMENT	119	117	3906.54	6828.207	625.941	0	311.00	1190.00	4720.00	44000

The unit of Propylene Glycol Concentration is ng/mL.
N = Number of observations (non-missing concentrations).
NALQ = Number of observations Above Lower limit of Quantification.
Unplanned post baseline visits are excluded.
Baseline is defined as the last evaluation taken before the time of the first dose of investigational product.
The lower limit of quantification is 100 ng/mL.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:37) Source Data: Table 16.2.5.4.1 Date of Generation: 21MAY2019 (23:02)

Figure 1. Propylene Glycol Systemic Concentrations by Visit



To assess if crisaborole ointment contributes to the existing propylene glycol levels detected at Screening, the difference of concentrations to the screening levels was correlated to %treated BSA for Day 8 and end of treatment visit. A likelihood ratio test conducted by comparing an intercept only model to a slope-intercept linear model utilizing %treated BSA as the independent variable identified no relationship between the changes in PG concentrations and %treated BSA on Day 8 (p-value = 0.8627) or end of treatment (p-value = 0.9565) visit.

Safety results

The primary objective of the study was to study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild-to-moderate AD. The primary endpoint is the incidence of treatment-emergent adverse events (AEs) (including application site reactions), serious AEs (SAEs), and clinically significant changes in height, weight, vital signs, electrocardiogram (ECG), and clinical laboratory parameters.

Overall, most participants (92.0%) were compliant with study treatment which was defined as 80–120%, inclusive, of the expected number of doses for each cohort.

In the safety analysis set (n= 137) mean (SD) duration of treatment was 27.2 (4.8) days, mean (SD) total number of applications was 52.9 (10.4).

Study treatment exposure and compliance were similar between the PK and non-PK cohort (more details see tables below).

Table 14.4.1.1
Crisaborole Protocol C3291002
Study Treatment Exposure and Compliance - Overall Safety Analysis Set

	Crisaborole 2% BID (N=137)
Duration of Treatment (days)[1]	
n	137
Mean	27.2
Std Dev	4.8
Median	28.00
Range(min,max)	(2,37)
Total Number of Applications	
n	137
Mean	52.9
Std Dev	10.4
Median	56.00
Range(min,max)	(4,74)
Total Number of Days of Dosing	
n	137
Mean	27.2
Std Dev	4.8
Median	28.00
Range(min,max)	(2,37)
Number and Percentage of Compliance	
No	11 (8.0)
Yes	126 (92.0)

Table 14.4.1.2
Crisaborole Protocol C3291002
Study Treatment Exposure and Compliance - PK Set

	Crisaborole 2% BID (N=21)		
	Day 1- Day 8 AM (N=21)	Post Day 8 AM (N=19)	Overall (N=21)
Duration of Treatment (day)[1]			
n	21	19	21
Mean	8.0	21.4	26.4
Std Dev	0.3	1.8	6.5
Median	8.00	21.00	28.00
Range(min,max)	(7,9)	(18,25)	(7,32)
Total Number of Applications			
n	21	19	21
Mean	15.0	40.4	51.6
Std Dev	0.6	4.2	13.2
Median	15.00	41.00	56.00
Range(min,max)	(13,17)	(29,49)	(13,64)
Total Number of Days of Dosing			
n	21	19	21
Mean	8.0	21.4	26.4
Std Dev	0.3	1.8	6.5
Median	8.00	21.00	28.00
Range(min,max)	(7,9)	(18,25)	(7,32)
Number and Percentage of Compliance			
No	0	2 (10.5)	3 (14.3)
Yes	21 (100.0)	17 (89.5)	18 (85.7)

Table 14.4.1.3
Crisaborole Protocol C3291002
Study Treatment Exposure and Compliance - Non-PK Set

	Crisaborole 2% BID (N=116)
Duration of Treatment (days)[1]	
n	116
Mean	27.3
Std Dev	4.5
Median	28.00
Range(min,max)	(2,37)
Total Number of Applications	
n	116
Mean	53.2
Std Dev	9.9
Median	56.00
Range(min,max)	(4,74)
Total Number of Days of Dosing	
n	116
Mean	27.3
Std Dev	4.5
Median	28.00
Range(min,max)	(2,37)
Number and Percentage of Compliance	
No	8 (6.9)
Yes	108 (93.1)

End of Treatment Visits are excluded.
[1] The total number of days from first to and including last day of study treatment
Compliance is defined as per SAP section 6.4.3.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:24) Source Data: Table 16.2.5.1.3 Date of Generation: 15MAY2019 (01:37)

Brief Summary of Adverse Events

A total of 192 all-causality TEAEs overall were reported in 88/137 (64.2%) participants and approximately half of those participants had TEAEs that occurred in a treatment area (see tables below). There were 3 participants with dose reductions or temporary discontinuations due to an AE but no permanent discontinuations from the study.

Table 9. Treatment-Emergent Adverse Events (All Causalities) - Overall

Number (%) of Subjects	Crisaborole 2% BID n (%)
Subjects evaluable for adverse events	137
Number of adverse events	192
Subjects with adverse events	88 (64.2)
Subjects with serious adverse events	1 (0.7)
Subjects with severe adverse events	1 (0.7)
Subjects discontinued from study due to adverse events (a)	0
Subjects discontinued study drug due to AE and continue study (b)	4 (2.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	3 (2.2)

Includes all data collected since the first dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:34) Source Data: Table 16.2.7 Date of Generation: 30APR2019 (11:58)
Table 14.3.1.2.1.1 is for Pfizer internal use.

Table 10. Treatment-Emergent Adverse Events (All Causalities) - Treatment Area

Number (%) of Subjects	Crisaborole 2% BID n (%)
Subjects evaluable for adverse events	137
Number of adverse events	59
Subjects with adverse events	43 (31.4)
Subjects with serious adverse events	0
Subjects with severe adverse events	1 (0.7)
Subjects discontinued from study due to adverse events (a)	0
Subjects discontinued study drug due to AE and continue study (b)	3 (2.2)
Subjects with dose reduced or temporary discontinuation due to adverse events	3 (2.2)

Includes all data collected since the first dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:34) Source Data: Table 16.2.7 Date of Generation: 30APR2019 (11:59)
Table 14.3.1.2.1.2 is for Pfizer internal use.

A total of 32 TEAEs overall that were considered treatment-related occurred in 22/137 (16.1%) participants. The majority of these TEAEs (22/32; 68.8%) occurred in treatment areas.

One SAE (febrile seizure) and 1 severe TEAE (atopic dermatitis) were reported in 1 participant each during the study, but the 2 events were determined by the investigator to be not related to study medication.

Incidence of Adverse Events

There were 88/137 (64.2%) participants with all-causality TEAEs (48 mild, 39 moderate and 1 severe). Of these 88 participants, 43 participants had TEAEs that occurred in a treatment area. For these all-causality TEAEs, 22 participants (16.1%) reported TEAEs that were considered treatment-related overall. The most frequently reported all-causality TEAEs (overall and occurring in a treatment area) by MedDRA preferred term (PT) were pyrexia and dermatitis atopic, respectively.

There were 63 participants with all-causality TEAEs reported in at least 4 participants overall, and the majority of TEAEs were mild in severity. For these all-causality TEAEs, 36 participants had TEAEs (36/63) that occurred in a treatment area (see tables below).

Table 11. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) - Overall Occurring in >= 4 Subjects

Number of Subjects Evaluable for AEs	Crisaborole 2% BID (N=137)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	35 (25.5)	27 (19.7)	1 (0.7)	63 (46.0)
Skin And Subcutaneous Tissue Disorders	20 (14.6)	11 (8.0)	1 (0.7)	32 (23.4)
Dermatitis atopic	5 (3.6)	3 (2.2)	1 (0.7)	9 (6.6)
Dermatitis diaper	6 (4.4)	3 (2.2)	0	9 (6.6)
Eczema	3 (2.2)	2 (1.5)	0	5 (3.6)
Dermatitis contact	2 (1.5)	2 (1.5)	0	4 (2.9)
Erythema	4 (2.9)	0	0	4 (2.9)
Rash	3 (2.2)	1 (0.7)	0	4 (2.9)
General Disorders And Administration Site Conditions	15 (10.9)	8 (5.8)	0	23 (16.8)
Pyrexia	10 (7.3)	3 (2.2)	0	13 (9.5)
Application site pain	3 (2.2)	2 (1.5)	0	5 (3.6)
Application site discomfort	3 (2.2)	1 (0.7)	0	4 (2.9)
Application site erythema	1 (0.7)	3 (2.2)	0	4 (2.9)
Infections And Infestations	14 (10.2)	9 (6.6)	0	23 (16.8)
Upper respiratory tract infection	6 (4.4)	4 (2.9)	0	10 (7.3)
Otitis media	1 (0.7)	5 (3.6)	0	6 (4.4)
Conjunctivitis	4 (2.9)	1 (0.7)	0	5 (3.6)
Ear infection	2 (1.5)	2 (1.5)	0	4 (2.9)
Nasopharyngitis	4 (2.9)	0	0	4 (2.9)
Gastrointestinal Disorders	11 (8.0)	3 (2.2)	0	14 (10.2)
Diarrhoea	9 (6.6)	1 (0.7)	0	10 (7.3)
Teething	2 (1.5)	2 (1.5)	0	4 (2.9)
Respiratory, Thoracic And Mediastinal Disorders	8 (5.8)	1 (0.7)	0	9 (6.6)
Cough	6 (4.4)	1 (0.7)	0	7 (5.1)
Rhinorrhoea	4 (2.9)	1 (0.7)	0	5 (3.6)
Total preferred term events	78	37	1	116

(a)If the same subject in a given treatment had more than one occurrence in the same system organ class, high level term or preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced
another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline
severities are imputed as mild. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
Includes all data collected since the first dose of study drug.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:34) Source Data: Table 16.2.7 Date of Generation: 05MAY2019 (22:37)
Table 14.3.1.2.2.3 is for Pfizer internal use.

Table 12. Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) - Treatment Area Occurring in >= 4 Subjects

Number of Subjects Evaluable for AEs	Crisaborole 2% BID (N=137)			
Severity(a)	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	21 (15.3)	14 (10.2)	1 (0.7)	36 (26.3)
General Disorders And Administration Site Conditions	7 (5.1)	5 (3.6)	0	12 (8.8)
Application site discomfort	3 (2.2)	1 (0.7)	0	4 (2.9)
Application site erythema	1 (0.7)	3 (2.2)	0	4 (2.9)
Application site pain	3 (2.2)	2 (1.5)	0	5 (3.6)
Skin And Subcutaneous Tissue Disorders	17 (12.4)	10 (7.3)	1 (0.7)	28 (20.4)
Dermatitis atopic	4 (2.9)	3 (2.2)	1 (0.7)	8 (5.8)
Dermatitis contact	2 (1.5)	2 (1.5)	0	4 (2.9)
Dermatitis diaper	2 (1.5)	2 (1.5)	0	4 (2.9)
Eczema	3 (2.2)	2 (1.5)	0	5 (3.6)
Erythema	4 (2.9)	0	0	4 (2.9)
Rash	3 (2.2)	1 (0.7)	0	4 (2.9)
Total preferred term events	25	16	1	42

(a)If the same subject in a given treatment had more than one occurrence in the same system organ class, high level term or preferred term event category, only the most severe occurrence is counted.
Subjects are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the subject experienced
another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline
severities are imputed as mild. Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
Includes all data collected since the first dose of study drug.
MedDRA v21.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 30APR2019 (00:34) Source Data: Table 16.2.7 Date of Generation: 05MAY2019 (23:22)
Table 14.3.1.2.2.4 is for Pfizer internal use.

