EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Amsterdam, 16 September 2021
EMA/717595/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Staquis

crisaborole

Procedure no: EMEA/H/C/004863/P46/006

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On the 9th of June 2021, the MAH submitted a study for Staquis (crisaborole ointment 2%), which includes a subset of paediatric patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

A short critical expert overview and the clinical study report (CSR) for study C3291037 have been provided.

On the 26th of August 2021 the Applicant provided responses to questions asked after the first round of assessment.

2. Scientific discussion

2.1. Information on the development program

The *Phase 3b/4 Study to Evaluate Efficacy and Safety of Crisaborole Ointment 2% in Paediatric and Adult Subjects (Ages 2 Years and Older) with Mild to Moderate Atopic Dermatitis* (C3291037) is part of the agreed EU PIP for crisaborole (EMA PIP decision [P/0276/2020] PIP Study 8); the PIP was discontinued on 20 October 2020 for business reasons including early termination of the C3291037 global study. The decision of early termination (LSLV December 2020) was not a result of any safety or efficacy concerns. Study C3291037 was designed to address a PDCO request during the PIP evaluation for a study comparing crisaborole to standard of care to define the position of crisaborole within the treatment paradigm of atopic dermatitis (AD).

CHMP comment:

In a letter sent on 19 October 2020 Pfizer informed the EMA regarding their decision to terminate the ongoing PIP Study 8 and to cancel the planned PIP Study 7 based solely on business reasons. On 26 October the applicant submitted a notification of PIP discontinuation. Pfizer does not plan to request a modification of the PIP to remove PIP Study 7 and Study 8.

The PDCO was informed in November 2020 about the regulatory status of Staquis (crisaborole) which was authorised in the EU on 27 March 2020 for treatment of adults and children from 2 years of age with mild to moderate atopic dermatitis.

Legal feedback was requested and received. In line with it a letter was sent to the applicant emphasising that Study 7 and Study 8 are the only 2 studies requested by the PDCO addressing important questions in the paediatric population. The company was reminded that the obligation to complete paediatric development (including the deferred studies) agreed with PDCO cannot be cancelled by a unilateral decision of Marketing Authorisation Holder (in particular in case where such PIP was used for purposes of applying for marketing authorisation which was granted).

Such PIP must be completed, unless it is modified in agreement with the PDCO by removing all outstanding PIP measures or granting a full product-specific waiver instead. Non-completion of a binding PIP establishes non-compliance with the requirements of the Paediatric Regulation, which the European Medicines Agency has an obligation to report to the European Commission. As a result, this breach of the Paediatric Regulation was reported to the European Commission.

2.2. Information on the pharmaceutical formulation used in the study

Staquis (Crisaborole) is presented as an ointment containing 20 mg/g (2% w/w) ointment in the EU.

Crisaborole (PF-06930164 or AN-2728) is a topical PDE-4 inhibitor, which inhibits the enzymatic activity of PDE-4 through binding to the PDE-4 catalytic site in a manner that is competitive with cAMP. PDE-4 inhibition results in an increase in cAMP that leads to a decrease in inflammation. Crisaborole suppresses inflammation and secretion of certain cytokines involved in AD (eg, TNF-α, IL-2, IL-4, IL-5, and IFNγ) as has been shown for other PDE-4 inhibitors. Crisaborole applied to human skin ex vivo or on AD lesions of participants reduces expression of key drivers of atopic inflammation including T-cell derived cytokines IL-13, IL-31, and IFNγ as well as innate markers of inflammation such as MMP-12. The ability of crisaborole to suppress several types of AD-related cytokines may contribute to its beneficial effects on AD.

Crisaborole was approved as a 2% w/w topical ointment for the treatment of mild-to-moderate AD in patients of age ≥2 years by the US FDA in December 2016 (EUCRISA®). EUCRISA was approved in Canada (June 2018) for topical treatment of mild to moderate AD in patients of age ≥2 years and approved under the trade name STAQUIS® in Israel (February 2019), Australia (February 2019), Hong Kong (April 2020), China (July 2020), and Taiwan (December 2020) for the same indication. STAQUIS was granted an EU Marketing Authorisation via the Centralised Procedure in March 2020 for the topical treatment of mild-to-moderate AD in patients of age ≥2 years with ≤40% BSA affected. The US FDA extended the age limit of the approval from 2 years down to 3 months in March 2020. The expanded age range down to 3 months is currently under review in Canada and Israel; this patient population has been approved in the UAE (November 2020) and Lebanon (December 2020).

The crisaborole formulation marketed in the US contains added 0.1% BHT, an antioxidant excipient. With the exception of Europe, this is the authorized formulation in all other countries where crisaborole is registered. As per the request from CHMP, the sponsor agreed to remove added BHT from the formulation to be marketed in the EU. The formulation approved in the US, with added 0.1% BHT, was used in Study C3291037.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study C3291037: *Phase 3b/4 Study to Evaluate Efficacy and Safety of Crisaborole Ointment 2% in Paediatric and Adult Subjects (Ages 2 Years and Older) with Mild to Moderate Atopic Dermatitis*

2.3.2. Clinical study

The MAH submitted a final report for study C3291037:

"Phase 3b/4 Study to Evaluate Efficacy and Safety of Crisaborole Ointment 2% in Paediatric and Adult Subjects (Ages 2 Years and Older) with Mild to Moderate Atopic Dermatitis"

Study Period:

Initiation date: 14 May 2018

Primary termination date: 11 December 2020

Trial completion: The study was terminated prematurely due to Sponsor business decision

Description

This was a Phase 3b/4, multicenter, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study of the efficacy, safety and local tolerability of crisaborole ointment, 2% in paediatric and adult participants (ages 2 years and older) with mild to moderate AD involving at least 5% treatable %BSA. Treatment was clinical assessor blinded for all treatment groups and double blinded for crisaborole ointment, 2% and vehicle treatment arm.

The study was designed to provide contextualization of the safety and efficacy of crisaborole compared with hydrocortisone butyrate cream, 0.1% (topical corticosteroid [TCS]) and pimecrolimus cream, 1% (topical calcineurin inhibitor [TCI]), the 2 prevalent treatment options for treatment of mild to moderate AD.

This study was originally designed to compare the treatment of crisaborole versus vehicle, and not powered to compare the treatment effect between crisaborole and TCS, as well as crisaborole and TCI.

Methods

Objective(s)

Primary Efficacy Objective:

- To compare the efficacy of crisaborole ointment, 2% applied BID versus vehicle in paediatric and adult subjects, aged 2 years and older, with mild to moderate AD.

Primary Safety Objectives:

- To evaluate the safety and local tolerability of crisaborole ointment 2% applied BID versus vehicle in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD.
- To evaluate the safety and local tolerability of hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD.

Secondary Objectives:

- To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle on additional efficacy endpoints over time in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD.
- To evaluate the efficacy of crisaborole ointment, 2% BID versus hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD.
- To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle, hydrocortisone butyrate cream 0.1% applied BID on patient/observer reported outcomes over time in paediatric and adult subjects (ages 2 years and older) with mild to moderate AD.

CHMP comment

The proposed clinical trial objectives are in general adequate to inform on (comparative) performance of IP compared to vehicle or active control. There was no planned formal hypothesis testing to establish whether crisaborole is superior to TCS or TCI, which was agreed in the latest PDCO discussion (EMEA-002065-PIP01-16-M01), but contextualization based on descriptive analyses was planned.

Study design

This was a Phase 3b/4, multicenter, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study of the efficacy, safety, and local tolerability of crisaborole ointment, 2% in paediatric and adult participants (ages 2 years and older) with mild to moderate AD involving at least 5% treatable %BSA evaluating crisaborole performance over the course of one treatment cycle (28 days). Treatment was clinical assessor blinded for all treatment groups and double blinded for crisaborole ointment, 2% and vehicle treatment arm.

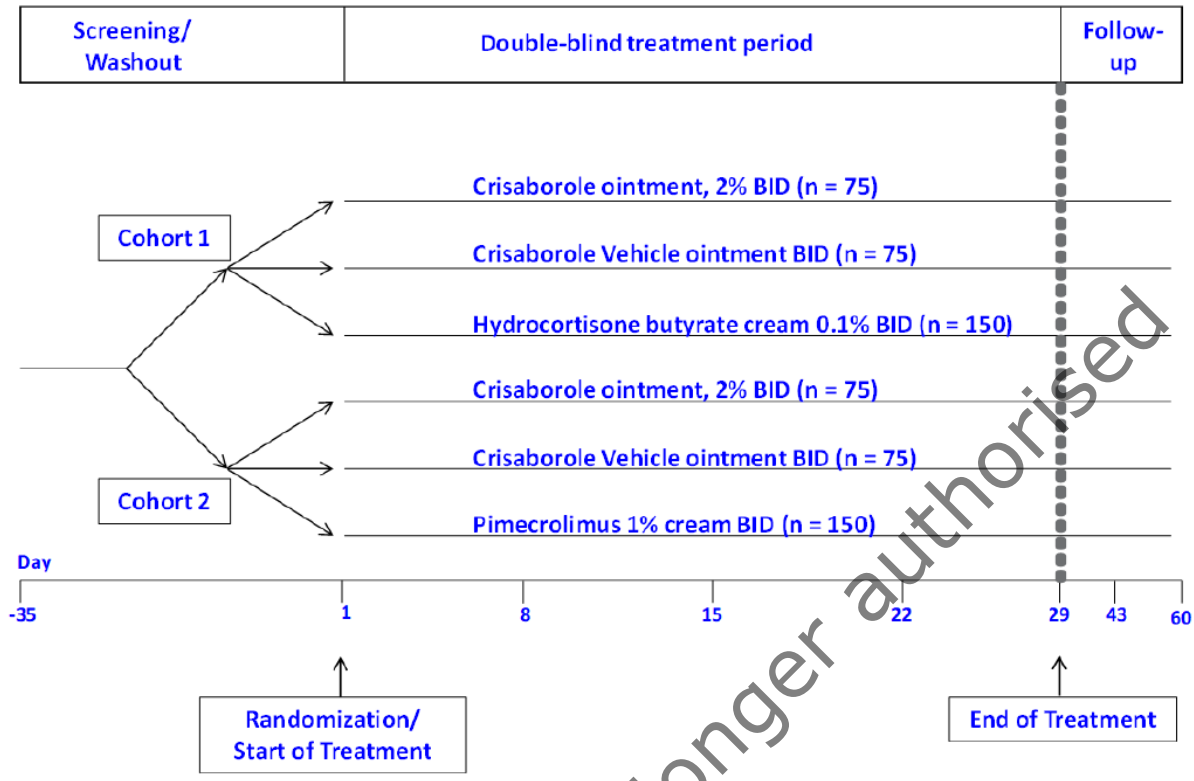
The study was designed to provide contextualization of the safety and efficacy of crisaborole compared with hydrocortisone butyrate cream, 0.1% (topical corticosteroid [TCS]) and pimecrolimus cream, 1% (topical calcineurin inhibitor [TCI]), the 2 prevalent treatment options for treatment of mild to moderate AD.

Following the screening period of up to 35 days, eligible participants were randomized (1:1:2) at Baseline/Day 1 visit to crisaborole 2%, vehicle, or active comparator (TCI or TCS). Randomization was stratified by eligibility for TCS or TCI treatment as per national approved labels. Cohort 1 included participants eligible for TCS therapy and Cohort 2 included participants not eligible for TCS therapy but eligible for TCI therapy.

Safety and efficacy assessments were conducted at the investigator site by a clinical assessor blinded to treatment assignment. Scheduled study visits were at Screening, Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (EoT/ ET), and Day 43 (or 14 Days after last dose for ET). A follow up visit was via telephone call on Day 60 (or ≥28 days after last dose for ET).

For the efficacy comparison of crisaborole versus vehicle, subjects from both Cohort 1 and Cohort 2 are included in the analysis, adjusted for cohort effect. For the efficacy comparison of crisaborole versus TCS, only subjects from Cohort 1 are included in the analysis. For the comparison of crisaborole versus TCI, only subjects from Cohort 2 are included in the analysis.

Figure 1: Design Schematic of Study C3291037



CHMP comment

The overall study design is appropriate to meet the objectives and in line with the PIP KBE (key binding elements). The proposed trial is a short time trial (one treatment cycle of 29 days) and does not inform on comparative performance during chronic treatment (which is likely in the concerned population).

As specified in the SAP (version 3), data from cohort 1 and 2 were pooled for the efficacy comparison of crisaborole versus vehicle. This is in line with the original SAP, which has been provided upon request.

Study population /Sample size

Originally, a total of 600 participants (including a maximum of N=90 adult patients) were planned to be included in the study: cohort 1 included participants eligible for TCS therapy and Cohort 2 included participants not eligible for TCS therapy but eligible for TCI therapy. Within each cohort 300 patients were planned to be randomized (1:1:2) to crisaborole 2%, vehicle, or active comparator.

Originally Planned Sample Size and Statistical Analyses

The sample size calculation was based on the comparison of crisaborole vs vehicle for the primary endpoint percent change in Eczema Area and Severity Index (EASI) from baseline to Day 29. The crisaborole and vehicle treatment arms of Cohort 1 and Cohort 2 were to be combined/pooled for the comparison of crisaborole vs vehicle analyses to achieve a statistically reliable sample size of 150 participants in each of the combined group. A sample size of 150 in each the crisaborole and vehicle groups would have provided 86% power to detect a 12% difference of EASI percent reduction from

baseline at Day 29 between crisaborole and vehicle at the 0.05 (2-sided) significance level, assuming the common standard deviation of EASI percent reduction from baseline at Day 29 is 34%.

The sample size of 75 in each of the crisaborole cohorts and the twice bigger sample size of 150 for each of the active comparator groups topical corticosteroid (hydrocortisone butyrate cream 0.1%; TCS) or topical calcineurin inhibitor (pimecrolimus cream 1%; TCI) would not have had sufficient power for the comparison of crisaborole vs TCS or TCI. With such a sample size, the half width of the 95% confidence interval for the difference of EASI percent reduction from baseline at Day 29 between crisaborole and either of the active comparators would have been 9.4%.

Key inclusion criteria:

- Age 2 years or older at the Screening visit/time of informed consent/assent.
- Clinical diagnosis of AD according to the criteria of Hanifin and Rajka.
- AD involvement of ≥5% Treatable %BSA (excluding the scalp) at Baseline/Day 1.
- ISGA score of Mild (2) or Moderate (3) (excluding the scalp) at Baseline/Day 1.
- Cohort specific inclusion criteria:
    - Cohort 1: Participants considered to be a candidate for hydrocortisone butyrate cream, 0.1% therapy according to the national approved labeling.
    - Cohort 2: Participants not considered candidates for treatment with a topical corticosteroid because it was either inadvisable or not appropriate according to the national approved labeling. This may have included: intolerance to or lack of effect of TCSs or use on the body regions where treatment with TCS may have been inappropriate.

Key exclusion criteria:

- Any clinically significant medical disorder, condition, or disease (including active or potentially recurrent non-AD dermatological conditions and known genetic dermatological conditions that overlap with AD, such as Netherton syndrome) or clinically significant physical examination finding that in the PI's or designee's opinion may interfere with study objectives.
- Unstable AD or a history of requirement for high/strong potency or very high/very strong potency topical corticosteroids to manage AD signs and symptoms.
- A significant active systemic or localized infection, including known actively infected AD.
- Cohort specific exclusion criteria:
    - Cohort 1: Has a contraindication for treatment with hydrocortisone butyrate cream 0.1% or meets warnings and precautions for use specifications in accordance with the national approved label or treatment with hydrocortisone butyrate cream, 0.1% is otherwise medically inadvisable.
    - Cohort 2: Has a contraindication for treatment with pimecrolimus cream, 1%, or meets warnings and precautions for use specifications in accordance with the national approved label or treatment with pimecrolimus cream, 1% is otherwise medically inadvisable.

CHMP comment

Study population

The key inclusion and exclusion criteria for patients with AD are considered appropriate to reflect the target population in the EU as they are comparable to previous studies conducted during the MAA of crisaborole in the EU. They also ensure a homogenous study population. Although a heterogeneous study population may increase external validity, a homogenous sample reduces variability, ensures comparability of the tested substances within the study, and may facilitate comparability to previous studies. For patient safety, randomization based on eligibility for TCS or TCI is considered appropriate.

Sample size

It was agreed in the PIP that a maximum of 90 adult patients (i.e. 15% of total n=600 patients), and at least 410 paediatric patients (68.3%) should be enrolled: 150 subjects from 2 to 6 years of age (25% of total), 140 subjects from 7 to less than 12 years of age (23.3% of total) and 120 subjects from 12 to less than 18 years of age (20% of total). Hence, a further 16.7% of total participants were presumably pre-specified to be potential paediatric patients <18 years of age, since the number of adult patients was limited to 90. Sample size planning was adequate to formally compare crisaborole vs vehicle. No formal comparison was planned for crisaborole vs active comparators, but as agreed in the latest PDCO discussion (EMEA-002065-PIP01-16-M01), contextualization of crisaborole was planned based on descriptive analyses.

Treatments

A thin layer of the IP was topically applied BID (12 ±4 hours apart) for 28 days to the treatable BSA (excluding the scalp) identified at Baseline/Day 1. The evening (PM) dose was to be applied approximately 8–16 hours after the morning (AM) dose. The tubes with IP were provided in cartons and labeled in a blinded fashion.

- Crisaborole ointment, 2% and vehicle ointment was supplied in 60 gram tubes
- Hydrocortisone butyrate cream, 0.1% was supplied in either 30 gram or 45 gram tubes
- Pimecrolimus cream, 1% was supplied in either 30 gram or 60 gram tubes

The IP was dispensed in a blinded fashion using an IRT system at each visit from Baseline/Day 1 to the Day 22 visit.

CHMP comment

The mode of application is sufficiently well defined to allow consistent dosing and is in line with the products' EU SmPC/PIL.

Blinding

Different tube presentations/fill sizes and physical properties of the creams and ointments pose a challenge for blinding. Steps to ensure blinding were taken: since the active comparator agents are sourced from other pharmaceutical companies and commercial availability of tube size varies by agent and region, a tamper-evident overwrap covering the entire body and crimp of the tube, was applied. Overwraps have also been used on the crisaborole tubes and the crisaborole vehicle tubes. Still, as these measures are likely not completely effective and physical properties of the creams and ointments do differ (active comparators), the treatment arms cannot be considered truly double-

blind. Only crisaborole and its corresponding vehicle will be double-blind relative to each other, since tube and product appearance are the same.

Outcomes/endpoints

Primary efficacy endpoint:

- Percent change from Baseline in the EASI total score at Day 29.

Primary safety endpoints:

- AEs, SAEs, local tolerability, discontinuations and clinically significant changes in vital signs and clinical laboratory parameters.

Secondary endpoints:

- Percent change from Baseline in EASI total score by scheduled time points except Day 29.
- Achievement of success in the ISGA (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline) by scheduled time points.
- Achievement of ISGA score of clear (0) or almost clear (1) by scheduled time points.
- Achievement of EASI75 (≥75% improvement from Baseline) by scheduled time points.
- Time to EASI75.
- Change from Baseline in % BSA by scheduled time points.
- Change from Baseline in Peak Pruritus NRS for subjects ≥12 years by scheduled time points.
- Change from Baseline in Patient Reported Itch Severity Scale - for subjects age 6-11 years by scheduled time points. Change from Baseline in Observer Reported Itch Severity Scale - for subjects <6 years by scheduled time points.
- Time to ≥2 point improvement from Baseline in Peak Pruritus NRS for subjects ≥12 years. Time to ≥3 point improvement from Baseline in Peak Pruritus NRS for subjects ≥12 years. Time to ≥2 point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects <6 years.
- Time to ≥3 point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects <6 years.
- Achievement of ≥2 point improvement from Baseline in Peak Pruritus NRS for subjects ≥12 years.
- Achievement of ≥3 point improvement from Baseline in Peak Pruritus NRS for subjects ≥12 years.
- Achievement of ≥2 point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects <6 years.
- Achievement of ≥3 point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects <6 years.
- Change from Baseline in DLQI (for Subjects 16 years and older), CDLQI (for Subjects 4-15 years), and DFI (Completed by parent/caregiver of Subjects 2-17 years) by scheduled time points.

CHMP comment

The planned primary and key secondary endpoints are acceptable and in line with KBE as agreed in the PIP.

Statistical Methods

The analysis sets were as follows:

- FAS: All randomized participants who receive ≥1 dose of the study drug.
- SAF: All participants who receive ≥1 dose of the study drug according to actual treatment received.

Efficacy endpoints

During the treatment period, descriptive statistics will be provided for observed percent change from baseline in EASI at Days 8, 15, 22, and 29. During follow-up, descriptive statistics will be provided for observed percent change from Day 29 to Day 43 in EASI.

Achievement of success in the ISGA (defined as an ISGA score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline) at Days 8, 15, 22, and 29 will be summarized. Achievement of ISGA of clear (0) or almost clear (1) at Days 8, 15, 22, and 29 will be summarized. Missing data will be classified as non-responder.

Achievement of EASI75 at Days 8, 15, 22, and 29 will be summarized. Missing data will be classified as non-responder. Time to event endpoints will be summarized using the KM method and estimated survival curves will be provided for time to EASI75. The median, quartiles, 95% CI for median and quartiles be estimated by the KM method.

Descriptive statistics will be provided for observed change from baseline in %BSA.

For peak pruritus NRS/Scale, weekly average score will be used in the analyses of change from baseline. Observed change from baseline in weekly average peak pruritus NRS/Scale at Days 8 (Week 1 average of Days 2-8), 15 (Week 2 average of Days 9-15), 22 (Week 3 average of Days 16-22), and 29 (Week 4 average of Days 23-29) for subjects ≥12 years will be summarized.

Achievement of ≥2-point and ≥3-point improvement from baseline in weekly average peak pruritus NRS at Days 8 (Week 1 average of Days 2-8), 15 (Week 2 average of Days 9-15), 22 (Week 3 average of Days 16-22), and 29 (Week 4 average of Days 23-29) will be summarized for subjects ≥12 years. Missing data will be classified as non-responder.

The Applicant specified in the SAP (version 3) that, due to low enrolment, Patient and Observer Reported Itch Severity Scale will not be summarized.

Descriptive statistics will be provided for observed change from baseline in DLQI for subjects ≥16 years, in CDLQI for subjects 4-15 years, and in DFI completed by parent/caregiver of subjects 2-17 years.

Safety Summaries

Safety analysis will be based on the SAF.

Safety data will be presented in tabular format and summarized descriptively, where appropriate. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous

outcome (eg, blood pressure, pulse rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly. Cohort 1 and cohort 2 will be combined for crisaborole and vehicle arms for all safety summaries and analyses.

Adverse Events

All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Local tolerability AEs/SAEs;
- Withdrawals from treatment/study due to AEs.

Laboratory Data

Laboratory data will be listed and summarized.

Vital Signs

Vital signs will be summarized at baseline, Day 29/End of treatment/Early termination visits.

Physical Examination

Physical examinations will be summarized at baseline, Day 29/End of treatment/Early termination visits.

CHMP comment

Initial plans for methodological approaches, endpoint analyses or pooling plans were provided upon request and are in line with the PIP. However, no valid justification is provided why Patient and Observer Reported Itch Severity Scale were not summarized.

Results

Recruitment/ Number analysed

Due to early study termination, less than 40% of planned participants were treated across the 4 treatment groups: A total of 235 participants were treated across 4 study treatment treatment groups, instead of originally planned 600 participants (39.2% of planned enrollment). The 2 populations defined in the SAP were FAS and SAF; both populations had 235 participants.

Disposition Events

Summary of disposition events during the treatment phase and follow-up phase is presented in Table 1 and Table 2.

Table 1: Disposition Events Summary (SAF)

	Vehicle (N=59)	Crisaborole 2% BID (N=58)			Hydrocortisone Butyrate 0.1% BID (N=71)	Pimecrolimus 1% BID (N=47)	Total (N=235)
		Cohort 1 (N=37)	Cohort 2 (N=21)	Total (N=58)			
Number (%) of Subjects	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Disposition Phase: Treatment							
Discontinued	12 (20.3)	6 (16.2)	1 (4.8)	7 (12.1)	5 (7.0)	4 (8.5)	28 (11.9)
Adverse Event	6 (10.2)	2 (5.4)	1 (4.8)	3 (5.2)	0	2 (4.3)	11 (4.7)
Lack of Efficacy	2 (3.4)	0	0	0	1 (1.4)	0	3 (1.3)
Lost to Follow-Up	2 (3.4)	3 (8.1)	0	3 (5.2)	3 (4.2)	0	8 (3.4)
Withdrawal By Subject	0	0	0	0	1 (1.4)	2 (4.3)	3 (1.3)
Withdrawal By Parent/Guardian	1 (1.7)	1 (2.7)	0	1 (1.7)	0	0	2 (0.9)
Other	1 (1.7)	0	0	0	0	0	1 (0.4)
Completed	47 (79.7)	31 (83.8)	20 (95.2)	51 (87.9)	66 (93.0)	43 (91.5)	207 (88.1)
Disposition Phase: Follow-Up							
Discontinued	5 (8.5)	5 (13.5)	1 (4.8)	6 (10.3)	6 (8.5)	1 (2.1)	18 (7.7)
Adverse Event	0	1 (2.7)	1 (4.8)	2 (3.4)	0	0	2 (0.9)
Lack of Efficacy	0	0	0	0	0	0	0
Lost to Follow-Up	2 (3.4)	4 (10.8)	0	4 (6.9)	5 (7.0)	0	11 (4.7)
Withdrawal By Subject	2 (3.4)	0	0	0	0	1 (2.1)	3 (1.3)
Withdrawal By Parent/Guardian	1 (1.7)	0	0	0	1 (1.4)	0	2 (0.9)
Other	0	0	0	0	0	0	0
Completed	54 (91.5)	32 (86.5)	20 (95.2)	52 (89.7)	65 (91.5)	46 (97.9)	217 (92.3)

Table 2: Disposition Events Summary (Subjects 2-17 Years) (SAF)

	Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)	Total (N=144)
		Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)			
Number (%) of Subjects	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Disposition Phase: Treatment							
Discontinued	00007 (018.4)	00004 (017.4)	00001 (007.1)	00005 (013.5)	00002 (005.1)	00001 (003.3)	00015 (010.4)
Adverse Event	00005 (013.2)	00002 (008.7)	00001 (007.1)	00003 (008.1)	00000 (000.0)	00001 (003.3)	00009 (006.3)
Lack of Efficacy	00001 (002.6)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (002.6)	00000 (000.0)	00002 (001.4)
Lost to Follow-Up	00000 (000.0)	00001 (004.3)	00000 (000.0)	00001 (002.7)	00001 (002.6)	00000 (000.0)	00002 (001.4)
Withdrawal By Parent/Guardian	00001 (002.6)	00001 (004.3)	00000 (000.0)	00001 (002.7)	00000 (000.0)	00000 (000.0)	00002 (001.4)
Completed	00031 (081.6)	00019 (082.6)	00013 (092.9)	00032 (086.5)	00037 (094.9)	00029 (096.7)	00129 (089.6)
Disposition Phase: Follow-Up							
Discontinued	00001 (002.6)	00002 (008.7)	00001 (007.1)	00003 (008.1)	00002 (005.1)	00000 (000.0)	00006 (004.2)
Adverse Event	00000 (000.0)	00001 (004.3)	00001 (007.1)	00002 (005.4)	00000 (000.0)	00000 (000.0)	00002 (001.4)
Lack of Efficacy	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Lost to Follow-Up	00000 (000.0)	00001 (004.3)	00000 (000.0)	00001 (002.7)	00001 (002.6)	00000 (000.0)	00002 (001.4)
Withdrawal By Parent/Guardian	00001 (002.6)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (002.6)	00000 (000.0)	00002 (001.4)
Completed	00037 (097.4)	00021 (091.3)	00013 (092.9)	00034 (091.9)	00037 (094.9)	00030 (100.0)	00138 (095.8)

Treatment Exposure and Compliance

The mean duration of treatment and total number of treatment applications were similar between treatment groups for all participants.

Age subgroups of 2-17 years and ≥18 years did not show any notable differences for duration of treatment and total number of treatment applications. Treatment compliance was lowest (68.4%) in the vehicle group for the age subgroup of 2-17 years (Table 3).

Table 3: Treatment Exposure and Compliance (Subjects 2-17 Years) (SAF)

	Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
		Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)		
Duration of Treatment [1]						
n	38	23	14	37	39	30
Mean	26.1	26.9	27.9	27.3	28.3	28.9
Std. Dev.	8.62	6.17	5.00	5.71	3.72	4.16
Median	29.0	29.0	29.0	29.0	29.0	29.0
Range (Min,Max)	(2, 43)	(7, 33)	(11, 32)	(7, 33)	(8, 33)	(13, 43)
Total Number of Applications [2]						
n	38	23	14	37	39	30
Mean	48.7	49.2	55.1	51.4	53.7	55.9
Std. Dev.	18.15	14.95	11.77	13.97	9.26	9.12
Median	56.0	55.0	58.0	57.0	56.0	57.5
Range (Min,Max)	(4, 86)	(14, 63)	(15, 64)	(14, 64)	(16, 66)	(26, 86)
Total Volume Administered (g)[3]						
n	38	23	14	37	38	30
Mean	140.01	155.05	148.19	152.45	125.47	190.87
Std. Dev.	182.732	211.738	149.618	188.396	96.739	240.612
Median	73.55	68.50	109.30	87.55	104.99	100.65
Range (Min,Max)	(10.2, 1009.4)	(6.3, 841.7)	(3.3, 593.1)	(3.3, 841.7)	(16.3, 437.3)	(7.4, 1243.1)
Number and Percentage of Subjects Compliant [4]						
No	00012 (031.6)	00006 (026.1)	00001 (007.1)	00007 (018.9)	00005 (012.8)	00003 (010.0)
Yes	00026 (068.4)	00017 (073.9)	00013 (092.9)	00030 (081.1)	00034 (087.2)	00027 (090.0)

Table 4: Treatment Exposure and Compliance (Subjects ≥18 Years) (SAF)

	Vehicle (N=21)	Crisaborole 2% BID (N=21)			Hydrocortisone Butyrate 0.1% BID (N=32)	Pimecrolimus 1% BID (N=17)
		Cohort 1 (N=14)	Cohort 2 (N=7)	Total (N=21)		
Duration of Treatment [1]						
n	21	14	7	21	32	17
Mean	26.6	26.8	28.4	27.3	28.6	25.1
Std. Dev.	5.79	6.86	0.98	5.62	5.84	9.53
Median	28.0	29.0	28.0	29.0	29.0	29.0
Range (Min,Max)	(8, 33)	(9, 32)	(27, 30)	(9, 32)	(9, 37)	(1, 34)
Total Number of Applications [2]						
n	21	14	7	21	32	17
Mean	50.8	53.2	56.0	54.1	55.8	47.1
Std. Dev.	11.57	13.56	2.31	11.09	11.60	19.58
Median	56.0	58.0	56.0	58.0	58.0	56.0
Range (Min,Max)	(15, 66)	(18, 63)	(52, 58)	(18, 63)	(18, 70)	(2, 68)
Total Volume Administered (g)[3]						
n	21	12	7	19	31	17
Mean	260.04	216.02	112.26	177.79	211.39	146.04
Std. Dev.	323.219	118.345	106.591	122.436	161.993	155.824
Median	147.30	192.35	59.00	181.50	185.80	104.90
Range (Min,Max)	(22.1, 1231.5)	(15.8, 413.4)	(3.9, 263.1)	(3.9, 413.4)	(23.9, 814.1)	(2.8, 589.0)
Number and Percentage of Subjects Compliant [4]						
No	00004 (019.0)	00002 (014.3)	00000 (000.0)	00002 (009.5)	00007 (021.9)	00005 (029.4)
Yes	00017 (081.0)	00012 (085.7)	00007 (100.0)	00019 (090.5)	00025 (078.1)	00012 (070.6)

CHMP comment

Number of participants per treatment group were balanced within the paediatric cohort. Adult patients receiving TCS were overrepresented, but this is not the main focus of the current procedure. Duration of treatment and number of applications were similar across treatment groups and there were no differences in the adult and paediatric populations. Some trends were observed: Compliance was higher in the crisaborole group compared to vehicle, and higher in adults compared to the paediatric group. Of note, in the paediatric subset compliance was higher in the active comparator groups (TCI and TCS) compared to crisaborole. In contrast, in the adult subset compliance was lower in the active comparator groups (TCI and TCS) compared to crisaborole and vehicle.

As can be expected, total volume administered was higher in the adult study population (larger BSA).

Most referred tables are displayed in a non-intuitive and somewhat confusing way, possibly due to an error during the data export process. It is assumed that data integrity is not compromised. Yet, more comprehensive tables, in particular for paediatric subsets, would be easier to follow.

It is noted that in the provided results tables only one vehicle group is displayed (the two cohorts were pooled). While it is not completely comprehensible whether this was pre-specified, the decision is understood and can be endorsed for the descriptive analyses.

Protocol Deviations

The 3 most common categories for IPDs are as follows:

- Approximately 29.8% of participants in the category of investigational product, of which "Compliance for the active treatment period is less than 80 percent or more than 120 percent" was reported the most frequently (20.9% of SAF).
- Approximately 24.3% of participants in the category of visit schedule of which "Visit performed but not per protocol/outside protocol window" was reported the most frequently (15.7% of SAF).
- Approximately 17.4% of participants in the category of informed consent of which "Informed Consent Document and/or Assent were not properly signed and/or dated and/or completed at Screening Visit" was reported most frequently (14.5% of SAF).

CHMP comment

Listed protocol deviations are not likely to alter study conclusions, since they occurred in all treatment arms (from Study Report Body: Table 16.2.2.1: Listing of Important Protocol Deviations).

Baseline data

Baseline demographic characteristics in the SAF were generally balanced across treatment groups (Table 5).