Of the all-causality TEAEs reported in at least 4 participants overall, 12 participants (8.8%) reported TEAEs that were considered treatment-related and it did not include the 1 severe TEAE reported. However, of the all causality TEAEs reported in at least 4 participants that occurred in a treatment area, more than half of participants had events (21/36) that were considered treatment related. The most frequently reported treatment related TEAEs (overall and occurring in a treatment area) were application site pain (5/12), application site discomfort (4/12), and erythema (4/12).

Analysis of Adverse Events

The most frequently reported all-causality TEAEs overall were pyrexia, upper respiratory tract infection, and diarrhea (see above):

- Thirteen participants (9.5%) had pyrexia; none were determined by the investigator to be related to study medication, and 11 of 13 events resolved within 1 to 3 days.

- Ten participants (7.3%) had upper respiratory tract infection; only 1 was determined by the investigator to be related to study medication, and 7 of 10 events resolved between 3 to 12 days.
- Ten participants (7.3%) had diarrhea; none were determined by the investigator to be related to study medication, and 8 of 10 events resolved between 1 to 4 days. Eight of those participants were >12 months of age, which is the age when new foods are being introduced. All but 1 event was mild in severity; the single event of diarrhea that was moderate in severity occurred during the Follow-Up Phase.

TEAEs occurring in a treatment area were commonly considered treatment related. This included application site pain, application site discomfort, and erythema, with the majority of AEs reported as mild in severity. All events resolved by the end of the study.

Body location affected by AEs was collected. The locations that were reported to be affected most frequently were face (17 participants), leg and back (8 participants each, and abdominal skin and arm (7 participants each).

A total of 14 participants experienced TEAEs that reflected symptoms of AD (PT: dermatitis atopic or eczema) during the study. Of these 14 participants, 8 participants had TEAE onset that occurred on or before Day 29, and the remaining 6 participants had TEAE onset that began after Day 29 (after crisaborole treatment). For 11 of these 14 participants, the event had resolved by the end of the study.

One participant had a TEAE of vomiting that was mild in severity, was determined by the investigator to be not related to study medication and resolved the following day.

One participant had an AE of weight decreased that occurred during the Follow-Up (post-treatment cessation) Phase.

TEAEs potentially attributable to systemic PDE-4 inhibition (diarrhea, vomiting, and weight decreased) were reported, but none were determined by the investigator to be related to study medication. No other TEAEs potentially associated with systemic PDE-4 inhibition (e.g. insomnia, nausea, serious infections, malignancy), or typical of TCS use (e.g. skin atrophy, striae formation, telangiectasia, pigmentation changes) were observed in this study.

Permanent Discontinuations from the Study Due to Adverse Events

There were no permanent discontinuations from the study due to AEs, all participants discontinued during the Treatment Phase, entered the Follow-Up Phase, and completed the study.

Dose Reductions, Temporary and Permanent Discontinuations from Study Drug Due to Adverse Events

One participant had an AE of application site erythema that led to a dose reduction, and it was determined by the investigator to be related to study medication.

Two participants had AEs leading to temporary discontinuation of study drug:

- One participant had an AE of exacerbation of dermatitis atopic and was determined by the investigator to be not related to study medication.

- One participant had 3 AEs of application site reaction (face, bilateral arm, and back) and 1 AE of dermatitis contact that were all determined by the investigator to be related to study medication.

All AEs leading to dose reduction or temporary discontinuation were of moderate severity and resolved by the end of the study.

Four other participants permanently discontinued from study drug during the Treatment Phase due to an AE (all of moderate severity) and continued to enter the Follow-Up Phase and completed the study: One participant had an SAE of febrile convulsion (PK cohort) and 1 participant had an AE of dermatitis infected (non-PK cohort), both of which were determined by the investigator to be not related to study medication. One participant had an AE of application site pain and 1 participant had an AE of application site discomfort (both participants were in the non-PK cohort). Both of these AEs were determined by the investigator to be related to study medication. All AEs leading to discontinuation from study drug resolved by the end of the study.

Other Serious Adverse Events

One participant experienced an SAE of febrile convulsion and was permanently withdrawn from study drug. The participant proceeded to complete the Follow-Up Phase. This SAE resolved on the same day and was determined by the investigator to be not related to study medication.

Other Significant Adverse Events

One participant had an AE of "defect conduction intraventricular" of mild severity and was referred to a cardiologist for evaluation. The participant had ECGs (Screening and Day 8) showing sinus tachycardia without conduction delay. ECG on Day 27 (end of treatment visit) showed sinus tachycardia and intraventricular conduction defect (IVCD). IVCD (verbatim term) was reported as an AE of mild severity. The event resolved on Day 37. Elevated anion gap was present prior to study drug dosing (Day -16) and on Day 27; 27 mEq/L and 25 mEq/L (reference range 7-18 mEq/L), respectively. Lactic acid was within normal range prior to study drug dosing (Day -16) but elevated on Day 27; 11 mg/dL and 21 mg/dL (reference range 4-20 mg/dL), respectively. PG was 3220 ng/mL (Day -16) and increased to 5130 ng/mL (Day 27), however, osmolality gap was not elevated at Day -16 (-15 mOsm/kg) or Day 27 (-5 mOsm/kg). Transient intraventricular conduction defect was accompanied by increased lactic acid level and but was not accompanied by an osmolar gap.

One participant had an anaphylactic reaction during the Follow-Up (post-treatment cessation) Phase which was attributed to a food allergy and was determined by the investigator to be not related to study medication.

Deaths

There were no deaths in the study.

Clinical Laboratory Results

Clinical laboratory evaluations included hematology (hemoglobin, hematocrit, red blood cell count, platelet count, WBC count and differential) and chemistry (blood urea nitrogen, glucose (non-fasting), creatinine, sodium, potassium, chloride, bicarbonate, alanine aminotransferase, aspartate

aminotransferase, total bilirubin, alkaline, phosphatase, albumin, total protein, lactate, calculation of osmolal gap, calculation of anion gap).

Two participants between age 6 and 8 months had baseline serum creatinine 0.3 mg/dL and at the end of the study (Day 28 and Day 29, respectively), serum creatinine was 0.4 mg/dL (range 0.1-0.3 mg/dL). No confirmations of the out-of-range values were obtained. At baseline, blood urea nitrogen was 9 mg/dL and 10.1 mg/dL, respectively, and 11 mg/dL and 14 mg/dL at the end of the study (Day 28 and Day 29, respectively). No serum sodium or potassium abnormalities were associated, and no AEs were reported in either participant.

Eight (8) crisaborole-treated participants had an osmolality gap of +10 or greater. Blood concentrations of PG and lactic acid levels are summarized below for the 8 participants.

- Five (5) of those had increase in osmolality gap after baseline; two (2) had increase in propylene glycol concentration after baseline. Peak PG concentrations were below the mean value at baseline and EOS. Only 1 participant had an elevated lactic acid level at end of study.
- Three (3) had elevated baseline osmolality gap that returned to normal at end of study (EOS); two (2) had increase in PG concentration after baseline. Peak PG concentrations were below the mean value at baseline and EOS. Only 1 participant had an elevated lactic acid level at end of study.

According to the MAH no clinically meaningful patterns or trends were observed in abnormalities of hematology or blood chemistry.

Height and Weight

Increases in body length/height and weight were observed in keeping with normal growth and development. None of these changes were clinically meaningful.

One participant had an AE of weight decreased of approximately 5.59% that occurred during the Follow-Up (post-treatment cessation) Phase compared with end of treatment on Day 27. The AE was attributed by the investigator as being due to inadequate caloric intake and was not related to study medication.

Vital Signs

Some participants had vital signs values with ⩾20 mm Hg or ⩾30 mm Hg increase or decrease from baseline in diastolic and systolic blood pressure, respectively, but these changes were not reported as AEs. None of these changes were clinically meaningful.

Electrocardiograms

Electrocardiographic QT interval corrected using Fridericia's formula (QTcF) intervals were summarized based upon Pfizer data standards for ECG parameters. QTcF AEs pose particular challenges in pediatric clinical trials because normal ECG values are based on relatively small studies in children. Per FDA guidance, the relevance of prolonged QTcF to clinical outcomes is not clearly

understood in children. Normative data accurately characterizing the influence of age in an actively developing pediatric population are absent.

Despite extensive resources having been committed to this effort (ie, the Cardiac Safety Research Consortium), setting a consensus definition of 'abnormal' as a safety signal in a pediatric trial is difficult. Therefore, the definition of "normal" for QTcF analysis purposes in reliant upon consensus for adult populations.

Of the 135 pediatric participants, using ECG criteria established for adults, identified 10 (7.4%) participants with prolongation of the QTcF interval >30 msec compared with baseline. No participant had a QTcF >500 msec. Only 1 of the 10 participants had a reported increase in QTcF >60 msec (68 msec) from baseline. Board-certified cardiologist review (overread) was initiated after completion of the study to further review findings from pediatric ECG data.

Of the 10 participants with ECG readings with prolonged QTcF post-baseline >30 msec, 5 participants had a decrease in PG blood concentrations over baseline and 2 had only a baseline value. Three participants had an increase in PG concentration post-baseline and elevated anion gap and/or lactic acid level:

- One participant had PG concentrations of 2,340 ng/mL and 3,650 ng/mL (no reference range), non-elevated osmolality gap (-4 Osm/kg and -5 Osm/kg), elevated anion gap of 21 mEq/L and 23 mEq/L (reference range 7-18 mEq/L) on Day -16, and lactic acid levels 23 mg/dL (reference range 4-20 mg/dL) and 12 mg/dL, on Day 29, respectively. Board-certified cardiology overread of this participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present.
- One participant had PG concentrations of 215 ng/mL and 1,020 ng/mL (no reference range), non-elevated osmolality gap 3 Osm/kg (Day -13; no Day 31 result), elevated anion gap of 29 mEq/L (Day -13; no Day 31 result) (reference range 7-18 mEq/L), and lactic acid levels 23 mg/dL and 12 mg/dL (reference range 4-20 mg/dL) on Day -13 and Day 31, respectively. Board-certified cardiology overread of this participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present.
- One participant had PG concentrations 133 ng/mL and 27,500 ng/mL (no reference range), non-elevated osmolality gap -7 Osm/kg and -10 Osm/kg, elevated anion gap of 21 mEq/L and 24 mEq/L (reference range 7-18 mEq/L), and normal lactic acid level (15 mg/dL and 19 mg/dL [reference range 4-20-mg/dL]) on Day -7 and Day 29, respectively. Board-certified cardiology review (overread) documented the presence of movement artifact and tachycardia (HR 182 bpm) impairing measurement of baseline and follow-up QT intervals. Board-certified cardiology overread of this participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present.
- One participant had prolonged QTcF Global at baseline (prior to dosing with study drug) and had PG concentrations 8670 ng/mL and 12,900 ng/mL, non-elevated osmolality gap (-3 Osm/kg and 1 Osm/kg), elevated anion gap of 22 mEq/L and 22 mEq/L (reference range 7-18 mEq/L), and lactic acid levels 14 mg/dL and 16 mg/dL (reference range 4-20 mg/dL), on Day -8 and Day 31, respectively. Board-certified cardiology overread of the participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present post-baseline.
- One participant had PG concentration 3520 ng/mL (Day -7), anion gap of 29 mEq/L (reference range 7-18 mEq/L), and lactic acid level of 30 mg/dL (reference range: 4-20 mg/dL) on Day -7. No post-baseline laboratory values were obtained. Board-certified

cardiology overread of the participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present post-baseline.