Table 5: Overall Demographic and Baseline Characteristics (SAF)

	Vehicle (N=59)	Crisaborole 2% BID (N=58)			Hydrocortisone Butyrate 0.1% BID (N=71)	Pimecrolimus 1% BID (N=47)	Total (N=235)
		Cohort 1 (N=37)	Cohort 2 (N=21)	Total (N=58)			
Age (Years):							
2-6	00014 (023.7%)	00010 (027.0%)	00005 (023.8%)	00015 (025.9%)	00016 (022.5%)	00011 (023.4%)	00056 (023.8%)
7-11	00012 (020.3%)	00005 (013.5%)	00005 (023.8%)	00010 (017.2%)	00010 (014.1%)	00008 (017.0%)	00040 (017.0%)
12-17	00012 (020.3%)	00008 (021.6%)	00004 (019.0%)	00012 (020.7%)	00013 (018.3%)	00011 (023.4%)	00048 (020.4%)
>=18	00021 (035.6%)	00014 (037.8%)	00007 (033.3%)	00021 (036.2%)	00032 (045.1%)	00017 (036.2%)	00091 (038.7%)
n	59	37	21	58	71	47	235
Mean	19.8	22.0	20.7	21.5	19.6	21.1	20.4
Std. Dev.	18.22	19.81	18.29	19.12	16.28	18.20	17.79
Median	13.0	15.0	15.0	15.0	14.0	15.0	14.0
Range (Min,Max)	(2, 65)	(2, 78)	(2, 67)	(2, 78)	(2, 71)	(2, 72)	(2, 78)
Gender:							
Male	00024 (040.7%)	00013 (035.1%)	00010 (047.6%)	00023 (039.7%)	00028 (039.4%)	00021 (044.7%)	00096 (040.9%)
Female	00035 (059.3%)	00024 (064.9%)	00011 (052.4%)	00035 (060.3%)	00043 (060.6%)	00026 (055.3%)	00139 (059.1%)
Race:							
White	00038 (064.4%)	00023 (062.2%)	00015 (071.4%)	00038 (065.5%)	00044 (062.0%)	00037 (078.7%)	00157 (066.8%)
Black or African American	00017 (028.8%)	00012 (032.4%)	00002 (009.5%)	00014 (024.1%)	00023 (032.4%)	00006 (012.8%)	00060 (025.5%)
Asian	00002 (003.4%)	00001 (002.7%)	00002 (009.5%)	00003 (005.2%)	00001 (001.4%)	00003 (006.4%)	00009 (003.8%)

Native Hawaiian or Other Pacific Islander	00001 (001.7%)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (000.4%)
Multiracial	00001 (001.7%)	00001 (002.7%)	00002 (009.5%)	00003 (005.2%)	00001 (001.4%)	00000 (000.0)	00005 (002.1%)
Not Reported	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00002 (002.8%)	00001 (002.1%)	00003 (001.3%)
Ethnicity:							
Hispanic or Latino	00006 (010.2%)	00001 (002.7%)	00000 (000.0)	00001 (001.7%)	00011 (015.5%)	00004 (008.5%)	00022 (009.4%)
Not Hispanic or Latino	00053 (089.8%)	00036 (097.3%)	00021 (100.0%)	00057 (098.3%)	00060 (084.5%)	00043 (091.5%)	00213 (090.6%)
Height (cm):							
n	59	37	21	58	71	47	235
Mean	142.63	144.22	145.91	144.83	146.07	148.55	145.40
Std. Dev.	29.007	29.082	27.572	28.312	29.013	28.700	28.665
Median	148.80	154.94	157.50	154.94	157.48	159.00	154.94
Range (Min,Max)	(82.6, 200.0)	(85.6, 182.9)	(91.5, 179.0)	(85.6, 182.9)	(87.6, 182.0)	(84.0, 190.0)	(82.6, 200.0)
Weight (kg):							
n	59	37	21	58	71	47	235
Mean	48.86	57.00	53.33	55.67	58.59	54.61	54.63
Std. Dev.	27.976	36.629	34.393	35.575	35.932	29.585	32.772
Median	45.30	55.00	43.50	51.70	54.00	58.90	52.50
Range (Min,Max)	(10.0, 126.6)	(13.6, 146.5)	(14.8, 121.2)	(13.6, 146.5)	(12.5, 146.6)	(12.7, 112.9)	(10.0, 146.6)
Body Mass Index (kg/m**2):							
n	59	37	21	58	71	47	235
Mean	21.72	24.59	22.41	23.80	24.66	22.37	23.25
Std. Dev.	7.475	10.613	8.394	9.848	9.242	6.427	8.519
Median	20.16	21.56	18.60	20.37	21.46	21.57	21.08
Range (Min,Max)	(12.9, 53.0)	(12.3, 63.1)	(13.7, 44.5)	(12.3, 63.1)	(13.9, 46.5)	(14.4, 36.8)	(12.3, 63.1)
Duration of Dermatitis Atopic (Years):							
n	59	37	21	58	71	47	235
Mean	11.74	13.89	16.93	15.00	12.12	13.32	12.97
Std. Dev.	11.968	15.124	15.048	15.036	11.796	13.218	12.969
Median	7.54	7.42	11.06	9.12	9.22	9.44	8.78
Range (Min,Max)	(0.4, 50.1)	(0.1, 60.9)	(0.3, 48.6)	(0.1, 60.9)	(0.0, 45.7)	(0.7, 57.5)	(0.0, 60.9)
Prior TCS/TCI Treatment:							
Yes	00019 (032.2%)	00011 (029.7%)	00011 (052.4%)	00022 (037.9%)	00020 (028.2%)	00028 (059.6%)	00089 (037.9%)
No	00040 (067.8%)	00026 (070.3%)	00010 (047.6%)	00036 (062.1%)	00051 (071.8%)	00019 (040.4%)	00146 (062.1%)
Prior Medications for AD:							
Yes	00028 (047.5%)	00017 (045.9%)	00017 (081.0%)	00034 (058.6%)	00036 (050.7%)	00034 (072.3%)	00132 (056.2%)
No	00031 (052.5%)	00020 (054.1%)	00004 (019.0%)	00024 (041.4%)	00035 (049.3%)	00013 (027.7%)	00103 (043.8%)
Geographic Region:							
US	00038 (064.4%)	00029 (078.4%)	00009 (042.9%)	00038 (065.5%)	00056 (078.9%)	00019 (040.4%)	00151 (064.3%)
European Countries	00021 (035.6%)	00008 (021.6%)	00012 (057.1%)	00020 (034.5%)	00015 (021.1%)	00028 (059.6%)	00084 (035.7%)
[redacted]							
Investigator's Static Global Assessment (ISGA):							
(2) MILD	00020 (033.9%)	00014 (037.8%)	00007 (033.3%)	00021 (036.2%)	00033 (046.5%)	00024 (051.1%)	00098 (041.7%)
(3) MODERATE	00039 (066.1%)	00023 (062.2%)	00014 (066.7%)	00037 (063.8%)	00038 (053.5%)	00023 (048.9%)	00137 (058.3%)

n	59	37	21	58	71	47	235
Mean	2.7	2.6	2.7	2.6	2.5	2.5	2.6
Std. Dev.	0.48	0.49	0.48	0.48	0.50	0.51	0.49
Median	3.0	3.0	3.0	3.0	3.0	2.0	3.0
Range (Min,Max)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)
Eczema Area and Severity Index (EASI) Total Score:							
n	59	37	21	58	70	47	234
Mean	11.20	9.19	10.60	9.70	8.67	9.47	9.73
Std. Dev.	8.195	5.471	7.526	6.264	5.924	5.832	6.657
Median	10.20	8.20	8.80	8.50	7.00	8.30	8.00
Range (Min,Max)	(2.0, 43.6)	(2.0, 25.1)	(1.6, 26.0)	(1.6, 26.0)	(1.2, 30.4)	(1.4, 28.0)	(1.2, 43.6)
Percent Body Surface Area (%BSA):							
n	59	37	21	58	70	47	234
Mean	17.36	15.59	17.78	16.38	14.18	13.81	15.45
Std. Dev.	14.907	11.801	17.815	14.158	12.090	15.008	13.938
Median	11.00	12.00	10.00	10.90	9.85	8.00	10.00
Range (Min,Max)	(5.0, 65.0)	(3.0, 60.0)	(2.5, 71.0)	(2.5, 71.0)	(5.0, 64.0)	(5.0, 77.0)	(2.5, 77.0)
Peak Pruritus NRS - subjects >=12 years:							
n	33	22	11	33	44	27	137
Mean	5.67	5.62	4.53	5.26	6.00	6.07	5.76
Std. Dev.	2.333	2.399	1.906	2.278	2.244	1.980	2.223
Median	5.57	5.86	4.29	5.33	6.07	6.00	5.86
Range (Min,Max)	(1.0, 9.7)	(2.3, 10.0)	(1.1, 8.0)	(1.1, 10.0)	(0.0, 10.0)	(1.9, 10.0)	(0.0, 10.0)
Dermatology Life Quality Index (DLQI):							
n	22	17	7	24	31	20	97
Mean	8.5	8.4	5.4	7.5	9.1	10.2	8.8
Std. Dev.	4.89	5.29	3.69	4.99	5.92	6.80	5.67
Median	8.0	8.0	6.0	6.5	7.0	9.5	8.0
Range (Min,Max)	(1, 18)	(1, 17)	(1, 11)	(1, 17)	(1, 24)	(2, 26)	(1, 26)
Children's Dermatology Life Quality Index (CDLQI):							
n	27	14	12	26	30	17	100
Mean	7.6	7.9	9.8	8.8	8.2	7.3	8.0
Std. Dev.	4.47	3.65	4.00	3.85	5.96	5.08	4.89
Median	6.0	7.0	9.5	8.5	7.0	7.0	7.0
Range (Min,Max)	(2, 19)	(2, 15)	(4, 16)	(2, 16)	(1, 25)	(1, 17)	(1, 25)
Dermatitis Family Impact (DFI):							
n	38	23	13	36	38	30	142
Mean	6.8	6.4	6.3	6.4	8.0	8.2	7.3
Std. Dev.	6.98	4.79	5.30	4.91	6.27	6.15	6.12
Median	4.0	5.0	5.0	5.0	6.0	7.5	6.0
Range (Min,Max)	(0, 30)	(0, 21)	(0, 15)	(0, 21)	(0, 23)	(0, 24)	(0, 30)

The age subgroup of 2-17 years had a total of 144 participants in SAF and FAS, the age subgroup of ≥ 18 years had a total of 91 participants in SAF and FAS.

Within the age subgroups of 2-17 years (Table 6) and ≥18 years, baseline demographic characteristics were generally balanced across treatment groups.

Table 6: Demographic and Baseline Characteristics (Subjects 2-17 Years) (SAF)

	Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)	Total (N=144)
		Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)			
Age (Years):							
2-6	00014 (036.8%)	00010 (043.5%)	00005 (035.7%)	00015 (040.5%)	00016 (041.0%)	00011 (036.7%)	00056 (038.9%)
7-11	00012 (031.6%)	00005 (021.7%)	00005 (035.7%)	00010 (027.0%)	00010 (025.6%)	00008 (026.7%)	00040 (027.8%)
12-17	00012 (031.6%)	00008 (034.8%)	00004 (028.6%)	00012 (032.4%)	00013 (033.3%)	00011 (036.7%)	00048 (033.3%)
>=18	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
n	38	23	14	37	39	30	144
Mean	8.3	8.8	9.1	8.9	8.1	9.5	8.7
Std. Dev.	4.66	5.37	4.57	5.01	4.45	5.15	4.78
Median	8.0	7.0	8.5	8.0	9.0	9.5	8.5
Range (Min,Max)	(2, 17)	(2, 17)	(2, 16)	(2, 17)	(2, 15)	(2, 17)	(2, 17)
Gender:							
Male	00018 (047.4%)	00009 (039.1%)	00006 (042.9%)	00015 (040.5%)	00020 (051.3%)	00013 (043.3%)	00066 (045.8%)
Female	00020 (052.6%)	00014 (060.9%)	00008 (057.1%)	00022 (059.5%)	00019 (048.7%)	00017 (056.7%)	00078 (054.2%)
Race:							
White	00027 (071.1%)	00019 (082.6%)	00011 (078.6%)	00030 (081.1%)	00030 (076.9%)	00025 (083.3%)	00112 (077.8%)
Black or African American	00007 (018.4%)	00004 (017.4%)	00000 (000.0)	00004 (010.8%)	00009 (023.1%)	00003 (010.0%)	00023 (016.0%)
Asian	00002 (005.3%)	00000 (000.0)	00001 (007.1%)	00001 (002.7%)	00000 (000.0)	00001 (003.3%)	00004 (002.8%)
Native Hawaiian or Other Pacific Islander	00001 (002.6%)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (000.7%)
Multiracial	00001 (002.6%)	00000 (000.0)	00002 (014.3%)	00002 (005.4%)	00000 (000.0)	00000 (000.0)	00003 (002.1%)
Not Reported	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (003.3%)	00001 (000.7%)
Ethnicity:							
Hispanic or Latino	00005 (013.2%)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00007 (017.9%)	00003 (010.0%)	00015 (010.4%)
Not Hispanic or Latino	00033 (086.8%)	00023 (100.0%)	00014 (100.0%)	00037 (100.0%)	00032 (082.1%)	00027 (090.0%)	00129 (089.6%)
Height (cm):							
n	38	23	14	37	39	30	144
Mean	129.29	130.80	134.10	132.05	128.89	136.72	131.44
Std. Dev.	26.908	28.860	26.414	27.633	28.624	28.943	27.859
Median	133.50	132.10	134.00	131.00	137.00	135.50	132.60
Range (Min,Max)	(82.6, 178.0)	(85.6, 182.9)	(91.5, 179.0)	(85.6, 182.9)	(87.6, 170.2)	(84.0, 176.0)	(82.6, 182.9)
Weight (kg):							
n	38	23	14	37	39	30	144
Mean	32.97	37.52	33.49	36.00	33.87	40.15	35.49
Std. Dev.	17.953	24.311	16.915	21.643	18.139	23.965	20.304
Median	31.05	29.50	27.05	27.20	30.80	34.25	30.40
Range (Min,Max)	(10.0, 70.0)	(13.6, 113.4)	(14.8, 73.4)	(13.6, 113.4)	(12.5, 83.9)	(12.7, 107.5)	(10.0, 113.4)
Body Mass Index (kg/m**2):							
n	38	23	14	37	39	30	144
Mean	18.07	20.04	17.54	19.09	19.00	19.39	18.86
Std. Dev.	3.792	7.370	2.248	6.045	4.333	4.980	4.815
Median	17.03	18.31	17.72	17.75	18.16	17.67	17.71
Range (Min,Max)	(12.9, 26.0)	(12.3, 48.8)	(13.7, 22.9)	(12.3, 48.8)	(13.9, 34.9)	(14.4, 35.0)	(12.3, 48.8)
Duration of Dermatitis Atopic (Years):							
n	38	23	14	37	39	30	144
Mean	6.92	6.41	7.71	6.90	6.06	7.75	6.86
Std. Dev.	5.035	5.255	4.687	5.021	4.647	4.919	4.888
Median	5.37	3.75	7.01	4.89	4.33	6.54	5.25
Range (Min,Max)	(0.4, 17.0)	(1.2, 18.1)	(0.3, 15.6)	(0.3, 18.1)	(0.0, 14.9)	(1.4, 17.0)	(0.0, 18.1)
Prior TCS/TCI Treatment:							
Yes	00014 (036.8%)	00005 (021.7%)	00009 (064.3%)	00014 (037.8%)	00008 (020.5%)	00016 (053.3%)	00052 (036.1%)
No	00024 (063.2%)	00018 (078.3%)	00005 (035.7%)	00023 (062.2%)	00031 (079.5%)	00014 (046.7%)	00092 (063.9%)

Prior Medications for AD:							
Yes	00019 (050.0%)	00008 (034.8%)	00011 (078.6%)	00019 (051.4%)	00013 (033.3%)	00022 (073.3%)	00073 (050.7%)
No	00019 (050.0%)	00015 (065.2%)	00003 (021.4%)	00018 (048.6%)	00026 (066.7%)	00008 (026.7%)	00071 (049.3%)
Geographic Region:							
US	00023 (060.5%)	00017 (073.9%)	00005 (035.7%)	00022 (059.5%)	00030 (076.9%)	00010 (033.3%)	00085 (059.0%)
European Countries	00015 (039.5%)	00006 (026.1%)	00009 (064.3%)	00015 (040.5%)	00009 (023.1%)	00020 (066.7%)	00059 (041.0%)
[redacted]							
Investigator's Static Global Assessment (ISGA):							
(2) MILD	00014 (036.8%)	00008 (034.8%)	00006 (042.9%)	00014 (037.8%)	00018 (046.2%)	00015 (050.0%)	00006 (042.9%)
(3) MODERATE	00024 (063.2%)	00015 (065.2%)	00008 (057.1%)	00023 (062.2%)	00021 (053.8%)	00015 (050.0%)	00088 (057.6%)
n	38	23	14	37	39	30	144

Mean	2.6	2.7	2.6	2.6	2.5	2.5	2.6
Std. Dev.	0.49	0.49	0.51	0.49	0.51	0.51	0.50
Median	3.0	3.0	3.0	3.0	3.0	2.5	3.0
Range (Min,Max)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)	(2, 3)
Eczema Area and Severity Index (EASI) Total Score:							
n	38	23	14	37	38	30	143
Mean	11.57	8.63	10.90	9.49	9.51	9.89	10.13
Std. Dev.	9.073	5.526	8.799	6.918	6.527	5.983	7.264
Median	9.10	7.40	8.10	7.40	8.10	9.05	8.20
Range (Min,Max)	(2.8, 43.6)	(2.0, 22.8)	(1.6, 26.0)	(1.6, 26.0)	(1.2, 26.0)	(1.4, 28.0)	(1.2, 43.6)
Percent Body Surface Area (%BSA):							
n	38	23	14	37	38	30	143
Mean	18.19	16.04	20.52	17.74	16.05	15.11	16.86
Std. Dev.	16.493	12.297	20.710	15.879	14.073	17.676	15.865
Median	10.00	14.00	10.25	12.00	9.75	9.00	10.00
Range (Min,Max)	(5.0, 65.0)	(5.0, 60.0)	(2.5, 71.0)	(2.5, 71.0)	(5.0, 64.0)	(5.0, 77.0)	(2.5, 77.0)
Peak Pruritus NRS - subjects >=12 years:							
n	12	8	4	12	12	10	46
Mean	4.77	4.67	3.57	4.31	5.30	5.86	5.02
Std. Dev.	2.187	2.013	0.617	1.725	2.355	2.006	2.095
Median	4.79	3.75	3.43	3.54	5.32	6.00	4.92
Range (Min,Max)	(1.0, 7.7)	(2.6, 8.0)	(3.0, 4.4)	(2.6, 8.0)	(0.0, 8.7)	(3.2, 8.7)	(0.0, 8.7)
Dermatology Life Quality Index (DLQI):							
n	1	4	0	4	0	4	9
Mean	5.0	4.5	-	4.5	-	7.0	5.7
Std. Dev.	-	3.11	-	3.11	-	6.00	4.33
Median	5.0	4.5	-	4.5	-	6.0	5.0
Range (Min,Max)	(5, 5)	(1, 8)	-	(1, 8)	-	(2, 14)	(1, 14)
Children's Dermatology Life Quality Index (CDLQI):							
n	27	14	12	26	30	17	100
Mean	7.6	7.9	9.8	8.8	8.2	7.3	8.0
Std. Dev.	4.47	3.65	4.00	3.85	5.96	5.08	4.89
Median	6.0	7.0	9.5	8.5	7.0	7.0	7.0
Range (Min,Max)	(2, 19)	(2, 15)	(4, 16)	(2, 16)	(1, 25)	(1, 17)	(1, 25)
Dermatitis Family Impact (DFI):							
n	38	23	13	36	38	30	142
Mean	6.8	6.4	6.3	6.4	8.0	8.2	7.3
Std. Dev.	6.98	4.79	5.30	4.91	6.27	6.15	6.12
Median	4.0	5.0	5.0	5.0	6.0	7.5	6.0
Range (Min,Max)	(0, 30)	(0, 21)	(0, 15)	(0, 21)	(0, 23)	(0, 24)	(0, 30)

Baseline Disease Characteristics

- Median duration of AD: 8.78 years (range across groups: 7.54 years to 9.44 years)
- Received prior TCS/TCI treatment: 37.9% (range across groups: 28.2% to 59.6%) participants had received prior TCS/TCI treatment. TCS group had the least and TCI had the most proportion of participants with prior TCS/TCI treatment
- ISGA: Baseline AD was assessed as moderate in 58.3% (range across groups: 48.9% to 66.1%) and mild in 41.7% (range across groups: 33.9% to 51.1%) of the participants. Mean ISGA score was 2.6 (range across groups: 2.5 to 2.7).
- Median EASI total score was 8.00; (range across groups: 7.0 to 10.20)
- Median %BSA affected was 10.0 (range across groups: 8.0 to 11.0)
- Median Peak Pruritis NRS (for age ≥12 years) score was 5.86 (range across groups: 5.33 to 6.07)
- Median DLQI (for age ≥16 years) score was 8.0 (range across groups: 6.5 to 9.5)
- Median CDLQI (for age 4-15 years) score was 7.0 (range across groups: 6.0 to 8.5)
- Median DFI (for 2-17 years) score was 6.0 (range across groups: 4.0 to 7.5)

Within the age subgroups of 2-17 years and ≥18 years, baseline disease characteristics were generally balanced across treatment groups.

CHMP comment

For this procedure, results from the population <18 years of age (and potential differences to the adult population) are of interest. Apart from expected differences (height, weight, BMI, duration of AD and AD history/treatments), there were no major differences in demographic and baseline characteristics between the overall study population and paediatric subjects 2-17 years. Of note, adult patients were underrepresented in previous studies during the MAA (Staquis EPAR). Both the adult and the paediatric population in the present study seem representative for EU patients and thus collected results are considered relevant in that regard.

Proportional enrollment in pre-defined age subgroups within the paediatric population is in line with the agreed PIP, but no further results were shown for the respective age- subsets in the initial submission. This was likely due to the small sample sizes in the individual treatment groups as it seems unlikely that true differences in effects relative to age can be determined. Importantly, there were no relevant differences regarding efficacy or safety outcomes between the age-subsets, as confirmed by the Applicant upon request.

Overall, only 39.2% of planned patients were enrolled, yet the maximum number of adult patients (n=90) was reached. Since enrolment of paediatric participants is usually slower, the resulting overrepresentation of adult patients is not surprising. However, it has to be considered, that the actual enrolment of paediatric patients is even lower than the claimed 39.2% of planned participants.

Staquis is approved in EU for mild-moderate AD with affected BSA ≤40%. Across all treatment groups paediatric patients with considerably higher affected BSA (up to 77%) are included because the study enrolled also outside of the EU where no restriction according to BSA affected is labeled. Overall median %BSA affected was 10.0 (range across groups: 8.0 to 11.0). The Applicant stated that one single paediatric participant with baseline %BSA <5 was enrolled. This is considered unlikely to have

an impact on the outcome, in particular since no change for Investigator's Static Global Assessment (ISGA) was reported for this patient throughout the study.

Discontinuations

- During the treatment phase, the most common reasons for discontinuation were AE and lost to follow-up. Discontinuations for any reason were the highest in the vehicle group (20.3%).
- During the follow-up phase, the most common reasons for discontinuation were lost to follow-up and withdrawal by participant. Discontinuations for any reason were the highest in the crisaborole group (10.3%).
- Discontinuation due to a COVID-19 related reason was reported by 1 participant in the TCS group.
- In the subgroup of 2-17 years (Table 2), discontinuations during treatment phase were the highest in the vehicle group (7 participants, 18.4%) and the most common reason for discontinuation was AE (5 participants, 13.2%). Discontinuations during follow-up phase were the highest in the crisaborole group (3 participants, 8.1%) and the most common reason for discontinuation was AE (2 participants, 5.4%).

CHMP comment

Overall, during the treatment phase discontinuation rates are around 10% in the active treatment arms and higher in the vehicle arm (20%). The higher discontinuation rate could be due to lack of efficacy.

There were no apparent differences in disposition events during the treatment phase or follow-up phase between the overall study population and paediatric subjects 2-17 years, indicating that there are likely no differences between the paediatric and the adult population in the observed (small) sample. Unfortunately, no direct comparison between adults and paediatric patients was displayed in the dossier.

Efficacy results

Changes in the Planned Analyses

Number of participants enrolled in the study at the time of study termination was insufficient to allow meaningful inference and robust statistical analyses. As a result, all the safety data were summarized with Cohort 1 and Cohort 2 combined for crisaborole and vehicle groups. In addition, only descriptive summaries for primary efficacy and secondary efficacy endpoints pre-specified prior to the database lock were completed. Whenever possible, descriptive summaries were completed by age subgroup (2-17 years and ≥18 years). No summaries were generated for tertiary/exploratory endpoints.

The following secondary endpoints, pre-specified prior to the database lock, were not summarized, according to the Applicant:

- Change from baseline in Peak Pruritis NRS by scheduled time points (Subjects 6 to 11 Years of Age)

- Change from baseline in Peak Pruritis NRS by scheduled time points (observer version for subjects <6 years of age)
- Time to ≥2 point improvement from baseline in Peak Pruritis NRS (subjects ≥12 years)
- Time to ≥3 point improvement from baseline in Peak Pruritis NRS (subjects ≥12 years)
- Time to ≥2 point improvement from baseline in Peak Pruritis NRS (observer version for subjects <6 years)
- Time to ≥3 point improvement from baseline in Peak Pruritis NRS (observer version for subjects <6 years)
- Proportion of subjects with ≥2 point improvement from baseline in Peak Pruritis NRS (observer version for subjects <6 years) by scheduled time points
- Proportion of subjects with ≥3 point improvement from baseline in Peak Pruritis NRS (observer version for subjects <6 years) by scheduled time points

CHMP comment

Due to early study termination, less than 40% of planned participants were enrolled. The sample size was not considered sufficient by the Applicant to perform formal hypothesis testing and no statistical analyses were performed. Considering the limited sample size it seems logical to provide only descriptive summaries for primary and secondary efficacy endpoints. Descriptive summaries will at least provide some contextualization – though limited – of the treatment effect of crisaborole compared to TCS and TCI.

It is noted that the (wordings of) some of the above mentioned secondary endpoints are not in line with the planned endpoints listed in the study synopsis or study report. It is still unclear why these listed endpoints were chosen not to be reported. As a result, only data from patients ≥12 years of age are shown for the secondary PRO endpoints. A data driven decision cannot be fully ruled out, in particular since true blinding between crisaborole and active comparators is not ensured.

Primary Efficacy Endpoint:

Crisaborole vs Vehicle, Percent Change in EASI Total Score from Baseline at Day 29 (End of Treatment Period)

Data for the primary comparison suggest greater numerical improvement in the EASI total score in the crisaborole group than in the vehicle group.

In participants age 2-17 years, improvement in mean EASI total score from baseline at Day 29 was numerically greater in the crisaborole group (-49.47, SE: 6.142) than in the vehicle group (-26.62, SE: 8.313; Table 7).

Within age subgroups of paediatric participants (2-6 years, 7-12 years, 12-18 years) EASI total score was reduced from baseline to day 29 for all treatment groups and similar trends were seen across age subgroups.

Table 7: Descriptive Summary of Observed Value and Percent Change from Baseline in EASI Total Score at Day 29 (Subjects 2-17 Years) (FAS, OBS)

		Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
			Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)		
Analysis Visit	Summary Statistics						
Baseline	Observed Values						
	n	38	23	14	37	38	30
	Mean (SE)	11.57 (1.472)	8.63 (1.152)	10.90 (2.352)	9.49 (1.137)	9.51 (1.059)	9.89 (1.092)
	Std. Dev.	9.073	5.526	8.799	6.918	6.527	5.983
	Median	9.10	7.40	8.10	7.40	8.10	9.05
	Range (Min,Max)	(2.8, 43.6)	(2.0, 22.8)	(1.6, 26.0)	(1.6, 26.0)	(1.2, 26.0)	(1.4, 28.0)
Day 29	Observed Values						
	n	31	18	13	31	36	29
	Mean (SE)	8.14 (1.831)	4.99 (0.917)	4.23 (1.181)	4.67 (0.718)	2.74 (0.754)	4.04 (0.729)
	Std. Dev.	10.196	3.889	4.259	3.997	4.522	3.928
	Median	3.80	5.70	3.50	4.10	1.15	2.40
	Range (Min,Max)	(0.0, 44.6)	(0.0, 12.9)	(0.0, 14.4)	(0.0, 14.4)	(0.0, 21.5)	(0.0, 15.4)
	Percent Change from Baseline						
	n	31	18	13	31	36	29
	Mean (SE)	-26.62 (8.313)	-44.74 (7.533)	-56.02 (10.363)	-49.47 (6.142)	-75.50 (5.051)	-60.08 (5.919)
	Std. Dev.	46.283	31.960	37.366	34.195	30.305	31.877
	Median	-36.26	-48.81	-67.29	-50.00	-89.38	-68.97
	Range (Min,Max)	(-100.0, 81.8)	(-100.0, 19.4)	(-100.0, 27.3)	(-100.0, 27.3)	(-100.0, 15.6)	(-100.0, 26.4)

In participants age ≥18 years, improvement in mean EASI total score from baseline at Day 29 was numerically greater in the crisaborole group (-57.14, SE: 11.091) than in the vehicle group (-44.67 SE: 11.949).

Hence, the effect of the treatment (crisaborole vs vehicle) is of higher magnitude in participants age 2-17 years compared to participants age ≥18 years.

Secondary Endpoints:

Percent Change in EASI Total Score from Baseline to Scheduled Timepoints During Treatment Period (Except Day 29)

Improvement from baseline in mean EASI total score was numerically greater in crisaborole, TCS, and TCI groups than in vehicle group at all timepoints exclusive of Day 29.

In both subgroups, participants age 2-17 years (Table 8), and participants age ≥18 years, improvement from baseline in mean EASI total score was numerically greater in crisaborole, TCS, and TCI groups than in vehicle group at all timepoints exclusive of Day 29.

Table 8: Descriptive Summary of Observed Value and Percent Change from Baseline in EASI Total Score by Age Group (2-17 Years) (FAS, OBS)

		Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
Analysis Visit	Summary Statistics		Cohort1 (N=23)	Cohort2 (N=14)	Total (N=37)		
Baseline	Observed Values						
	n	38	23	14	37	38	30
	Mean (SE)	11.57 (1.472)	8.63 (1.152)	10.90 (2.352)	9.49 (1.137)	9.51 (1.059)	9.89 (1.092)
	Std. Dev.	9.073	5.526	8.799	6.918	6.527	5.983
	Median	9.10	7.40	8.10	7.40	8.10	9.05
	Range (Min,Max)	(2.8, 43.6)	(2.0, 22.8)	(1.6, 26.0)	(1.6, 26.0)	(1.2, 26.0)	(1.4, 28.0)
Day 8	Observed Values						
	n	37	19	14	33	33	29
	Mean (SE)	9.81 (1.613)	7.86 (1.249)	8.03 (3.278)	7.93 (1.535)	5.01 (0.784)	6.77 (0.901)
	Std. Dev.	9.811	5.442	12.265	8.820	4.502	4.850
	Median	6.00	6.50	4.65	5.60	4.60	5.60
	Range (Min,Max)	(0.4, 43.6)	(1.2, 22.8)	(0.4, 47.6)	(0.4, 47.6)	(0.0, 23.2)	(0.4, 21.6)
	Percent Change from Baseline						
	n	37	19	14	33	33	29
	Mean (SE)	-17.88 (6.034)	-18.57 (6.259)	-37.94 (13.455)	-26.79 (6.838)	-45.59 (4.892)	-34.20 (4.823)
	Std. Dev.	36.705	27.283	50.345	39.280	28.103	25.972
	Median	-20.00	-11.57	-58.43	-25.00	-48.25	-26.53
	Range (Min,Max)	(-86.5, 132.4)	(-79.3, 28.6)	(-88.2, 106.1)	(-88.2, 106.1)	(-100.0, 7.0)	(-90.0, 15.1)
Day 15	Observed Values						
	n	33	19	14	33	37	30
	Mean (SE)	8.82 (1.681)	6.02 (1.011)	7.78 (3.192)	6.76 (1.453)	4.05 (0.792)	6.17 (1.056)
	Std. Dev.	9.655	4.407	11.942	8.345	4.816	5.781
	Median	4.40	4.60	3.75	4.10	2.40	4.75
	Range (Min,Max)	(1.2, 43.6)	(1.1, 15.2)	(0.2, 41.8)	(0.2, 41.8)	(0.0, 21.2)	(0.0, 26.0)
	Percent Change from Baseline						
	n	33	19	14	33	37	30
	Mean (SE)	-25.77 (6.207)	-30.61 (5.939)	-45.02 (12.664)	-36.72 (6.376)	-58.96 (5.362)	-42.75 (5.816)
	Std. Dev.	35.658	25.886	47.385	36.625	32.617	31.854
	Median	-24.14	-36.84	-59.74	-37.84	-64.44	-41.16
	Range (Min,Max)	(-84.9, 86.8)	(-82.2, 13.3)	(-96.3, 81.0)	(-96.3, 81.0)	(-100.0, 0.0)	(-100.0, 23.1)
Day 22	Observed Values						
	n	32	18	13	31	35	26
	Mean (SE)	8.98 (1.871)	5.69 (0.918)	4.85 (1.588)	5.34 (0.840)	3.38 (0.808)	4.16 (0.748)
	Std. Dev.	10.585	3.893	5.727	4.678	4.781	3.814
	Median	4.10	5.50	3.00	3.60	2.00	2.50
	Range (Min,Max)	(0.0, 43.6)	(0.4, 13.6)	(0.4, 20.3)	(0.4, 20.3)	(0.0, 19.6)	(0.0, 13.9)
	Percent Change from Baseline						
	n	32	18	13	31	35	26
	Mean (SE)	-25.07 (8.720)	-30.95 (7.018)	-49.83 (9.530)	-38.87 (5.859)	-69.09 (5.329)	-59.86 (4.871)
	Std. Dev.	49.326	29.773	34.361	32.624	31.528	24.835
	Median	-22.32	-31.33	-54.55	-36.84	-76.19	-60.24
	Range (Min,Max)	(-100.0, 106.5)	(-80.0, 25.9)	(-96.3, -2.8)	(-96.3, 25.9)	(-100.0, 30.6)	(-100.0, -15.4)
Day 29	Observed Values						
	n	31	18	13	31	36	29
	Mean (SE)	8.14 (1.831)	4.99 (0.917)	4.23 (1.181)	4.67 (0.718)	2.74 (0.754)	4.04 (0.729)
	Std. Dev.	10.196	3.889	4.259	3.997	4.522	3.928
	Median	3.80	5.70	3.50	4.10	1.15	2.40
	Range (Min,Max)	(0.0, 44.6)	(0.0, 12.9)	(0.0, 14.4)	(0.0, 14.4)	(0.0, 21.5)	(0.0, 15.4)
	Percent Change from Baseline						
	n	31	18	13	31	36	29
	Mean (SE)	-26.62 (8.313)	-44.74 (7.533)	-56.02 (10.363)	-49.47 (6.142)	-75.50 (5.051)	-60.08 (5.919)
	Std. Dev.	46.283	31.960	37.366	34.195	30.305	31.877
	Median	-36.26	-48.81	-67.29	-50.00	-89.38	-68.97
	Range (Min,Max)	(-100.0, 81.8)	(-100.0, 19.4)	(-100.0, 27.3)	(-100.0, 27.3)	(-100.0, 15.6)	(-100.0, 26.4)

Percent Change in EASI Total Score from Day 29 to Day 43 (Follow-Up Period)

Because of the inherent variability associated with the small sample size, inferences cannot be drawn from the descriptive summaries. Furthermore, at the Day 43 visit; data were missing from more than half the participants at the Day 43 visit than at the Day 29 visit.