In light of movement artifact on multiple ECGs and the absence of consensus pediatric ECG interval criteria, no clinically meaningful changes in QTcF were confirmed in any of the 135 participants according to the MAH.

Physical Examinations

Few participants had abnormal physical examination findings in non-skin body systems. The most common findings were observed in skin (in 20/136 [14.7 %] patients at the end of treatment), consistent with the participant population in this study. No clinically meaningful findings were observed.

2.3.3. Discussion on clinical aspects

The MAH submitted the final clinical study report of the crisaborole ointment 2% Study C3291002 performed in paediatric patients 3 months - < 2 years of age with atopic dermatitis (AD). This Phase IV, multicenter, open label study was conducted to fulfil a postmarketing requirement in the US. This submission is done to meet the requirement of Art. 46 to submit paediatric data within 6 months from end of study. This is the first completed study with Crisaborole in patients < 2 years of age. The study was not part of the key binding elements of the EMA PIP (EMEA-002065-PIP01) in Europe. No changes to the product information (SmPC or PIL) are proposed within this procedure based on results from study C3291002.

This study was conducted with a Crisaborole formulation containing 0.1% Butylhydroxytoluene, BHT (approved in US, Canada, Israel, and Australia, but not EU). The formulation approved in the EU (trade name Staquis) does not contain BHT. The formulation without BHT will be used in the EU paediatric studies (PIP Measure 7; C3291031) which might enable comparison between the BHT- and the non-BHT formulation in the future.

Study design and methods

In the study under revision study C3291002, safety, efficacy and pharmacokinetics of Crisaborole ointment 2% (EUCRISA) were investigated over a 28 day treatment cycle. The target population was paediatric patients (3 months - < 2 years) with mild to moderate AD, which is in line with the currently approved indication in EU and US. Patients with at least 5% treatable BSA (body surface area) in the non-PK cohort or at least 35% treatable BSA in the PK cohort were to be included in the trial.

Inclusion/exclusion criteria were, except for age, comparable with other studies submitted for the MAA of Staquis in Europe which is a good prerequisite for comparison of data and study results are considered of interest also for a future European target population < 2 year of age.

The primary study endpoint was safety and was described as the incidence of treatment-emergent adverse events (including application site reactions), serious AEs (SAEs), and clinically significant changes in height, weight, vital signs, electrocardiogram (ECG), and clinical laboratory parameters, which seems usual for such a study.

Efficacy and pharmacokinetic endpoints were 'exploratory' and were evaluated as changes in AD lesions (changes in %BSA, ISGA, EASI and POEM scores) as well as plasma PK parameters (Cmax, Tmax, AUC_{0-12}, all at day 8 to describe PK in a steady state situation). Propylene glycol (PG)

concentrations were also measured. The amount of PG in the formulation was considered rather high during the initial MA in Europe and the respective analysis is therefore of interest. The choice of efficacy endpoints seems sensible as the relevant parameters are covered and well-established scores are used. The PK sampling is considered rather sparse in terms of time points evaluated (prior to dose, after 3 and after 12 hours at day 8) but seems sufficient to cover the expected minimum trough and maximum exposure levels as well as AUC at steady state.

Patients were instructed to use Crisaborole ointment 2% twice daily by applying a thin layer, or predefined amount (PK-subset only) to the affected body area over one treatment course of 28 days (Treatment-Phase) and were followed-up (Post-Treatment Follow-Up period) until day 57 (End of Study). AD is a chronic condition and patients are likely treated for longer periods of time/more than one 4-week course in clinical practice, therefore the study is not appropriate to assess delayed adverse effects or effects associated with chronic use.

Results

No formal statistical testing was applied and results were presented descriptively with no alpha control. Missing values were not imputed for safety, efficacy and PK endpoints, which could be considered a shortcoming of this trial. However, there were not many drop-outs or missing data problems and there was no considerable loss to follow-up, therefore no relevant impact on observed results is expected.

The study included a total of 137 patients (Full & Safety Analysis Set), the majority of which were male (64.2%), white (61.3%) and between 9 to < 24 months of age (68.6%). An imbalance towards male subjects was found also in the phase III trials in older patients during the Staquis MAA and, despite contradicting literature on the matter which describe an imbalance towards female patients in children for AD (1.3 to 1) (Kang et al. 2003), this does not seem of high relevance for the assessment of the data. The PK-subset consisted of 21 subjects with moderate AD with a mean of 53.5 % (min/max: 35.0%/79.0%) treatable BSA at baseline. Two analyses based on only 13/21 subjects (5 excluded due to sampling site issue or 18/21 subjects (including 5 with sampling issues) were provided. The sample is considered sufficiently large to allow for a solid description/assessment of steady state PK in the target patients and the cohort represents a 'worst case scenario' with sufficiently high exposure (In the EU Staquis is indicated for patients with a maximum of 40% BSA affected).

Over the 28-day treatment duration most participants (92.0%) were compliant with study treatment (defined as 80 to 120%, inclusive, of the expected number of doses for each cohort). Of the 137 patients enrolled, 128 (93.4%) completed the treatment phase and 132 (96.4%) completed the follow-up phase, indicating good compliance with treatment recommendations and also indicating acceptable tolerability of study drug.

It is noted that the overall study design is uncontrolled and open-label, which afflicts conclusions on results with some uncertainty.

Safety:

192 mostly mild and moderate TEAEs were recorded in 88 out of the 137 participants (64.2%). Approximately half of those participants had TEAEs that occurred in a treatment area.

Approximately 16% of participants had treatment-emergent adverse events (TEAEs) that were considered treatment-related. The most frequently reported treatment-related TEAEs (overall and occurring in a treatment area) were application site pain, application site discomfort, and erythema. This is in line with what has been observed in older patients and application site reactions are reflected in the product information as common side effect.

One serious TEAE (febrile seizure) and 1 severe TEAE (atopic dermatitis) were reported in 1 participant each during the study, but the 2 events were determined by the investigator to be not related to study medication. No deaths occurred.

Diarrhea was reported in 10/137 (7.3%) subjects (9 mild, 1 moderate) and vomiting in a single subject (0.7%). Out of the 10 patients with diarrhea, 8 events resolved between 1-4 days and 8 patients were > 1 year old. The single event of diarrhea that was moderate in severity occurred during the Follow-Up Phase. No details on whether these events were related to % BSA affected at baseline are provided, yet there was no trend indicating increased gastrointestinal AE incidence with higher application rates. All events were determined by the investigator as unrelated to treatment. Upper respiratory tract infections were reported in 10/137 participants (7.3%), 1 was determined by the investigator to be related to study medication. No details on why this one case was considered related are given and therefore the issue cannot be further investigated. It is acknowledged that both gastrointestinal and respiratory complaints are common in children and often symptoms of childhood disease. However, gastrointestinal disorders and respiratory infections are also known off-target effects of systemic PDE-4 inhibitors. In the two main clinical phase III studies for Staquis, reported frequencies in patients aged 2-4 years old for both diarrhea and vomiting were 2.1% in the treatment and 0.0% in the vehicle group (occurring through day 29). Upper respiratory tract infection in this age group were reported in 3.1% of the treatment and 6.0% of the vehicle arm. The rates of these events of interest are thus slightly higher in the population < 2 years of age compared to the Staquis dataset. The subset of 2-4 years olds was small in these studies and higher event rates were recorded in older subjects. As study C3291002 has no control group, no proper comparative assessment regarding the occurrence of GI disorders or upper respiratory tract infections can be made. While there are no strong indices for Crisaborole playing a role in childhood upper respiratory tract infections or GI disorders, this should be further monitored and will be a subject of importance for potential label claims in the future. To better understand whether there could be a relation to exposure, the MAH provided data on Crisaborole exposure (Cmax only, AUC not provided) for patients with AEs, also falling within the scope of potential PDE4 off target effects, from study C3291002. No potential relation to treatment became apparent based on Cmax.

Safety results from the two main clinical phase 3 studies supporting the Staquis MA indicated a higher rate of AEs with higher doses of Crisaborole and higher % BSA affected (higher exposure). As no subgroup analysis had initially been provided for the C3291002 dataset, the MAH had been asked to provide additional analyses to determine whether quality, quantity and severity of AEs were correlated with % BSA affected at baseline or crisaborole dose, PG exposure and patient age (below and above 1 years of age). The updated analyses overall do not support a strong link between quality, quantity or severity of AEs with the covariates of interest. It appears that there was a tendency of treatment-related AEs occurring with higher frequency in the >40% BSA affected at baseline subgroup compared to the groups with smaller %BSA. It is noted that the European target population is restricted to patients with ≤40% BSA.

The MAH reported that most TEAEs resolved within short periods of time and clarified that amongst 5 TEAEs ongoing at the end of study 4 were AD/eczema and 1 was URTI (in a patient not eligible for Staquis in the EU due to high %BSA affected who was lost to follow-up).

Propylene glycol is associated with cardiac and neurological disorders at high doses and young children are considered especially vulnerable. Also, other adverse events/laboratory anomalies have been described in association with prolonged and/or high exposure (e.g. hyperosmolality, renal dysfunction, CNS disorders, respiratory disorders, etc.). PG normally does not penetrate intact skin and the degree of penetration through injured skin might depend on the extent of skin damage. Considering that patients with higher % BSA affected at baseline than those eligible for Staquis

treatment in the EU (≤ 40% BSA; see above) are included in this study, the results should allow for a conservative estimation of PG exposure over a one month treatment period also in (future) paediatric EU patients. Median (min;max) PG concentrations in this study were reported as 1020 ng/mL (0; 30000) in N=135 at screening and as 1190 ng/mL (0; 44000) in N= 119 at the end of treatment. An additional measuring time point at day 8 in N=19 patients (PK subset) resulted in a median of 916 ng/mL (138; 8130), thus in lower concentrations compared to the other measuring time points, although the PK cohort had considerably higher %BSA affected compared to the rest of the study population and consequently higher PG exposure would have been expected. However, based on the median/mean values, no proper assessment of exposure changes over time can be made. The change to baseline in the individual patient would be necessary to give further insight. However, as none of the PG results indicate that crisaborole elevates systemic PG concentrations above the currently accepted threshold of 50 mg/kg/day for children ≥ 1 month to < 5 years (EMA/CHMP/704195/2013) no respective questions are asked. 28 days of treatment might be too short to reflect accumulation of PG in the system. No clear correlation of PG exposure with increase in osmolality gap was observed, although two patients who had an increase in osmolality gap also had an increase in PG concentration after treatment with crisaborole.