Table 9: Descriptive Summary of Observed Value and Percent Change from Day 29 to Day 43 in EASI Total Score (Subjects 2-17 Years) (FAS, OBS)

		Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
			Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)		
Analysis Visit	Summary Statistics						
Day 29	Observed Values						
	n	31	18	13	31	36	29
	Mean (SE)	8.14 (1.831)	4.99 (0.917)	4.23 (1.181)	4.67 (0.718)	2.74 (0.754)	4.04 (0.729)
	Std. Dev.	10.196	3.889	4.259	3.997	4.522	3.928
	Median	3.80	5.70	3.50	4.10	1.15	2.40
	Range (Min,Max)	(0.0, 44.6)	(0.0, 12.9)	(0.0, 14.4)	(0.0, 14.4)	(0.0, 21.5)	(0.0, 15.4)
Day 43	Observed Values						
	n	12	10	9	19	20	18
	Mean (SE)	5.35 (1.714)	4.97 (1.203)	5.31 (2.161)	5.13 (1.169)	5.30 (1.441)	5.16 (1.313)
	Std. Dev.	5.938	3.803	6.484	5.094	6.444	5.570
	Median	2.70	4.75	3.20	3.50	3.60	3.35
	Range (Min,Max)	(0.0, 19.0)	(0.6, 11.2)	(0.4, 21.9)	(0.4, 21.9)	(0.0, 23.6)	(0.0, 22.0)
	Percent Change from Day 29						
	n	11	8	8	16	14	15
	Mean (SE)	45.22 (44.575)	56.00 (40.913)	251.25 (113.506)	153.62 (63.499)	109.41 (31.750)	56.15 (30.717)
	Std. Dev.	147.838	115.719	321.043	253.995	118.799	118.965
	Median	0.00	17.48	119.57	42.53	107.40	2.99
	Range (Min,Max)	(-57.1, 466.7)	(-16.7, 337.5)	(-66.7, 900.0)	(-66.7, 900.0)	(-50.0, 300.0)	(-59.4, 333.3)

CHMP comment

The column displaying mean percent changes from day 29 seems incorrect or is not sufficiently explained.

Achievement of Success in ISGA at Scheduled Timepoints During Treatment Period

In both subgroups, participants age 2-17 years, and participants age ≥18 years, proportion of participants who achieved success in ISGA was numerically greater in crisaborole, TCS, and TCI groups than in vehicle group at most timepoints. A descriptive summary of proportion of participants age 2-17 years who achieved success in ISGA (score of Clear or Almost Clear, with ≥2 grade improvement from baseline) is presented in Table 10.

Table 10: Achievement of 'Clear' or 'Almost Clear' with ≥2 Grade Improvement from Baseline in ISGA over Time (Subjects 2-17 Years) (FAS, NR)

		Vehicle (N=38)	Crisaborole 2% BID (N=37)			Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
			Cohort 1 (N=23)	Cohort 2 (N=14)	Total (N=37)		
Analysis Visit	Summary Statistics						
Day 8	N*	38	23	14	37	39	30
	n (%)	00002 (005.3)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00002 (005.1)	00000 (000.0)
Day 15	N*	38	23	14	37	39	30
	n (%)	00001 (002.6)	00001 (004.3)	00002 (014.3)	00003 (008.1)	00008 (020.5)	00002 (006.7)
Day 22	N*	38	23	14	37	39	30
	n (%)	00002 (005.3)	00001 (004.3)	00001 (007.1)	00002 (005.4)	00011 (028.2)	00005 (016.7)
Day 29	N*	38	23	14	37	39	30
	n (%)	00002 (005.3)	00003 (013.0)	00002 (014.3)	00005 (013.5)	00020 (051.3)	00007 (023.3)

Achievement of ISGA Score of Clear or Almost Clear at Scheduled Timepoints During Treatment Period

In both subgroups, participants age 2-17 years, and participants age ≥18 years, proportion of participants who achieved ISGA score of Clear or Almost Clear was numerically greater in crisaborole, TCS, and TCI groups than in vehicle group at most timepoints.

EASI75 (≥75% Improvement from Baseline) Achieved at Scheduled Timepoints During Treatment Period

The proportion of participants who achieved EASI75 (≥75% improvement from baseline) were numerically greater in crisaborole, TCS, and TCI groups than in vehicle group at all timepoints.

Time to EASI75 Crisaborole vs Vehicle

The Kaplan-Meier analysis to estimate the time to first EASI75 suggested that the time to response was faster in the crisaborole group than in the vehicle group. As per the KM analysis, median time to first achieve EASI75 was 43.0 days in the crisaborole group and not evaluable in the vehicle group. Despite small sample sizes, same trends were seen across all age subgroups.

Time to EASI75 Crisaborole vs Active Control

The differences in the number of evaluable participants at the study visits in each treatment group may negatively impact the groups with the smaller number of participants, therefore any trends observed in these small populations may not be reliable.

As per the KM analysis, median time to first achieve EASI75 was 36.0 days and 23.0 days in crisaborole cohort 1 and TCS group, respectively; and 43.0 days and 32.0 days in crisaborole cohort 2 and TCI group, respectively. Within age subgroups, no clear trends could be observed and plots for crisaborole cohorts and active control groups overlapped.

Change in %BSA from Baseline to Scheduled Timepoints During Treatment Period

In participants age 2-17 years, improvement from baseline in mean %BSA was numerically greater in the crisaborole, TCS, and TCI groups than in vehicle group at most timepoints.

In participants age ≥18 years, improvement from baseline in mean %BSA appears to be numerically greater in the crisaborole, TCS, and TCI groups than in vehicle group at most timepoints.

Change from Baseline in Peak Pruritus NRS by Scheduled Time Points (Subjects ≥12 Years of Age)

Numerical change from baseline in weekly average mean Peak Pruritis NRS score appears to be greater in crisaborole, TCS, and TCI groups than in vehicle at most timepoints.

Achievement of ≥2 Point Improvement from Baseline in Peak Pruritus NRS (Subjects ≥12 years)

Proportions of participants with ≥2 point improvement in weekly average mean Peak Pruritis NRS score from baseline to Day 8, 15, 22, and 29 appear consistently greater only in TCS group compared to other treatment groups (Table 11).

Table 11: Achievement of ≥2 Point Improvement from Baseline in Weekly Average Peak Pruritus NRS (Subjects ≥12 Years) over Time (FAS, NR)

		Vehicle (N=31)	Crisaborole 2% BID (N=32)			Hydrocortisone Butyrate 0.1% BID (N=42)	Pimecrolimus 1% BID (N=26)
			Cohort 1 (N=22)	Cohort 2 (N=10)	Total (N=32)		
Analysis Visit	Summary Statistics						
Day 8	N*	31	22	10	32	42	26
	n (%)	3 (9.7)	5 (22.7)	2 (20.0)	7 (21.9)	21 (50.0)	1 (3.8)
Day 15	N*	31	22	10	32	42	26
	n (%)	9 (29.0)	5 (22.7)	3 (30.0)	8 (25.0)	31 (73.8)	7 (26.9)
Day 22	N*	31	22	10	32	42	26
	n (%)	9 (29.0)	5 (22.7)	2 (20.0)	7 (21.9)	32 (76.2)	9 (34.6)
Day 29	N*	31	22	10	32	42	26
	n (%)	10 (32.3)	7 (31.8)	2 (20.0)	9 (28.1)	32 (76.2)	9 (34.6)

Achievement of ≥3 Point Improvement from Baseline in Peak Pruritus NRS (Subjects ≥12 years)

Proportions of participants with ≥3 point improvement in weekly average mean Peak Pruritis NRS score from baseline to Day 8, 15, 22, and 29 appear consistently greater only in TCS group compared to other treatment groups (Table 12).

Table 12: Achievement of ≥3 Point Improvement from Baseline in Weekly Average Peak Pruritus NRS (Subjects ≥12 Years) over Time (FAS, NR)

		Vehicle (N=29)	Crisaborole 2% BID (N=29)			Hydrocortisone Butyrate 0.1% BID (N=40)	Pimecrolimus 1% BID (N=26)
			Cohort 1 (N=19)	Cohort 2 (N=10)	Total (N=29)		
Analysis Visit	Summary Statistics						
Day 8	N*	29	19	10	29	40	26
	n (%)	2 (6.9)	0	1 (10.0)	1 (3.4)	11 (27.5)	0
Day 15	N*	29	19	10	29	40	26
	n (%)	5 (17.2)	3 (15.8)	2 (20.0)	5 (17.2)	21 (52.5)	3 (11.5)
Day 22	N*	29	19	10	29	40	26
	n (%)	4 (13.8)	4 (21.1)	0	4 (13.8)	25 (62.5)	4 (15.4)
Day 29	N*	29	19	10	29	40	26
	n (%)	6 (20.7)	5 (26.3)	1 (10.0)	6 (20.7)	24 (60.0)	6 (23.1)

Other Peak Pruritis-NRS Endpoints

As specified in the final SAP (Version 3, dated 10 November 2020), analyses for the remaining endpoints for Peak Pruritis NRS were not conducted because of small sample size.

Change from Baseline in DLQI and CDLQI Scores and DFI Score Completed by Parent/Caregiver by Scheduled Time Points

DLQI was administered to participants ≥16 years of age, a subset of FAS. CDLQI was administered to participants 4-15 years of age, a subset of FAS. DFI was administered to participants in the age subgroup of 2-17 years. Numerical change from baseline in DLQI, CDLQI and DFI scores appears to be greater in crisaborole, TCS, and TCI groups than in vehicle at most timepoints.

CHMP comment

It is acknowledged that – despite limited sample size – data for the primary comparison (crisaborole vs vehicle, Percent Change in EASI Total Score from Baseline at Day 29) suggest greater numerical improvement in the crisaborole group than in the vehicle group.

It is acknowledged that group sizes are small already and that further subgroup assessment might not make sense in all cases. Upon request, the Applicant provided paediatric age subgroup data, which show that EASI reduced from baseline to day 29 for all treatment groups and similar trends were seen across age subgroups. While time to achieve EASI75 was faster in the crisaborole group than in the vehicle group across all age subgroups, no clear trends could be observed within age subgroups comparing crisaborole vs active controls. It is noted that the effect of the treatment (crisaborole vs vehicle) is numerically larger in participants age 2-17 years, at the same time compliance in paediatric patients in the crisaborole group was lower compared to adults.

TCI and TCS show numerically larger effects compared to crisaborole in most analysed secondary endpoint observations/timepoints. TCS appears to be superior to other treatments, while TCI seems to be similarly or slightly more effective than crisaborole.

Overall, the efficacy results confirm the beneficial effect of crisaborole compared to vehicle in the paediatric target population and suggest lower potency compared to the well-established TCI and TCS alternatives.

Safety results

Cohort 1 and 2 were combined for crisaborole and vehicle groups for all safety summaries.

CHMP comment

Safety summaries are presented with combined data for crisaborole and vehicle groups from cohort 1 and 2. This is acceptable since no differential safety outcomes are expected between the cohorts, baseline and disease characteristics are sufficiently similar between the groups. Data grouped by age within the paediatric population showed – as expected due to small sample sizes – high variability but also no apparent differences within age subgroups.

Adverse Events

- The proportion of participants who experienced all-causality TEAEs ranged from 16.9 % to 51.1% across treatment groups.

- No participants reported an SAE in any treatment group and 1 adult participant in the crisaborole group reported a severe TEAE.
- 3 paediatric participants, all in the crisaborole treatment group, discontinued from the study due to AEs (Table 13).
- 6 participants (5 paediatric) in the vehicle treatment group and 2 participants (1 paediatric) in the TCI treatment group discontinued study drug due to AEs, but remained in the study.
- Low TEAE and discontinuation rates were observed in both age sub-groups (2-17 years and ≥ 18 years) of crisaborole-treated participants.

Table 13: Treatment-Emergent Adverse Events (All Causalities) - Overall (Subjects 2-17 Years) (SAF)

	Vehicle	Crisaborole 2% BID	Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
Number (%) of Subjects	n (%)	n (%)	n (%)	n (%)
Number of Subjects Evaluable for AEs	00038 (000.0)	00037 (000.0)	00039 (000.0)	00030 (000.0)
Number of adverse events	00024 (000.0)	00028 (000.0)	00009 (000.0)	00020 (000.0)
Subjects with adverse events	00013 (034.2)	00016 (043.2)	00006 (015.4)	00017 (056.7)
Subjects with serious adverse events	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Subjects with severe adverse events	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Subjects discontinued from study due to adverse events (a)	00000 (000.0)	00003 (008.1)	00000 (000.0)	00000 (000.0)
Subjects discontinued study drug due to AE and continue study (b)	00005 (013.2)	00000 (000.0)	00000 (000.0)	00001 (003.3)
Subjects with dose reduced or temporary discontinuation due to adverse events	00002 (005.3)	00000 (000.0)	00000 (000.0)	00000 (000.0)

Most of the TEAEs reported were mild in the crisaborole, TCS and TCI groups; 20 out of 25 AEs, 10 out of 12 AEs, and 16 out of 24 AEs classified as mild in the crisaborole, TCS, and TCI groups, respectively. A severe TEAE (PT: headache) was reported by 1 adult participant in the crisaborole group.

Adverse Events by SOC

The most frequently reported SOCs (≥5% of participants in any treatment group) were: General Disorders and Administration Site Conditions, Skin and Subcutaneous Tissues Disorders, Infections and Infestations, and Nervous System Disorders.

General Disorders and Administration Site Conditions SOC TEAEs were reported with frequencies across the treatment groups ranging from 2 participants (reported in the TCS group; 2.8%) to 10 participants (reported in the crisaborole group; 17.2%); reports in the crisaborole group were more frequent in participants age 2-17 years. Application site pain, reported in 13.8% of participants treated with crisaborole, was reported more frequently in participants age 2-17 years (6 participants, 16.2%; Table 14) than in participants age ≥18 years (2 participants, 9.5%); no other application site-related AEs were reported in ≥5% of participants in the crisaborole group for either age subgroup.

Skin and subcutaneous tissue disorders SOC TEAEs were reported by 18.6% and 19.1% of participants in the vehicle and TCI groups, respectively, and 13.8% and 5.6% of participants in the crisaborole and TCS group, respectively; dermatitis atopic PT was the most frequently reported PT in the vehicle and TCI groups. All participants reporting dermatitis atopic in the vehicle group and in the TCS group were age 2-17 years (vehicle: 7 participants, 18.4%; TCS: 2 participants, 5.1%; Table 14); in each of the

other treatment groups the incidence of dermatitis atopic was similar between participants in both age subgroups.

Table 14: Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term (All Causalities) - Overall (Subjects 2-17 Years) (SAF)

Number of Subjects Evaluable for AEs	Vehicle (N=38)	Crisaborole 2% BID (N=37)	Hydrocortisone Butyrate 0.1% BID (N=39)	Pimecrolimus 1% BID (N=30)
Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	13 (34.2)	16 (43.2)	6 (15.4)	17 (56.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (10.5)	6 (16.2)	2 (5.1)	1 (3.3)
Application site pain	1 (2.6)	6 (16.2)	0	0
Pyrexia	2 (5.3)	0	2 (5.1)	1 (3.3)
INFECTIONS AND INFESTATIONS	3 (7.9)	5 (13.5)	2 (5.1)	9 (30.0)
Nasopharyngitis	2 (5.3)	1 (2.7)	0	1 (3.3)
Rhinitis	0	2 (5.4)	1 (2.6)	3 (10.0)
Viral upper respiratory tract infection	0	1 (2.7)	0	2 (6.7)
NERVOUS SYSTEM DISORDERS	0	2 (5.4)	0	1 (3.3)
Headache	0	2 (5.4)	0	1 (3.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (5.3)	2 (5.4)	0	1 (3.3)
Cough	1 (2.6)	2 (5.4)	0	1 (3.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	10 (26.3)	6 (16.2)	3 (7.7)	6 (20.0)
Dermatitis atopic	7 (18.4)	2 (5.4)	2 (5.1)	5 (16.7)
Eczema	0	2 (5.4)	0	1 (3.3)

Infections and infestations SOC TEAEs were observed most frequently in the crisaborole and TCI groups. The majority of events were common or childhood illness. There were two infections involving the skin; a PT of Skin infection was reported in TCS group and a PT of Furuncle was reported in crisaborole group.

Headache PT was the most frequently reported Nervous System Disorders SOC TEAE. All incidences of headache PT were assessed as not related to study treatment.