Prolongation of the QTcF interval >30 msec compared with baseline was reported in 10/135 (7.4%) patients (using ECG criteria established for adults), no participant had a QTcF >500 msec. Diastolic pressure increase ≥20 mm Hg in 8/135 (5.9%), diastolic pressure decrease ≥20 mm Hg in 18/135 (13.3%), systolic pressure increase ≥30 mm Hg in 3/136 (2.2%) systolic pressure decrease ≥30 mm Hg in 4/136 (2.9%) subjects was reported. The relevance of these findings is currently unknown as obviously the quality of multiple ECGs was not adequate and also because there seems to be no consensus on pediatric ECG interval criteria. Questions were asked to further look into these ECG findings and the MAH clarified that 2/10 events of prolonged QTcF intervals and changes in blood pressure occurred in the same subjects. However, no clear pattern of QTcF prolongation with concomitant change in blood pressure became evident and these cardiac findings were not seen in the very young patients (< 6 months of age) or in patients with high % BSA (> 40%) affected. PG levels were not associated. Yet, it is noted that QTcF abnormalities were not reported in adult patients receiving crisaborole ointment 2% during the main clinical studies. Moreover, QTcF monitoring in the study under assessment would not be considered as "thorough QT/QTc study" according to ICH E14 as several study elements (e.g. control group, positive control) were missing, making meaningful conclusions on QTcF interval prolongation difficult. While it is reassuring that none of the children in this study reported a QTcF interval > 450 msec or increase from baseline >60 msec, it is noted that drugs which prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. The issue should be further monitored post marketing.

One participant had a significant AE of "defect conduction intraventricular" of mild severity and was referred to a cardiologist for evaluation. The participant had ECGs (Screening and Day 8) showing sinus tachycardia without conduction delay. ECG on Day 27 (end of treatment visit) showed sinus tachycardia and intraventricular conduction defect (IVCD). IVCD (verbatim term) was reported as an AE of mild severity. The event resolved on Day 37 and was determined by the investigator to be related to study medication. The MAH explained that this case of "defect conduction intraventricular" occurred in one patient with a very high %BSA affected (98%). While the investigator initially found the AE related to study medications, no further details are available why this assessment was made. Although it seems unlikely that this event was triggered by crisaborole or propylene glycol plasma concentration this cannot be verified or excluded based on the data available of this single observed case. A warning in the SmPC seems not warranted as the relation to treatment is not finally determined and no further data to investigate the connection are available. The issue should, however, be closely monitored by the MAH post-marketing.

A total of 9 participants (6.6%) discontinued treatment during the study. Four participants (2.9%) permanently discontinued treatment due to an AE of moderate severity (febrile seizure, atopic dermatitis, application site pain, application site discomfort). There were 3 participants with dose reductions or temporary discontinuations due to an AE but no permanent discontinuations from the study.

In the EU, Staquis is indicated for treatment of mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected which differs from the US label, where there is no restriction for treatment based on %BSA affected. In the study under revision a substantial proportion of patients included (38/137; 27.7%) had > 40% body surface area (BSA) affected at baseline. Thus, the doses of Eucrisa investigated are likely above those used in the EU with Staquis. Therefore, the results discussed in this procedure somewhat represent a worst-case scenario for the EU setting in terms of safety assessment. This is also enhanced by the fact that EUCRISA contains the potentially irritating excipient BHT while Staquis does not.

Overall, while a relationship between high % BSA affected and increased adverse event incidence/severity in paediatric patients 3-24 months of age cannot be finally excluded based on the data provided, the provided data do not indicate an increased sensitivity to AEs.

Efficacy:

All efficacy endpoints were considered exploratory endpoints in this study and results need to be interpreted with caution considering the limitations of the study design.

Success in Investigator's Static Global Assessment (ISGA)- defined as a score of clear or almost clear with a 2-grade improvement from baseline- was achieved in in 20.0% (95% CI: 13.6; 27.7) of participants at Day 8 and increased to 30.2% (95% CI: 22.5; 38.9) at Day 29. ISGA response of clear or almost clear (without the 2-grade improvement) was achieved by 40.7% (95% CI: 32.4; 49.5) of participants at Day 8 and increased to 47.3% (95% CI: 38.4; 56.3) of participants at Day 29.Eczema Area and Severity Index (EASI) scores decreased by a mean (SD) of 49.56% (42.16) at Day 15 and by 57.53% (37.33) at Day 29 compared with baseline. Mean treatable % BSA decreased by a mean (SD) of 13.61 (17.52) at Day 15 and by 15.24 (17.20) at Day 29 compared with baseline. Total mean Patient-Oriented Eczema Measure (POEM) scores improved (decreased) by a mean (SD) of 6.9 (5.34) at Day 8 and by 8.5 (5.83) at Day 29 compared with baseline. All domains assessed in POEM had mean scores that improved from baseline, including domains related to pruritus and sleep.

Overall, the data support the overall notion of a beneficial effect also in the age cohort of 3-24 months old patients.

Pharmacokinetics:

All pharmacology endpoints were considered exploratory endpoints in this study. Standard PK parameters were evaluated.

Plasma crisaborole mean (SD) values obtained on day 8 (steady state) during three time points (before morning dose, 3 hours ±20 minutes after morning dose; 12 hours ±1 hour after morning dose) in 18 subjects were 3320 ng/mL (8750) for Cmax and 25080 h*ng/mL (66481) for AUC_{0-12}. Earlier findings from a maximal use study in 33 subjects 2 to 17 years of age with a mean ± SD BSA involvement of 49 ± 20% (range 27% to 92%) showed a mean ± SD maximum plasma concentration (Cmax) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for crisaborole on Day 8 of 127 ± 196 ng/mL and 949 ± 1240 ng*h/mL, respectively (Staquis SmPC). While a high variability of exposure was seen in both datasets and a comparison across studies has obviously limitations, it is noted that exposure in the younger age cohort studied in C3291002 is significantly higher compared to the results obtained in the maximal use study. This

is striking as patients with less %BSA affected were included in this trial. This indicates that patients <2 years of age could be more prone to systemic exposure and thus to (adverse) systemic effects compared to older patients. The present study C3291002 is not appropriate to conclude on the (ir)relevance of the observed plasma levels due to the rather small sample size, the open label nature and the uncontrolled design. The safety results observed do not give rise to particular concern, and the impact of (high) crisaborole plasma levels in children below 2 years of age will be evaluated in potential future regulatory interactions concerning extension of the target population, considering all data available at that time. No potential relation of AEs of interest to high levels of crisaborole blood levels became apparent.

The MAH states that the PK cohort consisted of 21 subjects, 5 of which were considered outliers due to sampling deviations (improper preparation of phlebotomy sites) at one site (identified after study database closure). Yet it is unclear, why the PK results were reported from 18 (and not 21) subjects. Additionally, in the clinical overview another PK analysis involving 13 subjects (excluding 5 outliers from a single study site due to sampling issues) of the PK cohort was included (labelled Table 3), which could not be found in the CSR. According to this table, mean (SD) plasma crisaborole values obtained on day 8 at steady state in 13 subjects of the PK cohort for Cmax (ng/mL) and AUC0-12 (h*ng/mL) were 163 (100) and 1164 (550), respectively, more closely resembling the PK profile obtained from older subjects as specified in the SmPC.

3. Rapporteur's overall conclusion and recommendation

Safety data obtained in paediatric patients (3 months to < 2 years of age) with mild to moderate atopic dermatitis in study C3291002 seem to be largely comparable with data generated in older patients ≥ 2 years of age, with most adverse reactions pertaining to application site reactions. PK data indicate that exposure could be higher in this age cohort compared to older subjects, but the relevance of these findings is not known at this point in time. No specific concerns on potential PDE4 off-target effects or other adverse events with crisaborole arise from the submitted small, uncontrolled 4-week OLE study. Efficacy data overall support the notion of a beneficial effect observed in older patients. Cardiac findings (defect conduction intraventricular and QTcF prolongations noted in a subset of paediatric patients) require close monitoring post-marketing. The PAM is considered approvable.

☒ **Fulfilled**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. it is unclear whether quality, quantity and severity of AEs were correlated with % BSA affected at baseline, doses administered or exposure levels. A potential relation of observed AEs and in particular of observed AEs falling within the scope of potential PDE4 off-target effects should be further investigated by the MAH. At the same time, the safety profile of crisaborole in patients with very high plasma levels should be discussed separately and relevant patient characteristics of patients with high exposure (e.g. 4th quartile) should be outlined (age, BSA affected etc…) and compared to the rest of the study sample. In addition, differences in AE patterns related to age (of interest would be below and above 1 year of age) should be outlined and discussed, if applicable.

2. The MAH is asked to provide details on cases of TEAEs (pyrexia, respiratory tract infections, diarrhea; TEAEs reflecting symptoms of AD) that did not resolve within short periods of time and clarify how these cases were followed-up.
3. To further look into cardiac findings, the MAH is asked to clarify whether the events of prolonged QTcF intervals and changes in blood pressure occurred in the same subjects and provide data on relevant baseline and disease characteristics (age, %BSA affected and PG concentrations measured) for respective subjects.
4. The MAH is asked to further discuss the case of "defect conduction intraventricular" occurring in one subject in relation to crisaborole treatment. It should be explained why a relation to treatment was assumed by the physician in the first place and whether an underlying pharmacological rationale is assumed. Relevant patient characteristics (age, %BSA affected, the duration of treatment and total exposure until AE recording, PG levels etc.) should be provided. If a relation to treatment is indeed considered likely by the MAH, the relevance of this finding in relation to the current EU product information should be discussed.
5. Laboratory assessments were not completed in 41/137 (30.0%) patients as samples could not be collected or processed. An explanation for the underlying reasons and a discussion on the estimated impact of missing data on clinical laboratory results should be provided, especially regarding missing data in patients with AEs or in patients that discontinued treatment.

The timetable is a 30 days response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1

It is unclear whether quality, quantity and severity of AEs were correlated with % BSA affected at baseline, doses administered or exposure levels. A potential relation of observed AEs and in particular of observed AEs falling within the scope of potential PDE4 off-target effects should be further investigated by the MAH. At the same time, the safety profile of crisaborole in patients with very high plasma levels should be discussed separately and relevant patient characteristics of patients with high exposure (e.g. 4th quartile) should be outlined (age, BSA affected etc…) and compared to the rest of the study sample. In addition, differences in AE patterns related to age (of interest would be below and above 1 year of age) should be outlined and discussed, if applicable.

Response to Q1:

To evaluate the potential impact of Baseline %BSA affected by atopic dermatitis on rate and type of AEs, the MAH has summarized AEs by Baseline BSA category. The BSA categories are 0.1-<16%, 16-40% and >40%. Across the three categories, between 59% and 68% of subjects reported an AE (Table 1). Three of the 4 subjects who discontinued study drug due to an adverse event had a Baseline BSA over 40%. There was only 1 severe AE reported and that was a subject in the 16-40%BSA category. This AE was considered not related to study treatment. Adverse events that were deemed to be related to treatment by the Investigator were reported by 15.5%, 12.2%, and 21.1% of subjects in the 0.1-<16%, 16-40% and >40 %BSA categories, respectively. In summary, subjects in the two highest %BSA categories were more likely to report an AE compared to the lowest %BSA category and more subjects in the highest category discontinued treatment due to an AE. By definition, subjects with higher %BSA at baseline have more extensive atopic dermatitis and may be more prone to AEs for that reason.

Table 1. Treatment Emergent Adverse Events by Baseline %BSA (All Causalities)

Number (%) of Subjects	Baseline %BSA			
	0.1-<16% n %	16-40% n (%)	>40% n (%)	Total n (%)
Subjects evaluable for adverse events	58	41	38	137
Number of adverse events	76	54	62	192
Subjects with adverse events	34 (58.6)	28 (68.3)	26 (68.4)	88 (64.2)
Subjects with serious adverse events	0	0	1 (2.6)	1 (0.7)
Subjects with severe adverse events	0	1 (2.4)	0	1 (0.7)
Subjects discontinued from study due to adverse events [a]	0	0	0	0
Subjects discontinued study drug due to AE and continue Study [b]	1 (1.7)	0	3 (7.9)	4 (2.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (1.7)	1 (2.4)	1 (2.6)	3 (2.2)

a Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study

b Subjects who have an AE record that indicates that the action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study.

To evaluate the potential impact of dose administered on frequency and type of AEs, the MAH has summarized AEs by study drug dose categories. The categories are based on the amount of study drug applied with each dose and categorized into tertiles. Between 53% and 68% of subjects in each category reported an AE (Table 2). Fewer subjects in the highest dose category reported AEs compared to the two lower dose categories. Adverse events that were deemed to be related to treatment by the Investigator were reported by 13.6%, 25.0% and 11.1% of subjects in the <33%, 33-66% and >66% application rate categories, respectively. In summary, when evaluating AEs by dose (application rate), there was no trend for subjects with higher application rates to report AEs more frequently. Subjects in the highest application rate category were less likely to report AEs compared to subjects in the two lower application rate categories.

Table 2. Treatment Emergent Adverse Events by Drug Application Rate (All Causalities)

	Drug Application Rate				
Number (%) of Subjects n (%)	**<33 percentile (1.61 mg/cm^2) n (%)**	**33-66 percentile (1.61-2.56 mg/cm^2) n (%)**	**>66 percentile (2.56 mg/cm^2) n (%)**	**Not Calculated n (%)**	**Total n (%)**
Subjects evaluable for adverse events	44	44	45	4	137
Number of adverse events	63	70	50	9	192
Subjects with adverse events	30 (68.2)	30 (68.2)	24 (53.3)	4 (100.0)	88 (64.2)
Subjects with serious adverse events	0	0	0	1 (25.0)	1 (0.7)
Subjects with severe adverse events	0	1 (2.3)	0	0	1 (0.7)
Subjects discontinued from study due to adverse events [a]	0	0	0	0	0
Subjects discontinued study drug due to AE and continue Study [b]	1 (2.3)	1 (2.3)	1 (2.2)	1 (25.0)	4 (2.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	0	1 (2.3)	2 (4.4)	0	3 (2.2)

a Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study

b Subjects who have an AE record that indicates that the action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study

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These same %BSA and application rate categories were used to summarize AEs by severity (Table 3). Overall, most AEs were mild or moderate. A numerically higher proportion of subjects in the highest BSA category (>40 %BSA at Baseline) had moderate AEs compared with the other BSA categories. There was no apparent trend toward greater severity of AEs with increase in dose. There were no meaningful differences in the types of AEs reported across the three application rate categories. For all 3 categories, <33 percentile, 33-66 percentile and >66 percentile, the SOCs most frequently affected were Infections and infestations (31.8%, 34.1%, 26.7%, respectively) and Skin and subcutaneous tissues disorders (27.3%, 34.1%, 20.0%, respectively).

Table 3. Summary of All Causality and Treatment-related Adverse Events by Severity

BSA Category									
	0.1-<16% BSA N = 58			**16-40% BSA N = 41**			**>40% BSA N = 38**		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
All Causality	20 (34.5)	14 (24.1)	0	15 (36.6)	12 (29.3)	1 (2.4)	13 (34.2)	13 (34.2)	0
Treatment -related	8 (13.8)	1 (1.7)	0	4 (9.8)	1 (2.4)	0	4 (10.5)	4 (10.5)	0
Application Rate Category*									
	<33 Percentile (1.61 mg/cm^2) N = 44			**33-66 Percentile (1.61-2.56 mg/cm^2) N = 44**			**>66 Percentile (2.56 mg/cm^2) N = 45**		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
All Causality	23 (52.3)	7 (15.9)	0	14 (31.8)	15 (34.1)	1 (2.3)	9 (20.0)	15 (33.3)	0
Treatment -related	4 (9.1)	2 (4.5)	0	8 (18.2)	3 (6.8)	0	4 (8.9)	1 (2.2)	0

*Four subjects were excluded from this summary because they had application rates that could not be calculated.

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Adverse events of the gastrointestinal system, especially vomiting and diarrhoea, are often associated with systemic PDE-4 inhibition (See CSR Section 12.2.3). To evaluate whether these events are reported more frequently with higher doses of crisaborole, a summary of AEs affecting the gastrointestinal disorders system organ class by severity is provided in Table 4. A total of 14 subjects (10.9%) reported AEs that coded to the Gastrointestinal disorders system organ class (SOC). This total includes 10 subjects (7.3%) who reported diarrhoea and 1 subject (0.7%) who reported vomiting. There was no trend of more subjects reporting these AEs with increasing dose. More subjects in the lower application rate category reported gastrointestinal symptoms compared to the highest application rate category.

Table 4. Summary of All Causality Adverse Events in the Gastrointestinal Disorders System Organ Class

Application Rate Category*									
	<33 Percentile (1.61 mg/cm^2) N = 44			33-66 Percentile (1.61-2.56 mg/cm^2) N = 44			>66 Percentile (2.56 mg/cm^2) N = 45		
System organ class Preferred term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Gastro-intestinal disorders	5 (11.4)	1 (2.3)	0	4 (9.1)	0	0	2 (4.4)	2 (4.4)	0
Diarrhoea	4 (9.1)	0	0	3 (6.8)	0	0	2 (4.4)	1 (2.2)	0
Vomiting	1 (2.3)	0	0	0	0	0	0	0	0

*Four subjects were excluded from this summary because they had application rates that could not be calculated

Among the 21 subjects enrolled in the pharmacokinetic (PK) cohort, exposure to crisaborole was assessed in 18 subjects. Baseline characteristics of the 5 subjects with the highest exposures are provided in Table 5.

Table 5. Characterization of PK Subjects with Highest Crisaborole Cmax

Subject Number	Baseline %BSA	Cmax (ng/mL)	Number of AEs reported
1	48.0	640	1
2	43.0	1030	1
3	56.0	26700	1
4	56.0	937	7
5	59.0	28000	0

Brief narratives are provided for the four subjects from Table 5 with an AE.

A subject had 48.0 % BSA at Baseline. Beginning on Day –5 during the pre-treatment phase, a nontreatment-emergent AE of radial head dislocation was reported. The AE was considered by the Investigator to be not related to study treatment and resolved.

A subject had 43.0 %BSA at Baseline. Beginning on Day 7, an AE of lip injury (verbatim term: "cut to lip") was reported. The AE was mild, considered by the Investigator to be not related and resolved on Day 10.

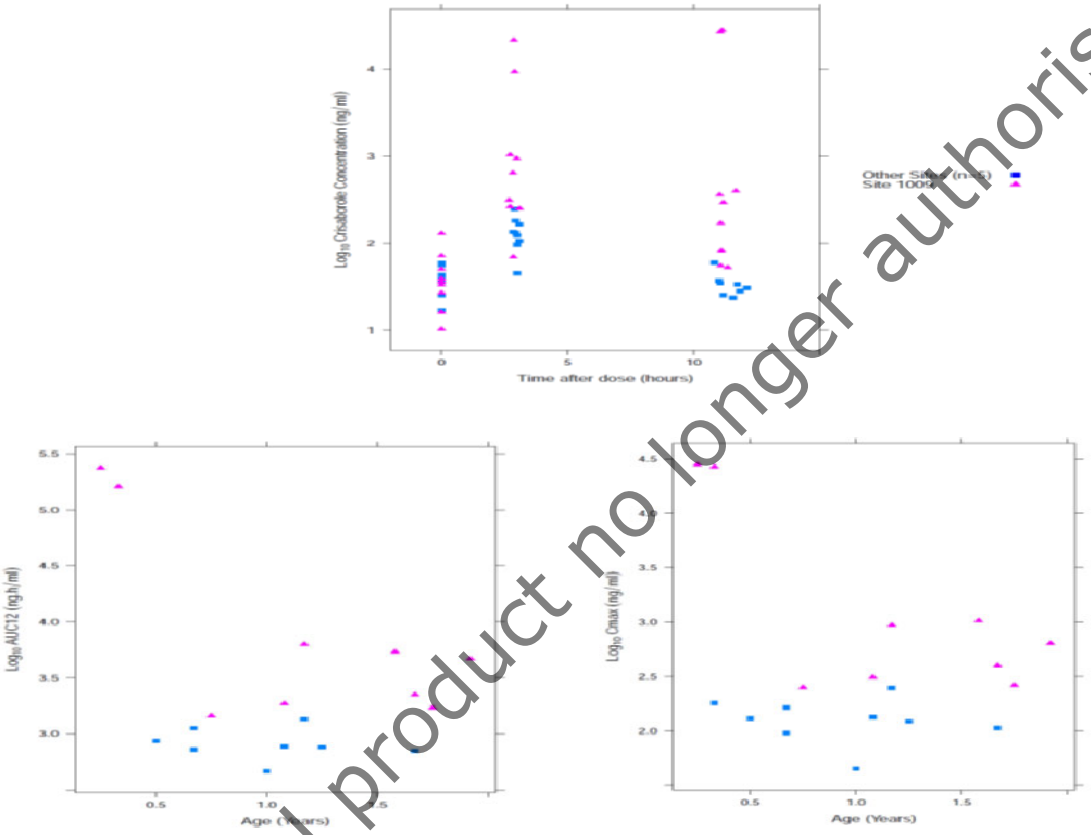
A subject had 56.0 % BSA at Baseline. Beginning on Day 20, an AE of upper respiratory tract infection was reported. The AE was moderate, considered by the Investigator to be not related and ended on Day 54.

A subject who had 56.0 % BSA at Baseline had the following events. Beginning on Day 14, two AEs of application site reaction of moderate severity were reported; one affecting the face, the other affecting the arms. Both events were considered by the Investigator to be related, led to interruption of study drug treatment and resolved on Day 15. Beginning on Day 17, an AE of application site reaction of moderate severity affecting the back was reported. The AE was considered by the Investigator to be related, led to interruption of study drug treatment and resolved on Day 18. Beginning on Day 18 an AE of dermatitis contact of moderate severity affecting a treatment area on the back was reported. The AE was considered by the Investigator to be related, led to interruption of study drug treatment and resolved on Day 22. Beginning on Day 18 an AE of impetigo of moderate severity affecting a treatment area on the back was reported. The AE of impetigo was considered by the Investigator to be not related to study drug and resolved on Day 22.
Beginning on Day 28 an AE of upper respiratory tract infection of mild severity was reported. The AE was considered by the Investigator to be not related to study drug and resolved on Day 31.
Beginning on Day 39 an AE of otitis media acute of moderate severity was reported. The AE was considered by the Investigator to be not related to study drug and resolved on Day 54.

It is important to acknowledge that the subjects identified in Table 5 from Site 1009 were deemed outliers based on the nonlinear regression analysis described in Section 6.1.3 of PMAR-EQDD-C329a-DP4-956 which was included as an appendix to CSR for C3291002. Furthermore, site

personnel confirmed that they did not follow the phlebotomy site cleaning procedures recommended in the protocol. A detailed description of the impact of Site 1009 on the PK results of C3291002 is also provided in Appendix 5 of PMAR-EQDD-C329a- DP4-956 under the heading of "Sensitivity analysis of the Influence of Center 1009 on Model Selection". A key observation for the data from Site 1009 was that the pharmacokinetic concentrations observed from Site 1009 trended toward being higher than the data from
5 other sites that contributed subjects to the PK cohort. Of specific concern is the observation that the time 0 concentrations do not suggest a differentiation between Site 1009 and other sites. Site 1009 differentiates from the other sites only for the postdose concentrations at
3 and 12 hours by a large magnitude (Figure 1).