TEAEs potentially attributable to systemic PDE-4 inhibition (GI Disorders SOC) occurred infrequently; these TEAEs occurred with similar incidence across the 4 treatment groups and were assessed as not related to the study treatment. No other TEAEs potentially associated with systemic PDE-4 inhibition (eg, insomnia, anxiety, suicide ideation, serious infections, malignancy) were observed.

Local Tolerability

The incidence of all-causality TEAEs in the treatment area was lowest in the TCS (active comparator) treatment group (2.8%) and the incidence was similar across all other treatment groups (20.3%, 22.4% and 17.0% for vehicle, crisaborole, and TCI groups, respectively) (Table 15).

Table 15: Treatment-Emergent Adverse Events (All Causalities) - Treatment Area (SAF)

Number (%) of Subjects	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)
Number of Subjects Evaluable for AEs	59	58	71	47
Number of adverse events	13	17	2	11
Subjects with adverse events	12 (20.3)	13 (22.4)	2 (2.8)	8 (17.0)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
Subjects discontinued from study due to adverse events (a)	0	2 (3.4)	0	0
Subjects discontinued study drug due to AE and continue study (b)	6 (10.2)	0	0	2 (4.3)
Subjects with dose reduced or temporary discontinuation due to adverse events	2 (3.4)	1 (1.7)	0	0

In the treatment area, application and instillation site reactions were experienced most frequently in the crisaborole treatment group (9 participants, 15.5%) and observed in all age subgroups (Table 16). Dermatitis and eczema were reported most frequently in the vehicle treatment group (10 participants, 16.9%; Table 17).

Table 16. Summary of Application Site Reactions by Treatment and Age Groups

Age Group	High Level Term Preferred Term	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)
2-6 Years	**N**	**14**	**15**	**16**	**11**
	Application and instillation site reactions	2 (14.3)	4 (26.7)	0	0
	Application site pain	1 (7.1)	4 (26.7)	0	0
	Application site pruritus	1 (7.1)	0	0	0
7-11 Years	**N**	**12**	**10**	**10**	**8**
	Application and instillation site reactions	0	1 (10.0)	0	0
	Application site pain	0	1 (10.0)	0	0
12-17 Years	**N**	**12**	**12**	**13**	**11**
	Application and instillation site reactions	0	1 (8.3)	0	0
	Application site pain	0	1 (8.3)	0	0
	Application site pruritis	0	1 (8.3)	0	0
≥18 Years	**N**	**21**	**21**	**32**	**17**
	Application and instillation site reactions	0	3 (14.3)	0	2 (11.8)
	Application site discharge	0	0	0	1 (5.9)
	Application site erythema	0	0	0	1 (5.9)
	Application site exfoliation	0	1 (4.8)	0	0
	Application site pain	0	2 (9.5)	0	2 (11.8)
	Application site pruritus	0	0	0	1 (5.9)
	Application site swelling	0	0	0	1 (5.9)

Table 16. Summary of Application Site Reactions by Treatment and Age Groups

Age Group	High Level Term Preferred Term	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)

Table 17: Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class, High Level Term and Preferred Term (All Causalities) - Treatment Area (SAF)

Number of Subjects Evaluable for AEs	Vehicle (N=59)				Crisaborole 2% BID (N=58)			
Severity(a)	Mild	Mod.	Sev.	Total	Mild	Mod.	Sev.	Total
Number (%) of Subjects: by SYSTEM ORGAN CLASS High Level Term and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	00004 (006.8)	00008 (013.6)	00000 (000.0)	00012 (020.3)	00009 (015.5)	00004 (006.9)	00000 (000.0)	00013 (022.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	00001 (001.7)	00001 (001.7)	00000 (000.0)	00002 (003.4)	00007 (012.1)	00002 (003.4)	00000 (000.0)	00009 (015.5)
Application and instillation site reactions	00001 (001.7)	00001 (001.7)	00000 (000.0)	00002 (003.4)	00007 (012.1)	00002 (003.4)	00000 (000.0)	00009 (015.5)
Application site discharge	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Application site erythema	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Application site exfoliation	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00000 (000.0)	00001 (001.7)
Application site pain	00001 (001.7)	00000 (000.0)	00000 (000.0)	00001 (001.7)	00006 (010.3)	00002 (003.4)	00000 (000.0)	00008 (013.8)
Application site pruritus	00000 (000.0)	00001 (001.7)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00001 (001.7)
Application site swelling	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	00003 (005.1)	00008 (013.6)	00000 (000.0)	00011 (018.6)	00002 (003.4)	00004 (006.9)	00000 (000.0)	00006 (010.3)
Dermatitis and eczema	00002 (003.4)	00008 (013.6)	00000 (000.0)	00010 (016.9)	00002 (003.4)	00004 (006.9)	00000 (000.0)	00006 (010.3)
Dermatitis atopic	00002 (003.4)	00005 (008.5)	00000 (000.0)	00007 (011.9)	00001 (001.7)	00003 (005.2)	00000 (000.0)	00004 (006.9)
Dermatitis contact	00000 (000.0)	00002 (003.4)	00000 (000.0)	00002 (003.4)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Eczema	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00002 (003.4)	00001 (001.7)	00000 (000.0)	00003 (005.2)
Skin irritation	00000 (000.0)	00001 (001.7)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Telangiectasia and related conditions	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Telangiectasia	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Urticarias	00001 (001.7)	00000 (000.0)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Urticaria	00001 (001.7)	00000 (000.0)	00000 (000.0)	00001 (001.7)	00000 (000.0)	00000 (000.0)	00000 (000.0)	00000 (000.0)
Total preferred term events	00004 (000.0)	00009 (000.0)	00000 (000.0)	00013 (000.0)	00010 (000.0)	00007 (000.0)	00000 (000.0)	00017 (000.0)

Adverse Events – Treatment Related

Investigator-reported treatment-related TEAEs were reported most frequently in the crisaborole group. Most treatment-related TEAEs were mild. No severe or serious treatment-related TEAEs were reported by any participants (Table 18).

Table 18: Treatment-Emergent Adverse Events (Treatment Related) - Overall (SAF)

Number (%) of Subjects:	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)
Number of Subjects Evaluable for AEs	59	58	71	47
Number of adverse events	11	15	1	8
Subjects with adverse events	9 (15.3)	11 (19.0)	1 (1.4)	4 (8.5)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
Subjects discontinued from study due to adverse events (a)	0	2 (3.4)	0	0
Subjects discontinued study drug due to AE and continue study (b)	5 (8.5)	0	0	1 (2.1)
Subjects with dose reduced or temporary discontinuation due to adverse events	2 (3.4)	1 (1.7)	0	0

The SOCs with the highest incidence of (≥5% in any treatment group) treatment-related TEAEs were general disorders and administration site conditions, and skin and subcutaneous tissue disorders. Application site pain, the most frequently reported treatment-related AE PT, was reported in 1 participant (1.7%) in the vehicle group, 8 participants (13.8%) in the crisaborole group, 0 participants in the TCS group, and 2 participants (4.3%) in the TCI group. Dermatitis atopic PT was reported in the vehicle group (4 participants, 6.8%) and the crisaborole group (2 participants, 3.4%)(Table 19).

Table 19: Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term (Treatment Related) - Overall (SAF)

Number of Subjects Evaluable for AEs Number (%) of Subjects: by SYSTEM ORGAN CLASS and Preferred Term	Vehicle (N=59) n (%)	Crisaborole 2% BID (N=58) n (%)	Hydrocortisone Butyrate 0.1% BID (N=71) n (%)	Pimecrolimus 1% BID (N=47) n (%)
With Any Adverse Event	9 (15.3)	11 (19.0)	1 (1.4)	4 (8.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (3.4)	9 (15.5)	0	2 (4.3)
Application site pain	1 (1.7)	8 (13.8)	0	2 (4.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (13.6)	4 (6.9)	1 (1.4)	0
Dermatitis atopic	4 (6.8)	2 (3.4)	0	0

Local Tolerability – Treatment Related

Of the total treatment-related TEAEs, most treatment-related TEAEs were reported in the treatment area; however, none of the treatment-related TEAEs reported in the treatment area were determined to be severe or serious. Application site pain and dermatitis atopic were the most frequently reported treatment related TEAE PTs in the treatment area among all treatment groups. There were few discontinuations due to treatment-related TEAEs experienced in the treatment area (Table 20).

Table 20: Treatment-Emergent Adverse Events (Treatment Related) - Treatment Area (SAF)

Number (%) of Subjects:	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)
Number of Subjects Evaluable for AEs	59	58	71	47
Number of adverse events	10	14	1	5
Subjects with adverse events	9 (15.3)	11 (19.0)	1 (1.4)	2 (4.3)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
Subjects discontinued from study due to adverse events (a)	0	2 (3.4)	0	0
Subjects discontinued study drug due to AE and continue study (b)	5 (8.5)	0	0	1 (2.1)
Subjects with dose reduced or temporary discontinuation due to adverse events	2 (3.4)	1 (1.7)	0	0

CHMP comment

In subjects age 2-17 years, the numbers of subjects with any TEAE were highest in the TCI treatment group, followed by crisaborole, vehicle and TCS groups. None of the reported TEAE were serious or severe. Application site pain was the most frequently reported TEAE in the crisaborole treatment group; the incidence was higher in participants age 2-17 years (6 participants, 16.2%) than in participants age ≥18 years (2 participants, 9.5%).

The most frequently reported treatment-related TEAEs were application site pain and dermatitis atopic. Treatment-related Dermatitis atopic was reported in the vehicle group (4 participants, 6.8%) and the crisaborole group (2 participants, 3.4%), but not in the active control groups, which could be a reflection of inferior efficacy. No paediatric data are shown for treatment-related TEAE.

Overall, treatment related TEAE in the treatment area were most frequent in the crisaborole group, followed by vehicle, TCI and TCS groups. Paediatric data were provided for local tolerability upon request. In the treatment area, application and instillation site reactions were observed in all age subgroups with highest frequency in the crisaborole group for the age subgroup of 2-6 years (26.7%; vs 10% for 7-11 years, 8.3% for 12-17 years and 14.3% for ≥18 years).

Discontinuations Due to Adverse Events

The incidence of permanent discontinuation from the study and/or study intervention due to any TEAE was low in the study. Three paediatric participants, all in the Crisaborole 2% BID treatment group, discontinued from the study due to TEAEs (Table 2, Table 13). Participant discontinuation was due to skin and subcutaneous tissue disorders (2 participants; PTs: dermatitis atopic, mechanical urticaria) and general disorders and administration site conditions (1 participant; PT: application site pain) SOCs. The TEAEs of application site pain and dermatitis atopic were determined to be treatment-related.

Six participants (5 paediatric) in the vehicle group and 2 participants (1 paediatric) in the TCI group permanently discontinued from the study intervention due to TEAEs, but remained in the study (Table 13). Participant discontinuation was due to skin and subcutaneous tissue disorders (7 participants) and general disorders and administration site conditions (1 participant) SOCs.

Four participants experienced dose reductions or temporary discontinuations from the study intervention due to TEAEs (Table 13); 2 paediatric participants in the vehicle group and 1 adult participant each in the crisaborole and TCS treatment groups.

CHMP comment

The overall rate of permanent discontinuation from the study due to any TEAE was low. All three discontinuations were reported in the crisaborole group in the paediatric population.

Clinical Laboratory Evaluation

Without regard to baseline abnormality, there was no meaningful difference between the treatment groups in the number of participants with a laboratory abnormality.

The most frequently occurring abnormalities across treatment groups (occurring in ≥18% of participants in all treatment groups) were increased eosinophils/leukocytes (%) and eosinophils (103/mm3). The proportion of participants with these abnormalities was numerically highest in the TCI and vehicle groups.

Incidences of laboratory test abnormalities were highest in participants aged 2-17 years (Table 21):

Laboratory abnormalities in eosinophils (103/mm3): ≥30% of participants 2-17 years in all treatment groups had abnormalities compared to only 1 participant ≥18 years each the TCS (3.4%) and TCI (6.3%) treatment groups having abnormalities.

Laboratory abnormalities in eosinophils/leukocytes (%): ≥33.3% of participants 2-17 years in every treatment group had abnormalities compared to participants ≥18 years where incidences were considerably lower for vehicle (2 participants, 10%), crisaborole (0 participants), and TCS (1 participant, 3.4%) treatment groups. Abnormality incidence in the TCI group was similar for all participants (participants 2-17 years: 10 participants, 35.7%; participants age ≥ 18: 5 participants, 31.3%).

Table 21: Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) (Subjects 2-17 Years) (SAF)

Laboratory Abnormalities: Number of Subjects Evaluable for Laboratory Abnormalities: Number (%) of Subjects with Laboratory Abnormalities:			Vehicle 32 16 (50.0%)		Crisaborole 2% BID 30 15 (50.0%)		Hydrocortisone Butyrate 0.1% BID 33 19 (57.6%)		Pimecrolimus 1% BID 29 14 (48.3%)	
Group	Parameter (Units)	Primary Criteria	N	n (%)	N	n (%)	N	n (%)	N	n (%)
HEMATOLOGY	Leukocytes (10^3/mm3)	<0.6x LLN	00032 (000.0)	00001 (003.1)	00030 (000.0)	00000 (000.0)	00033 (000.0)	00000 (000.0)	00028 (000.0)	00000 (000.0)
	Lymphocytes (10^3/mm3)	<0.8x LLN	00032 (000.0)	00000 (000.0)	00030 (000.0)	00000 (000.0)	00033 (000.0)	00001 (003.0)	00028 (000.0)	00000 (000.0)
	Lymphocytes/Leukocytes (%)	>1.2x ULN	00032 (000.0)	00002 (006.3)	00030 (000.0)	00002 (006.7)	00033 (000.0)	00001 (003.0)	00028 (000.0)	00000 (000.0)
	Neutrophils (10^3/mm3)	<0.8x LLN	00032 (000.0)	00003 (009.4)	00030 (000.0)	00000 (000.0)	00033 (000.0)	00000 (000.0)	00028 (000.0)	00000 (000.0)
	Neutrophils/Leukocytes (%)	<0.8x LLN	00032 (000.0)	00003 (009.4)	00030 (000.0)	00003 (010.0)	00033 (000.0)	00001 (003.0)	00028 (000.0)	00001 (003.6)
	Basophils/Leukocytes (%)	>1.2x ULN	00032 (000.0)	00001 (003.1)	00030 (000.0)	00005 (016.7)	00033 (000.0)	00001 (003.0)	00028 (000.0)	00003 (010.7)
	Eosinophils (10^3/mm3)	>1.2x ULN	00032 (000.0)	00013 (040.6)	00030 (000.0)	00009 (030.0)	00033 (000.0)	00012 (036.4)	00028 (000.0)	00011 (039.3)
	Eosinophils/Leukocytes (%)	>1.2x ULN	00032 (000.0)	00011 (034.4)	00030 (000.0)	00010 (033.3)	00033 (000.0)	00013 (039.4)	00028 (000.0)	00010 (035.7)
	Monocytes/Leukocytes (%)	>1.2x ULN	00032 (000.0)	00001 (003.1)	00030 (000.0)	00001 (003.3)	00033 (000.0)	00002 (006.1)	00028 (000.0)	00000 (000.0)
CLINICAL CHEMISTRY	Alkaline Phosphatase (U/L)	>3.0x ULN	00031 (000.0)	00000 (000.0)	00030 (000.0)	00001 (003.3)	00032 (000.0)	00000 (000.0)	00029 (000.0)	00000 (000.0)
	Potassium (mEq/L)	>1.1x ULN	00031 (000.0)	00000 (000.0)	00030 (000.0)	00000 (000.0)	00032 (000.0)	00001 (003.1)	00029 (000.0)	00000 (000.0)
	Bicarbonate (mEq/L)	<0.9x LLN	00031 (000.0)	00001 (003.2)	00030 (000.0)	00000 (000.0)	00032 (000.0)	00000 (000.0)	00029 (000.0)	00000 (000.0)

Some minor lab abnormalities were reported. One adult participant in the TCS group had elevated creatinine value reported as an AE classified as mild; however, it was considered not related to the study intervention by the investigator with a causality of a suspected lab error. No other lab abnormalities were reported as AEs. No laboratory abnormalities were considered clinically significant.

Vital Signs

Electrocardiograms were not collected for this study. No new safety issues were identified from other vital signs findings.

CHMP comment

Laboratory abnormalities in eosinophils were reported with high frequencies (≥30%) in all treatment groups among paediatric patients. This can be expected, since eosinophil numbers in peripheral blood are elevated in most AD patients and appear to correlate with disease activity.

2.3.3. Discussion on clinical aspects

The MAH submitted the final clinical study report of the crisaborole ointment 2% Study C3291037 performed in patients ≥ 2 years of age with atopic dermatitis (AD). Study C3291037 was part of the agreed EU PIP for crisaborole (EMA PIP decision [P/0276/2020] PIP Study 8). Study C3291037 was designed to address a PDCO request during the PIP evaluation for a study comparing crisaborole to standard of care to define the position of crisaborole within the treatment paradigm of AD. The Applicant explains that the PIP was discontinued on 20 October 2020 for business reasons including early termination of the C3291037 global study. Non-completion of a binding PIP establishes non-compliance with the requirements of the Paediatric Regulation, which EMA, per obligation, reported to the European Commission. The MAH is reminded that any change to a PIP needs to be agreed with the PDCO prospectively through a modification of the agreed PIP.

At the time of study termination only 237 participants were randomized and 235 participants treated, instead of the originally planned 600 (paediatric and adolescent) participants (39.2% of planned enrolment).

Study C3291037 was a Phase 3b/4, multicenter, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study of the efficacy, safety, and local tolerability of crisaborole ointment, 2% in paediatric and adult participants (ages 2 years and older) with mild to moderate AD involving at least 5% treatable %BSA. Treatment and vehicle performance was planned to be evaluated over the course of one treatment cycle (29 days) in N=600 patients (of which a maximum of 90 were planned to be adults, i.e. 15% of total participants). It was agreed in the PIP that at least 410 paediatric patients (i.e. 68.3% of total) should be enrolled: 150 subjects from 2 to 6 years of age (25% of total), 140 subjects from 7 to less than 12 years of age (23.3% of total) and 120 subjects from 12 to less than 18 years of age (20% of total). Hence, 16.7% of total participants have not been assigned to a specific age group a priori. Yet, since the number of adult patients was limited to 90, those 16.7% should implicitly be paediatric patients <18 years of age.

The proposed design entails two cohorts, one evaluating crisaborole, vehicle and hydrocortisone (cohort 1) and one evaluating crisaborole, vehicle and pimecrolimus (cohort 2). The primary efficacy endpoint was the percent change from baseline in the EASI total score at Day 29 comparing crisaborole vs. vehicle and the analysis was planned to test for superiority according to the PIP. Secondary endpoints were planned to evaluate the effect at other time points or via other measures

(EASI75, ISGA, Peak Pruritus NRS, %BSA changes, time to event endpoints etc…) and, importantly, the relative effect of crisaborole compared to TCI and TCS. Safety was the second primary endpoint of the study.

The overall study design, including objectives/endpoints and planned sample size, is appropriate to evaluate outcomes of interest and seems in line with the agreed PIP KBE (key binding elements). As the trial is a short time trial it does not inform on comparative performance during chronic use (which is likely in the target population). As the included treatments all have a rather quick onset of effect, 29 days however are deemed appropriate to allow for an interpretation of immediate comparative efficacy. For comparison of (long-term) safety the short study duration is less ideal. Some well-known complications with chronic TCS treatments only occur after longer treatment durations. Potential local adverse effects include infection, skin atrophy, telangiectasia, hypopigmentation, hypertrichosis, pustular eruptions, and eventually striae. The risk of these is higher for thinner skin (younger age, flexures, and face), prolonged and continuous usage, and occlusion. Eyelids are particularly problematic because local absorption of TCS can cause cataract and glaucoma. Systemic absorption of TCS sufficient to cause adverse effects is rare but hypothalamic-pituitary-adrenal axis suppression and reduced linear growth in children have been reported. Babies and children are at particular risk of absorption because of their high body surface area to weight ratio. TCIs may cause stinging, are relatively expensive, and have been suggested to increase cancer risk, although no case in children has been reported (Sathishkumar D. and Moss C. 2016). For crisaborole, which was only approved in 2020, local skin reactions are the main adverse reaction known. It is acknowledged that evaluation and comparison of potentially rare long-term safety events is not possible based on the provided trial. Also it is extremely unlikely that information on any not very common risk could be detected. Any such risks are likely to be evaluable only if the product is ever administered to very large numbers of subjects and this will be a matter of post-marketing efforts in the future.

The treatments come in different tube presentations/fill sizes and the physical properties of the creams and ointments differ, which pose a challenge for blinding. Therefore, the treatment arms cannot be considered truly double-blind. Only crisaborole and its corresponding vehicle are double-blind relative to each other, since tube and product appearance are the same.

The proposed key inclusion and exclusion criteria are considered appropriate to reflect the (paediatric) target population in the EU as they are comparable to previous studies conducted during the MAA of crisaborole in the EU. They also ensure a homogenous study population. Although a heterogeneous study population may increase external validity, a homogenous sample reduces variability, ensures comparability of the tested substances within the study, and may facilitate comparability to previous studies. TCS patients in cohort 1 were patients not eligible for TCI treatment and TCI patients in cohort 2 were not eligible for TCS, ensuring that each patient is treated in the best possible way.

As specified in the provided SAP version 3, data from cohort 1 and 2 were pooled for the efficacy comparison of crisaborole versus vehicle, which is in line with the original SAP and has been agreed in the PIP. By pooling vehicle and crisaborole groups, the planned sample size for each group (vehicle, crisaborole, pimecrolimus, hydrocortisone) was N= 150 and the planned size of each cohort was N=300. As due to the early termination only descriptive analyses are provided and the cohorts are deemed sufficiently comparable in terms of baseline (disease) characteristics, the pooling makes sense in the present case.

It was planned to establish comparability of crisaborole vs active comparators based on descriptive analyses as a secondary analysis, which was agreed in the latest PDCO discussion (EMEA-002065-PIP01-16-M01). Descriptive analyses are considered valuable to establish contextualization of crisaborole.

Results

A total of 237 participants were randomized and 235 participants were treated across the 4 treatment groups in the study. Of the 235 total study participants, 91 were adult patients ≥18 years, and 144 were in the age group of 2-17 years. Within the paediatric population, 56 (23.8% of total) were 2-6 years of age, 40 (17.0% of total) were 7-≤12 years of age, 48 (20.4% of total) were 12-≤18 years of age. This sample size was considered insufficient to conduct hypotheses testing and perform adequately powered statistical analyses according to the Applicant, therefore only descriptive summaries for efficacy and safety endpoints were summarized. The primary comparison of crisaborole vs vehicle was not possible as planned. However, within the paediatric cohort group sizes were balanced (considering vehicle and crisaborole groups were pooled) and reported results indicated the following efficacy trends:

At Day 29 crisaborole shows greater numerical improvement compared to vehicle in all reported endpoints, except two PRO outcomes. The crisaborole effect is numerically smaller compared to the TCS (and TCI) treatments across all age groups for most reported endpoints. TCS appears to be superior to the two other treatments, while TCI seems to be similarly or slightly more effective than crisaborole.

Results for certain secondary endpoints, e.g. some Patient Reported Outcomes (PRO) are not reported. For some reported outcomes (e.g. Time to EASI75), results were reported upon request separately for all predefined age subsets within the paediatric subgroup <18y. Time to EASI75 results indicate that onset of action was rather quick across treatment groups (and that the study duration of 29 days was likely sufficient to capture immediate response), and that age did not seem a predictive factor.

Overall demographic data were balanced across age and treatment groups. Due to the small sample sizes per age subset it seems unlikely that true differences relative to age could be determined based on the available data. Anyhow, upon request it was confirmed that no relevant differences regarding efficacy (or safety) were observed between the groups.

The majority of enrolled participants completed the study in all treatment and age groups. The highest discontinuation rate was observed in the vehicle group.

It is noted that in the Final Clinical Study Report many efficacy and safety tables are displayed in a non-intuitive way, presumably due to an error during the data export process (it seems too many zeros are printed before the actual results). It is assumed that data integrity is not compromised.

Upon request paediatric data were shown for local tolerability which is likely the most important safety objective of interest in this short-term trial. There were no relevant differences in the tolerability between the paediatric and adult population. In the treatment area, application and instillation site reactions were experienced most frequently in the crisaborole treatment group (9 participants, 15.5%) and observed in all age subgroups.

Within the treatment groups, most treatment-related TEAEs were recorded in the crisaborole group, followed by vehicle, pimecrolimus and lowest rates in the hydrocortisone group. The most frequently reported treatment-related TEAEs were application site pain and dermatitis atopic. Application site pain was the most frequently reported TEAE in the crisaborole treatment group; the incidence was higher in participants age 2-17 years (6 participants, 16.2%) than in participants age ≥18 years (2 participants, 9.5%).

Treatment-related Dermatitis atopic was reported in the vehicle group (4 participants, 6.8%) and the crisaborole group (2 participants, 3.4%), but not in the active control groups, which could be a reflection of inferior efficacy. Most of the TEAEs reported were mild; no SAEs and no deaths were

reported in the study. Three participants age 2-17 years in the crisaborole group discontinued from the study due to an adverse event (none in the other groups).

Overall, crisaborole showed a rather benign safety profile, but seemed inferior compared to the active comparators when comparing total number of adverse events and especially incidence of application site pain in this short-term trial. No new safety information was identified and observed safety events were consistent with those seen in other crisaborole studies involving participants in the same age range in the registrational studies. No new safety issues were identified from clinical laboratory or vital signs findings.

3. CHMP overall conclusion and recommendation

Limited data from a prematurely terminated comparative phase III/IV study support a larger effect of crisaborole compared to vehicle in paediatric patients 2-<18 years of age with mild to moderate atopic dermatitis over one 29-day treatment cycle.

Conclusions derived from this study are afflicted with some uncertainties pertaining to potentially selective data reporting, mistakes in graphic data display as well as due to impaired blinding, besides the small sample size and short study duration. However, a trend for inferior efficacy of crisaborole compared to TCS (and TCI) cannot be ignored, at the same time local tolerability seemed inferior to the active comparators. An update of the product information might be indicated as these observations are deemed relevant for users and prescribers and relevant results of all studies conducted in children should be presented (SmPC guideline). Based on historical data it could be assumed that crisaborole has some advantages compared to TCS (and maybe also TCIs) in long-term safety, but such cannot finally be assessed based on results from the presented study.

☒ Not fulfilled:

Based on the data submitted, the MAH should address the questions as detailed in the request for supplementary information (see section 5 below)

4. Additional clarification requested

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

1. The Applicant is asked to discuss an adaption of the product information to display relevant results from C3291037. Despite the limited sample size of the present study, observations are deemed relevant for users and prescribers.
2. No initial SAP and no initial study protocols are submitted. Therefore, initially planned endpoints and respective analyses, sample size calculations including expected drop-out rates or plans for pooling cannot be reviewed. The Applicant is asked to provide the initial SAP and study protocol and explain all relevant changes/adaptions made pertaining to the topics listed above, also in relation to the early study termination.
3. The Applicant is asked to present data for predefined paediatric subgroups: 2-6 years of age, 7-≤12 years of age, and 12-≥18years of age for the primary efficacy endpoint (percent change from baseline in EASI total score at day 29) and discuss potential differences in effect. In

addition, it should be confirmed that no relevant differences regarding efficacy (or safety) were observed between the age-subsets for other pre-defined endpoints.

4. No specific paediatric data are shown for time to EASI75 and local tolerability outcomes. The Applicant is asked to present these data for paediatric patients (and according to pre-defined age sub-sets, if feasible) and compare results to adult data, if possible.

5. The Applicant should explain why certain PRO data were not analysed or presented in the study report and how the choice was made on which analyses to conduct/present and which not. Data for all pre-defined secondary PRO endpoints and all age groups, including time to ≥2 and ≥ 3 point improvement from baseline should be presented, if feasible.

6. The number of paediatric subjects with <5% treatable %BSA at baseline should be provided and the aberrance to the inclusion criteria as well as potential impact on clinical outcomes should be commented on.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

1. The Applicant is asked to discuss an adaption of the product information to display relevant results from C3291037. Despite the limited sample size of the present study, observations are deemed relevant for users and prescribers.

Applicant´s Response

The MAH is providing the comparative data requested by CHMP through these query responses. The MAH has carefully considered this and does not propose updates to the product information for Staquis (crisaborole) based on the limited results of the early terminated Study C3291037.

Comparative data from this terminated study will not provide useful additional information to the prescribers for all of the following reasons:

- The study was not designed and was not powered to compare crisaborole to hydrocortisone or pimecrolimus. The primary objectives of the original protocol and implemented amendments were to compare the efficacy, safety, and local tolerability of crisaborole BID to vehicle and to evaluate the safety and local tolerability of hydrocortisone and pimecrolimus. See the Query #2 Response for details.
- The study was terminated early due to a business decision in October 2020. The decision to terminate was not based on efficacy or safety concerns of crisaborole.
- As the study was not powered to compare crisaborole to active comparators, and the final sample sizes were considerably smaller at the time of termination than those planned in the original protocol, any trends in the data would not be reliable and/or statistically or clinically meaningful.
- Due to early termination of the study there was a reduced sample size (only 39% [235/600] of planned participants were enrolled at termination) which was insufficient to allow robust statistical analyses; therefore, completion of the statistical analyses per the original statistical analysis plan was no longer appropriate.
- Prior to unblinding of any study data (database release on 15 January 2021), the statistical analysis plan (SAP) was updated on 10 November 2020. The reduced sample size posed important challenges for final analysis of the data, and analysis for the paediatric participants as a whole group, rather than by age subsets, was assessed to be the more appropriate way to summarize the limited data.
- The updates to the SAP reflected the sample size limitations of the terminated study. This included no statistical analyses and hypothesis testing for all endpoints, and only descriptive summaries for the primary endpoint and a subset of secondary endpoints based on assessments

performed by trained investigators. Please see Query # 2 Response for details and comparison of endpoints between the original Study C3291037 protocol and Amendment 3, as well as the final decisions.

- Summaries of the primary efficacy endpoint as well as treatment-emergent adverse events (TEAEs) by the pre-defined age cohorts are provided in the Query #3 response. Across age cohorts, Eczema Area and Severity Index (EASI) reduced from baseline to Day 29 for all 4 treatment groups. Mean percent change from baseline to Day 29 varies across age groups. Due to such a small sample size, this variation may happen and differences between treatment and age groups cannot be interpreted. The types and frequencies of TEAEs reported are similar across age cohorts.
- As requested by the CHMP, summaries of time to first achievement of EASI75 (ie, ≥75% improvement from Baseline) by the pre-defined age cohorts are provided in the Query #4 Response. However, because of the smaller-than-originally- planned sample size, further subdividing the population based on age groups renders even smaller sample sizes among the paediatric age groups and makes any meaningful interpretation or conclusions infeasible.
- Details and rationale for the subset of Patient-Reported Outcomes (PRO) endpoints included for analyses are provided in the Query #5 Response.
- Only one paediatric participant was enrolled with percent body surface area (%BSA) <5, with no impact on the clinical outcome (see Query #6 Response).

Assessment of Response:

Although it is true that the study was not designed and was not powered to compare crisaborole to hydrocortisone or pimecrolimus, it is highlighted that an estimation approach for comparison of crisaborole vs the TCS and TCI was deemed appropriate as a secondary analysis in the latest PDCO discussion (EMEA-002065-PIP01-16-M01). Despite limited sample size due to early termination, descriptive analyses are still considered relevant, and were a priori classified as secondary analysis. Although the amount of data is limited because the study was terminated prematurely, the results show obvious trends that should not be ignored. Information could be useful to inform treatment decisions and are thus potentially relevant for users and prescribers. It is acknowledged that this is a topic of further research. But the apparent limitations do not seem to justify withholding the findings, which should be publicly available and therefore presented in the SmPC (no publication of data from the terminated study seems planned).

The Applicant claims that the statistical analysis plan (SAP) was updated prior to unblinding of any study data. However, since true double-blinding was not possible between crisaborole and active comparators, introduction of a potential bias cannot be fully excluded at this point.

Conclusion:

Point not resolved (see section 5).

2. No initial SAP and no initial study protocols are submitted. Therefore, initially planned endpoints and respective analyses, sample size calculations including expected drop-out rates or plans for pooling cannot be reviewed. The Applicant is asked to provide the initial SAP and study protocol and explain all relevant changes/adaptions made pertaining to the topics listed above, also in relation to the early study termination.

Applicant´s Response

The initial Study C3291037 protocol and its amendment 3, and statistical analysis plan (SAP) and final SAP amendment, are provided as supportive documentation for this response.

As described in the CSR, Study C3291037 was terminated early (October 2020) by the MAH due to business decisions. The termination decision was not related to any safety or efficacy concerns regarding crisaborole. At the time of early termination, only 39% of the total planned sample size had been enrolled (see Table 2). Given the early termination and reduced total number of participants, the MAH decided to report the study results with the available sample size through an abbreviated clinical study report (in accordance with EMA Guidance, CPMP/ICH/137/95, July 1996).

The original SAP was approved on 16 May 2018 and version 3 of the SAP, which was used to develop the abbreviated Clinical Study Report, was approved on 10 November 2020.

Importantly, the revisions of the SAP were not influenced by any data results, given the fact that version 3 was approved on 10 November 2020 before randomization code release (12 January 2021) and database release (15 January 2021).

The changes applied to the statistical analysis plan listed here are detailed below:

- A descriptive summary was performed for the primary endpoint and the secondary efficacy endpoints based on assessments performed by trained investigators. A subset of PRO secondary endpoints was selected based on the final actual sample size.
- No summary/analysis was performed for pruritus-related secondary endpoints for paediatric participants in the 2-6 and 7-11 years age groups given that these subset groups were particularly small for these 2 age groups in which different instruments were used.
- For the age group 12 years and older, no summary/analysis was performed for Time to ≥ 2-point improvement from baseline in Peak Pruritus Numerical Rating Scale (NRS) and Time to ≥ 3-point improvement from baseline in Peak Pruritus NRS.
- No summary/analysis was performed for tertiary/exploratory endpoints.

Study Objective and Endpoints vs Changes to Analyses at Study Termination

The original study objective was to evaluate the efficacy and safety of crisaborole vs vehicle in participants with mild to moderate atopic dermatitis. As part of the study design, 2 active comparators were included. The study was not designed nor powered to compare statistically the efficacy between crisaborole and either of the 2 active comparators.

After the early termination of the study and with a reduced sample size, completion of statistical analysis per the original statistical analysis plan was not feasible. As such a small sample size (39% [235/600] of planned participants) was insufficient to allow meaningful and robust statistical analyses, a decision to report study results in an abbreviated manner was made. This decision was not influenced by data results, given that the decision was made before the database was released as described above.