Figure 1. PK Concentrations and Parameters from Site 1009 Relative to Other Sites

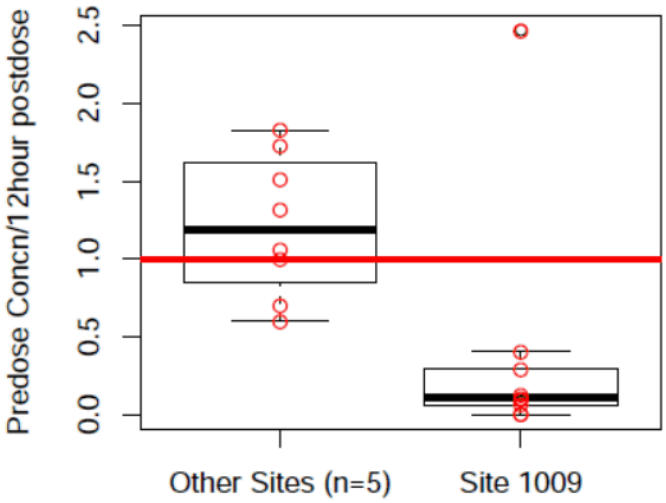


Source: Appendix 5 of PMAR-EQDD-C329a-DP4-956, Figure A17.

Additionally, the ratio of Day 8 concentrations at time 0 to 12 hours was consistently lower than 1 for the subjects from Site 1009 (Figure 2). The ratio of 0 hour to 12-hour concentrations at steady state are expected to be approximately 1 given the BID dosing regimen. A ratio consistently below 1 suggests a potential anomaly (either sampling, dosing or that these subjects are not at steady state) especially as the time 0 concentrations are in a similar range for Site 1009 and other sites. Hence, the potential for contamination of PK samples at site 1009 due to nonadherence to the phlebotomy procedures recommended in the protocol cannot be ruled out.

Overall, based on the analysis described in PMAR-EQDD-C329a-DP4-956, under typical crisaborole ointment usage conditions, crisaborole systemic exposures in pediatric populations down to 0.25 years (3 months) of age, at highest possible dose are unlikely to exceed the systemic exposures in adults at the highest possible adult dose.

Figure 2. Ratio of Concentrations at 0 hours (predose) to 12 hours (postdose) on Day 8



Source: Appendix 5 of PMAR-EQDD-C329a-DP4-956, Figure A18.

In summary, among those subjects in the PK cohort with the highest measured plasma levels of crisaborole, no concerning safety issues emerged. Only one of the 5 subjects had AEs considered related to study treatment and those were AEs reflecting local effects at the site of application.

To evaluate the potential impact of subject age, the MAH has summarized AEs by age at Screening. Per suggestion of the reviewer, Table 6 summarizes AEs by age category (3-<12 months of age and 12-<24 months of age). Overall, the proportions of subjects with AEs were comparable between the two groups. One subject experienced a serious AE and one subject experienced a severe AE and both subjects were in the 12-<24-month cohort. Similar proportions of subjects in both age groups either discontinued study drug or had a dose reduction or temporary discontinuation due to AEs.

Table 6. Treatment-emergent Adverse Events by Age Group (All Causalities)

	Age Group		
Number (%) of Subjects	**3-<12 Months n %**	**12-<24 Months n (%)**	**Total n (%)**
Subjects evaluable for adverse events	57	80	137
Number of adverse events	86	106	192
Subjects with adverse events	39 (68.4)	49 (61.3)	88 (64.2)
Subjects with serious adverse events	0	1 (1.3)	1 (0.7)
Subjects with severe adverse events	0	1 (1.3)	1 (0.7)
Subjects discontinued from study due to adverse events [a]	0	0	0
Subjects discontinued study drug due to AE and continue Study [b]	1 (1.8)	3 (3.8)	4 (2.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	2 (3.5)	1 (1.3)	3 (2.2)

a Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study

b Subjects who have an AE record that indicates that the action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued from study

The types of AEs reported were similar in the two age groups. In both age groups, AEs that coded to the Infections and infestations SOC were the most frequently reported; 20 subjects (35.1%) in the 3-<12 months group and 23 subjects (28.8%) in the 12-<24 months group. The most frequently reported AEs in this SOC included the high level terms Ear infections (5.3% and 11.3%

among the 3-<12 and 12-<24 month groups, respectively) and Upper respiratory tract infection (14.0% and 8.8% among the 3-<12 and 12-<24 month groups, respectively). Pyrexia was reported by 10.5% and 8.8% of subjects in the 3-<12 and 12-<24 months groups, respectively. Similar proportions of subjects in the two age groups reported AEs that coded to the Skin and subcutaneous tissues disorders SOC (28.1% and 26.3% among the 3-<12 and 12-<24 months groups, respectively). Crisaborole is associated with AEs affecting the application site such as application site pain. Similar proportions of subjects reported AEs that coded to the high-level term Application and instillation site reactions (10.5% and 11.3% among the 3-<12 and 12-<24-month groups, respectively).

In summary of all parts of this question, subjects in the two highest %BSA categories were more likely to report an AE compared to the lowest %BSA category and more subjects in the highest category discontinued treatment due to an AE. By definition, subjects with higher %BSA at baseline have more extensive atopic dermatitis and may be more prone to AEs for that reason. However, when summarizing AEs by dose (application rate) there was no trend for subjects with higher application rates to report AEs more frequently. Subjects in the highest application rate category were less likely to report AEs compared to subjects in the two lower application rate categories. Similarly, when evaluating AEs that may reflect systemic PDE-4 inhibition, there was no dose-related trend. More subjects in the lower application rate category reported gastrointestinal symptoms compared to the highest application rate category. Among those subjects in the PK cohort with the highest measured plasma levels of crisaborole, no concerning safety issues emerged. Only one of these subjects had AEs considered related to study treatment and those were AEs reflecting local effects at the site of application. Lastly, when comparing frequency and types of AE reported based on age, there were no apparent trends. The most frequently reported AEs among both 3-<12- month-old- and 12-<24 months old-subjects reflected symptoms of typical childhood illnesses, the disease under study or known effects of crisaborole.

Assessment of Response:

1. Analysis of AEs according to % BSA affected at baseline:

The MAH provided an analysis of adverse events based on %BSA affected at baseline, categorized into 3 severity strata (0.1- 16%; 16-40%, >40% BSA, n= 58, 41, 38 patients, respectively). These cut-offs are based on a categorization proposed by Chopra et al. (Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. 2017 Br J Dermatol. 177(5):1316-1321.). It is noted, that the categorization by Chopra et al. was done in adolescents and adults recruited from a single center. It seems acceptable to apply it also to the paediatric dataset in this context. The three groups seem sufficiently balanced in terms of group size to allow for inter-group comparisons. TEAEs were recorded in 58.6%, 68.3% and 68.4% of patients, respectively, and are thus most common in the two highest %BSA categories. The difference to the TEAE rate in the lowest %BSA affected group is not very pronounced, the relation does not seem to be linear (no increased AE rate in the highest %BSA affected group) and the overall small group sizes need to be considered when interpreting these results.

The MAH states that adverse events related to treatment were reported by 15.5%, 12.2%, and 21.1% of subjects in the 0.1-<16%, 16-40% and >40 %BSA categories, respectively. While it is noted that the number is highest in the highest %BSA group, the relation is not linear, which is reassuring.

It is noted that three of the 4 subjects who discontinued study drug due to an adverse event had a baseline BSA affected over 40%. This is reassuring given that Staquis is limited to patients ≤ 40% BSA affected in Europe. The only (n=1) severe AE reported throughout the study occurred in a subject in the 16-40% BSA category.

Overall, no clinically meaningful relationship between %BSA affected and treatment emergent AE rate with crisaborole use became apparent with the additional analysis provided, although this can still not be fully excluded based on the available data. Quality of AEs (e.g. by preferred term/system organ

class) was only considered by the MAH in relation to age groups, but not for other parameters. Most of the recorded AEs related to treatment were skin related. It seems comprehensible that such events would be recorded more frequently in patients with 'more severe' disease, and a higher %BSA affected could be an indicator of more severe disease.

2. Analysis of AEs according to drug application rate (crisaborole dose)

Drug application rate by tertiles (<33 percentile, 1.61 mg/cm2, n=44; 33-66 percentile 1.61-2.56 mg/cm2, n=44; > 66 percentile 2.56 mg/cm2, n=45) did not indicate a dose dependent increase in treatment-related AE rates (13.6%, 25.0% and 11.1% of subjects in the <33%, 33-66% and >66% application rate categories, respectively).

3. Analysis of AEs by severity

BSA category: No marked differences in all-causality or treatment related AEs of mild severity became apparent when comparing different BSA categories. A higher proportion of both all causality and treatment-related AEs of moderate severity were reported in subjects in the highest BSA category (>40 %BSA at Baseline) compared with the other two BSA categories (0.1-16% and 16-40% BSA affected). No obvious differences in AE severity can be seen when comparing the latter two categories with each other. However, this needs to be considered in the context of an overall small sample size.

Application rate category/dose: All causality related AEs of mild severity were reported in 52.3%, 31.8% and 20.0% in the <33, 33-66 and >66 percentile subgroups, respectively. All causality related AEs of moderate severity were reported in 15.9%, 34.1% and 33.3%, respectively. However, the proportion of treatment-related AEs of moderate intensity was comparable between all three groups. Overall, severity of treatment-related AEs does not seem to be affected by neither % BSA at baseline nor drug application rate (dose).

4. Incidence of gastrointestinal AEs

No trend of more subjects reporting gastrointestinal AEs (known anti-PDE-4 off-target effects) with increasing crisaborole dose applied became apparent in the studied patient group of 3 to < 24 months old patients.

5. Characterization of Crisaborole Safety in Subjects with high exposure

Plasma levels are only available from a subset of patients (n=18) with a BSA affected with a mean of 53.5% (min/max: 35.0%/79.0%). Per patient, three PK samples were taken on day 8; before morning dose, 3 and 12 hours post-dose. The MAH used approximate Cmax (value measured at assumed steady state) as parameter of interest to address this issue. Among the 5 subjects in the PK cohort with the highest measured plasma levels of crisaborole, no concerning safety issues emerged (4/5 subjects reported at least 1 AE, 1 subject had AEs considered related to study treatment) throughout the study. Crisaborole exposure in terms of AUC has not been discussed in relation to substance safety but would have been of interest as well and might even be more relevant than Cmax. AUC was mentioned in the list of exploratory endpoints and is thus believed to have been calculated. It could be assumed though that patients with higher Cmax also have rather high AUC values. No Cmax-dependent pattern of plasma crisaborole and adverse event quantity/quality became apparent and this would not be easy to assess based on such a small sample. All of the 4 subjects in

whom an AE was reported had baseline BSA affected >40% and would therefore not receive Staquis in the EU (label restriction to patients ≤ 40% BSA affected).

6. Treatment-emergent Adverse Events by Age Group

Frequency, types of AE (mainly URTI, ear infections, pyrexia) and AE severity did not suggest differences between 3-12 month olds compared to 12-24 month olds.

Final remark:

The MAH has provided the requested data which overall do not support a strong link between quality, quantity or severity of AEs with regard to % BSA affected at baseline, crisaborole doses administered, Cmax levels, PDE4 off target effects (gastrointestinal), or age. It appears that there was a tendency of treatment-related AEs occurring with higher frequency in the >40% BSA affected at baseline subgroup. This population is not included in the European label.

Conclusion:

Issue resolved/not further pursued.

Question 2:

The MAH is asked to provide details on cases of TEAEs (pyrexia, respiratory tract infections, diarrhea; TEAEs reflecting symptoms of AD) that did not resolve within short periods of time and clarify how these cases were followed-up.

Response to Q2:

Details for the following 11 adverse events occurring in 11 participants is provided in Table 1 and in narrative form below:

- Two (2) pyrexia cases that did not resolve within 3 days
- Three (3) upper respiratory tract infection cases that did not resolve within 12 days
- Two (2) diarrhoea cases that did not resolve within 4 days
- Four (4) atopic dermatitis/eczema cases with outcome of not resolved/not recovered

Table 1. Case Detail for Specified Treatment Emergent Adverse Events

Event	Baseline %BSA	Total IP volume (g) or *actual dose (g)	AE Study day/ #Days to resolve	Severity/ Outcome	Action taken to IP	PI assessment/ Alternative causality
Pyrexia	12	127.4	15/5	Moderate/resolved	Not changed	Not related/ 'Teething'
Pyrexia	73	*8.7	7/8	Moderate/resolved	Not changed	Not related/Virus
URI	36	129.3	31/21	Mild/resolved	NA (in FU period)	Not related/ Concurrent illness
URI	18	135	8/36	Mild/resolved	Not changed	Not related/Viral infection
URI	56	*5.3	20/34	Moderate/not resolved	Not changed	Not/related/Viral infection
Diarrhoea	8	27.8	16/8	Mild/resolve	Not changed	Not related/Viral infection
Diarrhoea	19	113.6	6/12	Mild/resolved	Not changed	Not related/Virus
AD/Eczema	55	239.5	32/ongoing	Moderate/not resolved	NA (in FU period)	Not related/Eczema not treated

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Table 1. Case Detail for Specified Treatment Emergent Adverse Events

Event	Baseline %BSA	Total IP volume (g) or *actual dose (g)	AE Study day/ #Days to resolve	Severity/ Outcome	Action taken to IP	PI assessment/ Alternative causality
AD/Eczema	12	37.3	38/ongoing	Mild/not resolved	NA (in FU period)	Not related/ Nontreatment
AD/Eczema	45	531.5	30/ongoing	Mild/not resolved	NA (in FU period)	Not related/Disease under study
AD/Eczema	9	42.2	30/ongoing	Mild/not resolved	NA (in FU period)	Not related/Stopping IP

AD=Atopic dermatitis; FU=Follow-up; g=gram (volume of investigational product); IP-investigational product; NA=not applicable; %BSA=percent body surface area; PI=Principal Investigator; PT=preferred term; URI=upper respiratory tract infection

Brief narratives for these cases are provided below:

Pyrexia

A subject with 12 %BSA experienced pyrexia on Study Day 15. Severity was assessed by the Investigator as moderate, study medication dose was not changed, and the event resolved in 5 days. The Investigator causality was not related to study medication with 'teething' provided as the alternative causality.

A subject with 73 %BSA experienced pyrexia on Study Day 7. Severity was assessed by the Investigator as moderate, study medication dose was not changed, and the event resolved in 8 days. The Investigator causality was not related to study medication with 'virus' provided as the alternative causality.

Upper Respiratory Tract Infection

A subject with 36 %BSA experienced upper respiratory tract infection on Study Day 31. Severity was assessed by the Investigator as mild, action taken with study medication was not applicable as the Treatment Period had ended and the subject was in the Follow-up Period. The event resolved in 21 days. The Investigator causality was not related to study medication with concurrent illness of upper respiratory infection provided as the alternative causality.

A subject with 18 %BSA experienced upper respiratory tract infection on Study Day 8. The severity was assessed by the Investigator as mild, study medication dose was not changed, and the event resolved in 36 days. The Investigator causality was not related to study medication with viral infection provided as the alternative causality. Concurrent AEs included mild intermittent asthma with acute exacerbation and otitis media.

A subject with 56 %BSA experienced worsening upper respiratory infection on Study Day 20. The severity was assessed by the Investigator as moderate, study medication dose was not changed. The participant was lost to follow up despite multiple attempts and certified letter sent. The event was still ongoing at time of lost to follow up. The Investigator causality was not related to study medication with viral infection provided as the alternative causality.

Diarrhoea

A subject with 8 %BSA experienced diarrhoea on
Study Day 16. The severity was assessed by the investigator as mild, study medication dose was not changed, and the event was resolved in 8 days. The Investigator causality was not related to study medication with viral infection provided as the alternative causality. Subject had also experienced pre-treatment event of Hand-foot-and-mouth disease ~23 days earlier and adverse events of pyrexia (Day 4) and viral rash (Day 7).

A subject with 19 %BSA experienced diarrhoea on Study Day 6. The severity was assessed by the Investigator as mild, study medication dose was not changed, and the event was resolved in 12 days. The Investigator causality was not related with virus provided as the alternative causality. The subject also experienced a concurrent adverse event of irritability.

Atopic dermatitis/Eczema

The four (4) events of AD/eczema all started during the Follow-up Period after study drug had ceased and all were ongoing at the time of the 28-day post-treatment telephone call (Day 57 Follow-up Telephone Call).

All subjects were confirmed to have received the protocol specified Follow-up telephone calls at Day 36 (7 days post-treatment) and Day 57 (28 days post-treatment) during which assessment of AEs and concomitant medications was required. Follow-up beyond Day 57 for nonserious AEs was allowed but not mandated per protocol (section 8.1.4.2), "Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment". However, none of these AEs were assessed as requiring continued follow-up beyond 28 days post-treatment.

Narratives for these cases are provided below:

A subject with 55 %BSA experienced eczema flare-up on Day 32. The event outcome was not resolved by end of the study (Day 57 Telephone Call). The severity was assessed by the Investigator as moderate and action taken with study drug was not applicable as treatment period had ended and subject was in the Follow-up Period. The Investigator causality was not related with eczema not treated provided as the alternative causality.

A subject with 12 %BSA experienced worsening atopic dermatitis on Study Day 38. The event was assessed as not resolved by end of the study (also Day 38). The severity assessed by the Investigator as mild and action taken with study drug was not applicable as Treatment Period had ended and the subject was in the Follow-up Period. The Investigator causality was not related with nontreatment provided as the alternative causality.

A subject with 45 %BSA experienced worsening atopic dermatitis on Day 30. The event outcome was not resolved by end of the study (Day 57 Telephone Call). The severity was assessed by the Investigator as mild and action taken with study drug was not applicable as Treatment Period had ended and subject was in the Follow-up Period. The Investigator causality was not related with disease under study listed as the alternative causality.

A subject with 9 %BSA experienced worsening of atopic dermatitis on Day 30. The event outcome was not resolved by end of the study (Day 57 Telephone Call). The severity was assessed by the investigator as mild and action taken with study drug was not applicable as Treatment Period had ended and subject was in the Follow- up Period. The Investigator causality was not related with stopping investigational product provided as the alternative causality.

Assessment of Response:

The MAH clarified that among 11 presumably unresolved TEAEs (in 11 subjects) 5 events were still ongoing. Amongst those 5, 4 events were 'atopic dermatitis/eczema'. The recording of these events could be a reflection of underlying disease or indicate lack of efficacy of treatment. The one other unresolved event of moderate URTI infection occurred in a subject with 56% BSA affected who was lost to follow-up despite efforts made by the investigator. Thus, the outcome of this event remains unknown.

The remaining 6/11 events (2 each of pyrexia, URTI, diarrhea) were assessed as unrelated to treatment by the investigator and had resolved by the end of study.

Conclusion

Issue resolved.

Question 3:

To further look into cardiac findings, the MAH is asked to clarify whether the events of prolonged QTcF intervals and changes in blood pressure occurred in the same subjects and provide data on relevant baseline and disease characteristics (age, %BSA affected and PG concentrations measured) for respective subjects.

Response to Q3:

A total of 10 subjects experienced an increase from Baseline/Screening in QTcF of 30 msec or more. The ECG data are discussed in the clinical study report (Section 12.5.3). Table 1 summarizes the age, %BSA, blood pressure (BP), QTcF, and serum propylene glycol (PG) levels for those 10 subjects. Note that no subject had a QTcF value of >500 msec.

Table 1. Listing of Subjects with post-Baseline QTcF Prolongation of 30 msec or more

Subject ID	%BSA	QTcF Interval, Single Beat (msec)				Systolic BP [a]			Diastolic BP [a]			PG Concentration (ng/mL)	
	Day 1	Screening	Day 1	Day 8	EOT	Day 1	Day 8	EOT	Day 1	Day 8	EOT	Screening	EOT
1	6.5	–	354	349	386	86	86	88	48	52	58	868	212
2	7.0	–	329	315	367	89	97	87	55	54	47	140	175
3	19.0	–	336	373	334	104	92	100	72	64	68	2340	3650
4	6.0	–	354	–	390	79	–	78	51	–	50	521	–
5	8.0	342	–	373	358	105	105	105	60	60	60	3680	974
6	15.0	–	339	339	375	83	90	95	64	60	70	3520	–
7	6.0	–	333	371	361	84	82	72	62	56	46	5070	3450
8	39.0	373 351	370	385	341	76	112	92	58	54	65	6100	1540
9	25.0	–	333	352	369	96	82	74	58	56	42	3380	126
10	18.0	–	297	313	365	80	84	84	58	62	62	133	27500

Source: C3291002 CSR Table 16.2.8.3.1, Table 16.2.8.3.3, Table 16.2.4.1, Table 16.2.5.4.1, Table 16.2.8.2.1.

[a] Criteria for BP were a value <37 mmHg or >63 mmHg for diastolic BP or a value <72 mmHg or >106 mmHg for systolic BP. Measurements at Screening and Day 1 were both prior to dosing and therefore represent Baseline.

Only one subject was reported to have a QTcF increase of >60 msec. This subject had 18 % BSA at Baseline. QTcF at Baseline was 297 msec and increased to 365 msec on Day 29. This was not reported as an adverse event. Systolic and diastolic BP were essentially unchanged over the course of the study. Board-certified cardiology review (overread) documented the presence of movement artifact and tachycardia (HR 182 bpm) impairing measurement of Baseline and follow-up QT intervals. Board-certified cardiology overread of this participant's ECGs confirmed neither a QTcF >500 msec nor increase in QTcF >60 msec were present. PG concentration was 133 ng/mL at Screening and 27,500 ng/mL (no reference range) at Day 29.

Among the 10 subjects with reported QTcF prolongation of >30 msec, two had potentially significant changes in BP (defined as a change from Baseline of 20 mmHg in systolic BP or a change of 30 mmHg in diastolic BP). One subject had a baseline systolic BP of 76 mmHg which increased to 112 mmHg at Day 8. Diastolic BP was essentially unchanged from baseline to Day 8 (58 mmHg and 54 mmHg, respectively). One subject had a baseline systolic BP of 96 mmHg that decreased to 74 mmHg at Day 29. Diastolic BP was 58 mmHg and 42 mmHg at Baseline and Day 29, respectively. PG levels in both subjects decreased from Screening to post-Screening measurements.

In summary, and as discussed in the clinical study report, in view of movement artefact on multiple ECGs and the absence of consensus pediatric ECG interval criteria, no clinically meaningful changes in QTcF were confirmed in any of the 135 subjects. There was no apparent pattern of change in BP accompanying the observed prolongations in QTcF. There was no apparent trend among these subjects with regard to baseline characteristics such as age or %BSA at Baseline. Furthermore, there was no apparent association between ECG findings and changes in PG levels over the course of the study.

Assessment of Response:

The MAH clarified that among the 10 subjects with QTcF prolongation of >30 msec, two subjects had potentially significant changes in blood pressure during the treatment period (one subject increase in systolic BP, one subject decrease in both systolic and diastolic BP). However, no clear pattern of QTcF prolongation with concomitant change in blood pressure became evident.

It is reassuring that these cardiac findings were not seen in the very young patients (< 6 months of age) or in patients with high % BSA (> 40%) affected and that PG levels were not associated.

It is noted that QTcF abnormalities were not reported in adult patients receiving crisaborole ointment 2% during the EU registrational clinical studies. Moreover, QTcF monitoring in the study under assessment would not be considered as "thorough QT/QTc study" according to ICH E14 as several study elements (e.g. control group, positive control) were missing, making meaningful conclusions on QTcF interval prolongation difficult. While it is reassuring that none of the children in this study reported a QTcF interval > 450 msec or increase from baseline >60 msec, it is noted that drugs which prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. Therefore, further post-marketing efforts should be made to closely monitor these findings.

Conclusion

Issue not further pursued, post-marketing data should be collected.

Question 4:

The MAH is asked to further discuss the case of "defect conduction intraventricular" occurring in one subject in relation to crisaborole treatment. It should be explained why a relation to treatment was assumed by the physician in the first place and whether an underlying pharmacological rationale is assumed. Relevant patient characteristics (age, %BSA affected, the duration of treatment and total exposure until AE recording, PG levels etc.) should be provided. If a relation to treatment is indeed considered likely by the MAH, the relevance of this finding in relation to the current EU product information should be discussed.

Response to Q4

A subject (see Section 12.3.1.3 of the CSR) experienced an adverse event of defect conduction intraventricular (investigator term: intraventricular conduction defect) during study participation. The subject is from the United States. The subject had no other significant past medical history. At baseline, the subject had 94.0 %BSA affected by atopic dermatitis. The subject was not included in the PK cohort so no data on crisaborole concentrations are available. Propylene glycol concentration was 3220 ng/mL (no reference range) on Study Day −16 (Screening) and 5130 ng/mL on Study Day 27. The subject received twice daily treatment with crisaborole for 26 days. The ECGs performed during the Screening period and on Study Day 8 showed sinus tachycardia, but no intraventricular-intra-atrial conduction abnormalities. Sinus tachycardia was not reported as an adverse event. The ECG performed on Study Day 27, at the End-of-Treatment Visit, showed sinus tachycardia and intraventricular conduction defect reported by the ECG Central Reader. Intraventricular conduction defect (investigator term) was reported as an adverse event of mild severity that resolved on Study Day 37. Sinus tachycardia was not reported as a separate adverse event. The subject was referred to a cardiologist. In the opinion of the Investigator, the adverse event was related to study medication, however. after additional follow-up with the Investigator, the rationale for this assessment was not further clarified. Given that crisaborole has shown no signal of cardiac toxicity in previous clinical studies including a thorough QT study there is no pharmacologic rationale for a relationship between this adverse event and exposure to crisaborole.

Assessment of Response:

The MAH explained that the case of "defect conduction intraventricular" occurred in one patient with a very high %BSA affected (98%). While the investigator initially found the AE related to study medications, no further details are available why this assessment was made. Although it seems unlikely that this event was triggered by crisaborole plasma concentration this cannot be verified or excluded based on this single observed case. A warning in the SmPC seems not warranted as this seems to be an isolated event and the relation to treatment is not finally determinable and no further data to investigate the connection are available. The issue should, however, be closely monitored by the MAH post-marketing.

It is further noted that in the EU only patients up to 40% BSA affected are covered by the label and that the affected patient discussed above would not fall within this definition.

Conclusion

Issue not further pursued.

Question 5:

Laboratory assessments were not completed in 41/137 (30.0%) patients as samples could not be collected or processed. An explanation for the underlying reasons and a discussion on the estimated impact of missing data on clinical laboratory results should be provided, especially regarding missing data in patients with AEs or in patients that discontinued treatment.

Response to Q5

There were 122 subjects with at least one observation of the given laboratory test following the initiation of treatment. A total of 15 subjects had no clinical laboratory results after the Screening Period. Laboratory results were present for over 80% of subjects for each test. A total of 80.3% (110 of 137) to 87.6% of subjects (120 of 137) had laboratory test results following the start of treatment for any given laboratory test. For instance, 113 of 137 subjects (82.5%) had hemoglobin results (CSR Table 14.3.4.1.2).

The Protocol Deviations (PD) section of the CSR (Section 10.3) states that 41 participants "did not have laboratory assessments completed, or samples were collected but could not be processed." The laboratory PDs do not mean that these subjects lacked all laboratory results, but rather that an issue occurred for a laboratory sample drawn that resulted in one or more missing laboratory parameters. A total of 21 subjects had important laboratory PDs post-treatment (Day 29, End of Treatment, or Early Termination), most of which were due to inability to collect the blood sample, as follows: failed attempts (8 subjects) which included parent/guardian unwillingness to proceed after a failed attempt and subject discomfort as reasons for not proceeding, "insufficient blood" (2 subjects), and being unable to collect blood (1 subject). Blood samples were not collected for another 3 subjects (no reason provided) and when the parent did not allow the blood draw (1 subject). The remaining 6 laboratory PDs were due to sample mishandling or hemolysis or a particular test not being done (such as subjects lacking the propylene glycol test).

One subject who permanently discontinued from the study due to the serious adverse event febrile convulsion completed all laboratory assessments (CSR Section 12.2.3.1, 12.3.1.2, 14.3.3.2). The other subjects with events requiring safety narratives (CSR Section 14.3.3.3) were also unaffected by missing laboratory assessments.

Study C3291002 enrolled relatively healthy children who would not be expected to have abnormal clinical laboratory parameters. The review of the data collected from completed/ongoing clinical studies and post marketing setting have not identified any risk related to clinical laboratory effects. During the study, no laboratory abnormalities were considered clinically significant (CSR Section 12.4.2.3) and none were reported as AEs (CSR Section 12.4.2). The PDs related to laboratory assessments did not have any meaningful impact on the safety of subjects, nor did they lead to any subject meeting criteria for withdrawal from the study (CSR Section 10.3). Subjects who withdrew due to adverse events were not affected by missing clinical laboratory results.

Assessment of Response:

The MAH clarified that laboratory datasets were incomplete in approx. 30% of patients due to different reasons which does not mean that the entire datasets were missing. A total of 21 subjects had important laboratory protocol-deviations post-treatment (inability to collect blood samples, sample mishandling, hemolysis). It is considered unlikely that missing data had a meaningful impact on safety evaluations.

Conclusion

Issue resolved.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Staquis Active substance: Crisaborole

Study title	Study number	Date of completion	Date of submission of final study report
PIP Study 1: 4-week definitive juvenile toxicity study in rats with a 1-week recovery period to evaluate food consumption, sexual maturation, functional observational battery, motor activity, acoustic startle response, clinical pathology, necropsy findings, organ weights and histopathology	003-NCL TX-055-01	17/10/2012 (Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018
PIP Study 2: 4-week definitive juvenile dermal toxicity study in Gottingen minipigs with a 1-week recovery period to evaluate clinical signs, bodyweight, food consumption, growth rate, clinical pathology, ECG and ophthalmoscopy	003-NCL TX-054-01 AN2728 TOPICAL OINTMENT	08/11/2012 (Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018
PIP Study 3: 4-week definitive juvenile toxicity study in rats with a 2-week recovery period to evaluate systemic safety, body weight, food consumption, motor activity, acoustic startle habituation, clinical pathology, including haematology and clinical chemistry, macroscopic and microscopic pathology	20093673 (16GR400)	04/08/2017(Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018

Clinical studies

Product Name: Staquis Active substance: Crisaborole

Study title	Study number	Date of completion	Date of submission of final study report
PIP Study 5: Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 2 to less than 18 years of age (and adults) with mild to-moderate atopic dermatitis.	AN2728-AD-302	27/04/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018
PIP Study 4: Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 2 to less than 18 years of age (and adults) with mild to-moderate atopic dermatitis.	AN2728-AD-301	29/04/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018
PIP Study 6: Open-label, uncontrolled, extension study to evaluate long-term safety of crisaborole ointment, 2% in children from 2 to less than 18 years of age (and adults) with mild-to-moderate atopic dermatitis.	AN2728-AD-303	27/10/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0101/2018
Study C3291028: A Phase 2b, Multi center, Randomized, Double-blind, vehicle-controlled, intra-participant study, to evaluate efficacy and safety of two regimens of crisaborole ointment 2% in japanese pediatric and adult participants (2 years and older) with mild to moderate atopic dermatitis	C3291028	LSLV December 2019	Article 46 submission by June 2020
Study C3291032: A Phase 3, Multicenter, Randomized, Double blind, Vehicle Controlled Study of the Efficacy and Safety of Crisaborole Ointment, 2% in Asian Pediatric and Adult Subjects (ages 2 years and older) with Mild to Moderate Atopic Dermatitis	C3291032	LSLV November 2021	Article 46 submission by May 2022
PIP Study 8: C3291037 - Assessor-blind, randomised, active- and vehicle -controlled study to evaluate efficacy and safety of crisaborole ointment, 2% compared to topical corticosteroid (TCS), topical calcineurin inhibitor (TCI) and vehicle in children from 2 to less than 18 years of age (and adults) with mild to moderate atopic dermatitis.	C3291037	Date of completion (LSLV) in current agreed PIP (P/0101/2018). is July 2020. Ongoing PIP modification to request a change in the LSLV to May 2021 (Procedure number: EMEA-002065-PIP01-16-M02)	Latest PIP decision: P/0101/2018 Based on PDCO agreement on the ongoing PIP modification procedure (Procedure number: EMEA-002065-PIP01-16-M02) to request a change to the LSLV for PIP Study 8, the Article 46 submission of Study C3291031 will be planned to be submitted by November 2022.
PIP Study 7: C3291031 - Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 1 month to less than 24 months of age with mild-to-moderate atopic dermatitis.	C3291031	Date of completion (LSLV) in current agreed PIP (P/0101/2018). is August 2021 Ongoing PIP modification to request a change in the LSLV to October 2022 (Procedure number: EMEA-002065-PIP01-16-M03).	Latest PIP decision: P/0101/2018 Based on PDCO agreement on the ongoing PIP modification procedure (Procedure number: EMEA-002065-PIP01-16-M03) which includes a request to change the LSLV for PIP Study 7, the Article 46 submission of Study C3291031 will be planned to be submitted by April 2023.
Study C3291035: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Maintenance Treatment and Flare Reduction with Crisaborole Ointment, 2%, Once Daily Over 52 Weeks in Pediatric and Adult Participants (Ages 2 Years and Older) with Mild-to-Moderate Atopic Dermatitis, who Responded to Twice Daily Crisaborole Ointment, 2%, Treatment	C3291035	LSLV July 2022	Article 46 submission by January 2023.
Study C3291034: A Phase 3, Multicenter, Open-label Study of the Long-term Safety of Crisaborole Ointment 2% in Chinese Pediatric and Adult Subjects (ages 2 years and older) with Mild to Moderate Atopic Dermatitis	C3291034	LSLV September 2022	Article 46 submission by March 2023