A subset of secondary endpoints were chosen for analyses for the final study summary. Because of the smaller-than-originally-planned sample size, further subdividing the population based on age groups for secondary endpoints renders even smaller sample sizes among the paediatric age groups. This makes any meaningful interpretation or conclusions for limited data infeasible. Therefore, the selection of secondary endpoints for the final study summary was based on endpoints from assessments performed by trained investigators and the individual age group sample sizes.

Further, the use of different instruments in the 2 age groups 2-6 and 7-11 years precluded pooling of the data. Therefore, pruritus-related secondary endpoints for paediatric participants in these 2 age groups were not summarized in the final analysis (for more details see Query #5 Response). Reliable statistical or clinically-meaningful conclusions could not be drawn from the descriptive summaries because of the inherent variability associated with such a small sample size.

Table 1 compares the planned endpoints in the original Study C3291037 Protocol and Amendment 3, and indicates which were included in the final analyses (from the final SAP). Changes from Amendments 1 and 2 were incorporated into Amendment 3.

Table 1. Comparison of Endpoints in Original Protocol and Amendment 3 of Study C3291037

Endpoints in FAP 16Mar2018	Endpoints in Amendment 3 12 August 2019	Included in final analyses
Primary Efficacy Endpoint		
Percent change from Baseline in the Eczema Area and Severity Index (EASI) total score at Day 29		Yes
Primary Safety Endpoints		
AEs, SAEs, local tolerability, discontinuations and clinically significant changes in vital signs and clinical laboratory parameters		Yes
Secondary Efficacy Endpoints		
• Percent change from Baseline in EASI total score by scheduled time points except Day 29.		Yes
• Proportion of participants achieving success in the Investigator's Static Global Assessment (ISGA) (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline) by scheduled time points.	• Achievement of success in the Investigator's Static Global Assessment (ISGA) (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline) by scheduled time points	Yes
• Proportion of participants with ISGA score of clear (0) or almost clear (1) by scheduled time points.	• Achievement of ISGA score of Clear (0) or Almost Clear (1) by scheduled time points.	Yes
• Proportion of participants with EASI75 (≥75% improvement from Baseline) by scheduled time points.	• Achievement of EASI75 (≥75% improvement from Baseline) by scheduled time points.	Yes
• Time to EASI75.		Yes
• Change from Baseline in % BSA by scheduled time points.		Yes
Secondary PRO Endpoints		
• Change from Baseline in Peak Pruritus Numerical Rating Scale (NRS) by scheduled time points (Version for Participants 12 years and older).		Yes
• Change from Baseline in Peak Pruritus Scale by scheduled time points (Version for Participants ≥6 and <12 years).	• Change from Baseline in Patient Reported Itch Severity Scale - for participants age 6-11 years by scheduled time points.	No
• Change from Baseline in Peak Pruritus NRS by scheduled time points (Observer version for Participants <6 years).	• Change from Baseline in Observer Reported Itch Severity Scale - for participants <6 years by scheduled time points.	No
• Time to ≥2 point improvement from Baseline in Peak Pruritus NRS (Participants ≥12 years).		No
• Time to ≥3 point improvement from Baseline in Peak Pruritus NRS for participants ≥12 years.		No
• Time to ≥2 point improvement from Baseline in Peak Pruritus NRS (Observer version for Participants <6 years).	• Time to ≥2 point improvement from Baseline in Observer Reported Itch Severity Scale - for participants <6 years.	No
• Time to ≥3 point improvement from Baseline in Peak Pruritus NRS (Observer version for Participants <6 years	• Time to ≥3 point improvement from Baseline in Observer Reported Itch Severity Scale - for participants <6 years.	No
• Proportion of participants with ≥2 point improvement from Baseline in Peak Pruritus NRS (Participants 12 years and older).	• Achievement of ≥2 point improvement from Baseline in Peak Pruritus NRS for participants ≥12 years.	Yes
• Proportion of participants with ≥3 point improvement from Baseline in Peak Pruritus NRS (Participants 12 years and older).	• Achievement of ≥3 point improvement from Baseline in Peak Pruritus NRS for participants ≥12 years.	Yes

• Proportion of participants with ≥2 point improvement from Baseline in Peak Pruritus NRS (Observer version for Participants <6 years).	• Achievement of ≥2 point improvement from Baseline in Observer Reported Itch Severity Scale - for participants <6 years.	No
• Proportion of participants with ≥3 point improvement from Baseline in Peak Pruritus NRS (Observer version for Participants <6 years).	• Achievement of ≥3 point improvement from Baseline in Observer Reported Itch Severity Scale - for participants <6 years.	No
• Change from Baseline in Dermatology Life Quality Index (DLQI) (for Participants 16 years and older), Children's Dermatology Life Quality Index (CDLQI) (for Participants 4-15 years), and Dermatitis Family Impact Questionnaire (DFI) (Completed by parent/caregiver of Participants 2-17 years) by scheduled time points.		Yes

Originally Planned Sample Size and Statistical Analyses

As described in the Study C3291037 Protocol Section 9.1, the sample size calculation was based on the comparison of crisaborole vs vehicle for the primary endpoint percent change in Eczema Area and Severity Index (EASI) from baseline to Day 29. The crisaborole and vehicle treatment arms of Cohort 1 and Cohort 2 were to be combined/pooled for the comparison of crisaborole vs vehicle analyses to achieve a statistically reliable sample size of 150 participants in each of the combined group. A sample size of 150 in each the crisaborole and vehicle groups would have provided 86% power to detect a 12% difference of EASI percent reduction from baseline at Day 29 between crisaborole and vehicle at the 0.05 (2-sided) significance level, assuming the common standard deviation of EASI percent reduction from baseline at Day 29 is 34%.

The sample size of 75 in each of the crisaborole cohorts and the twice bigger sample size of 150 for each of the active comparator groups topical corticosteroid (hydrocortisone butyrate cream 0.1%; TCS) or topical calcineurin inhibitor (pimecrolimus cream 1%; TCI) would not have had sufficient power for the comparison of crisaborole vs TCS or TCI. With such a sample size, the half width of the 95% confidence interval for the difference of EASI percent reduction from baseline at Day 29 between crisaborole and either of the active comparators would have been 9.4%.

The sample size within each Cohort would have provided sufficient precision to enable contextualization of the efficacy of crisaborole in treating participants with mild to moderate Atopic Dermatitis relative to each active comparator, but with no hypothesis testing for superiority or non-inferiority. While informative, even this original design would not have provided results that would lead to a change in the product information for crisaborole.

Planned vs Actual Sample Size in Paediatric Participants at Termination by Age Groups

For enrolment by paediatric age groups, the study planned to enrol at least 510 paediatric participants (target total enrolment was 600 participants) (see Table 2). At the time of termination only 144 paediatric participants had been enrolled.

Please see Study C3291037 Protocol Section 3 and Section 9.1 for details of sample size.

Table 2. Planned Enrolment by Age vs Actual Enrolment at Termination

Age	Planned	Actual at Termination
2 to 6 years	At least 150	56
7 to 11 years	At least 140	40
12 to 17 years	At least 120	48
Total Paediatric	**Approximately 510**	**144**
≥ 18 years	Up to 90	91
Total	**Approximately 600**	**235**

Planned Primary Endpoint Analyses

Initially, a mixed-effect model with repeated measures (MMRM) was planned for the analysis for the primary endpoint percent change from baseline to Day 29 in EASI and other continuous endpoints measured longitudinally for the comparison of crisaborole vs vehicle (combined Cohorts 1 and 2), crisaborole vs hydrocortisone (Cohort 1), and crisaborole vs pimecrolimus (Cohort 2). P-values would not be provided for crisaborole vs active comparators. The post-baseline missing values would be handled by MMRM, where the values are assumed to be missing at random.

For binary endpoints, Cochran Mantel Haenszel (CMH) testing was planned for comparison of crisaborole vs vehicle (combined Cohorts 1 and 2; controlling for cohort). No analysis for crisaborole vs hydrocortisone (Cohort 1) and crisaborole vs pimecrolimus (Cohort 2) was planned. Only descriptive summaries were planned for crisaborole vs active comparators.

The analysis or summary would be performed at each scheduled visit separately. If a participant had no data for a binary endpoint at a scheduled visit, this participant would be classified as a non-responder (NR) for that endpoint at that visit.

Missing Values and Dropout Rate

Based on initially planned analysis/summary as described above, missing values would be handled by MMRM for continuous endpoints and missing values would be imputed as Non-Responders for binary endpoints. The dropout rate was not planned for consideration for sample size calculation and data analysis.

Pooled Data

Based on the above initially planned analysis/summary agreed in the PIP (EMA PIP Decision: P/0276/2020), Cohorts 1 and 2 of crisaborole and vehicle were to be pooled for the comparison of crisaborole vs vehicle.

Assessment of Response:

Initially planned endpoints and respective analyses, sample size calculations including expected drop-out rates and plans for pooling are now provided by the Applicant. Only descriptive summaries were a priori planned for crisaborole vs active comparators and descriptive results can be valuable e.g. to inform a product information. Please also refer to assessment of response to request 1.

Regarding pruritus-related secondary endpoints for paediatric participants it is accepted that the use of different instruments in the 2 age groups 2-6 and 7-11 years precluded pooling of the data. Yet, it is not sufficiently justified why those endpoints could not be presented as descriptive summaries. Please also refer to assessment of response to request 5.

Sample size calculation is in line with the PIP, although it is not entirely clear why no dropout rate was planned for. Pooling of cohorts 1 and 2 for crisaborole and vehicle is considered appropriate and in line with the PIP.

Conclusion:

Point resolved.

3. The Applicant is asked to present data for predefined paediatric subgroups: 2-6 years of age, 7-≤12 years of age, and 12-≥18years of age for the primary efficacy endpoint (percent change from baseline in EASI total score at day 29) and discuss potential differences in effect. In addition, it should be confirmed that no relevant differences regarding efficacy (or safety) were observed between the age-subsets for other pre-defined endpoints.

Applicant´s Response

The MAH has summarized the primary efficacy endpoint as well as treatment-emergent AEs by the pre-defined age cohorts in this response.

As discussed in the Clinical Study Report, because of the considerably smaller-than- originally-planned sample size, it is not possible to draw conclusions based on the results of Study C3291037. Further subdividing the population based on age groups renders even smaller sample sizes among the paediatric age groups and makes any robust statistical or clinically meaningful interpretation or conclusions infeasible.

Based on descriptive summary statistics in below Table 1, the primary efficacy endpoint results show that, across age cohorts, Eczema Area and Severity Index (EASI) reduced from baseline to Day 29 for all 4 treatment groups; reduction is seen more in the active arms.

Mean percent change from baseline to Day 29 varies across age groups. Due to such a small sample size, this variation is expected. Inferences cannot be made from the apparent differences across the paediatric subgroups as well as compared to the adult population due to the inherent variability in the very small numbers of paediatric participants.

Treatment-emergent adverse events (TEAEs) are summarized by age group in the following Table 2, Table 3, Table 4, and Table 5. The types and frequencies of TEAEs reported are similar across age cohorts.

Table 1. Summary of Percent Change from Baseline in EASI Total Score at Day 29 by Age Group (FAS, Observed) C3291037

Age Group	Summary Statistics	Vehicle	Crisaborole 2% BID			Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
			Cohort 1	Cohort 2	Total		
2-6 Years	N/n	14/11	10/7	5/5	15/12	16/14	11/10
	Mean (SE)	13.58 (4.278)	4.77 (1.496)	4.96 (2.497)	4.85 (1.287)	1.43 (0.846)	4.85 (1.744)
	Std.Dev	14.188	3.957	5.584	4.460	3.165	5.516
	Median	7.20	5.80	3.50	4.30	0.20	1.80
	Range (Min, Max)	(1.9, 44.6)	(0.0, 10.1)	(0.4, 14.4)	(0.0, 14.4)	(0.0, 12.0)	(0.0, 15.4)
7-11 Years[a]	N/n	12/10	5/4	5/5	10/9	10/9	8/8
	Mean (SE)	5.16 (1.754)	6.23 (1.536)	3.66 (1.797)	4.80 (1.222)	2.93 (2.327)	3.80 (1.129)
	Std.Dev	5.546	3.073	4.018	3.666	6.981	3.195
	Median	2.25	5.75	2.00	4.10	0.80	2.50
	Range (Min, Max)	(1.2, 16.8)	(3.0, 10.4)	(0.2, 10.4)	(0.2, 10.4)	(0.0, 21.5)	(0.0, 7.8)
12-17 Years	N/n	12/10	8/7	4/3	12/10	13/13	11/11
	Mean (SE)	5.13 (1.897)	4.50 (1.737)	3.97 (1.994)	4.34 (1.296)	4.03 (0.979)	3.48 (0.833)
	Std.Dev	5.999	4.597	3.453	4.099	3.529	2.761
	Median	3.00	1.60	5.60	3.60	4.00	3.60
	Range (Min, Max)	(0.0, 20.0)	(0.4, 12.9)	(0.0, 6.3)	(0.0, 12.9)	(0.0, 12.4)	(0.0, 8.7)
≥18 Years	n	17	12	7	19	29	14
	Mean (SE)	5.18 (1.230)	3.58 (1.476)	5.21 (1.380)	4.18 (1.053)	1.96 (0.414)	3.51 (1.235)
	Std.Dev	5.071	5.113	3.650	4.591	2.232	4.621
	Median	3.40	1.65	4.80	2.20	1.20	2.50
	Range (Min, Max)	(0.0, 20.2)	(0.0, 16.4)	(0.8, 11.8)	(0.0, 16.4)	(0.0, 9.6)	(0.0, 18.5)

[redacted]

BID=twice daily; EASI= Eczema Area and Severity Index; FAS= full analysis set; SE=standard error

-FAS=Full Analysis Set: is defined as all randomized participants receiving at least one dose of investigational product. Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.

-Baseline is defined as the last evaluation taken before the first dose.

N: Number of participants in the analysis set.

n: Number of participants in the analysis set with non-missing data at a given visit.

a One participant in the 7-11 age group was excluded from analysis due to using the wrong questionnaire.

Table 2. Treatment-Emergent Adverse Events (All Causalities) - Overall (Participants 2-6 Years) (SAF) C3291037

	Vehicle	Crisaborole 2% BID	Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Subjects Evaluable for AEs	14	15	16	11
Number of adverse events	13	14	3	10
Subjects with adverse events	6 (42.9)	7 (46.7)	2 (12.5)	7 (63.6)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
Subjects discontinued from study due to adverse events (a)	0	1 (6.7)	0	0
Subjects discontinued study drug due to AE and continue study (b)	2 (14.3)	0	0	1 (9.1)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (7.1)	0	0	0

[redacted]

AE=adverse event; BID=twice daily; SAF= Safety Analysis Set: is defined as those participants who received at least one dose of the investigational product according to actual treatment received. Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.
- Includes all data collected since the first dose of study drug.
- Except for the Number of Adverse Events participants are counted only once per treatment in each row. Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not cause the participant to be discontinued from study.
N: Number of participants in the analysis set; n: Number of participants with events
MedDRA v23.1 coding dictionary applied.

Table 3. Treatment-Emergent Adverse Events (All Causalities) - Overall (Participants 7-11 Years) (SAF) C3291037

	Vehicle	Crisaborole 2% BID	Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Subjects Evaluable for AEs	12	10	10	8
Number of adverse events	2	6	2	4
Subjects with adverse events	2 (16.7)	3 (30.0)	2 (20.0)	4 (50.0)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
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 (8.3)	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (8.3)	0	0	0

[redacted]

AE=adverse event; BID=twice daily
SAF= Safety Analysis Set: is defined as those participants who received at least one dose of the investigational product according to actual treatment received.
Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.
- Includes all data collected since the first dose of study drug.
- Except for the Number of Adverse Events, participants are counted only once per treatment in each row. Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not cause the participant to be discontinued from study.
N: Number of participants in the analysis set; n: Number of participants with events
MedDRA v23.1 coding dictionary applied.

Table 4. Treatment-Emergent Adverse Events (All Causalities) - Overall (Participants 12-17 Years) (SAF) C3291037

	Vehicle	Crisaborole 2% BID	Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Subjects Evaluable for AEs	12	12	13	11
Number of adverse events	9	8	4	6
Subjects with adverse events	5 (41.7)	4 (33.3)	2 (15.4)	6 (54.5)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	0	0	0
Subjects discontinued from study due to adverse events (a)	0	2 (16.7)	0	0
Subjects discontinued study drug due to AE and continue study (b)	2 (16.7)	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	0

[redacted]
AE=adverse event; BID=twice daily
SAF= Safety Analysis Set: is defined as those participants who received at least one dose of the investigational product according to actual treatment received.
Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.
- Includes all data collected since the first dose of study drug.
- Except for the Number of Adverse Events participants are counted only once per treatment in each row. Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not cause the participant to be discontinued from study.
N: Number of participants in the analysis set; n: Number of participants with events
MedDRA v23.1 coding dictionary applied.

Table 5. Treatment-Emergent Adverse Events (All Causalities) - Overall (Participants >=18 Years) (SAF) C3291037

	Vehicle	Crisaborole 2% BID	Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Subjects Evaluable for AEs	21	21	32	17
Number of adverse events	7	16	8	19
Subjects with adverse events	5 (23.8)	9 (42.9)	6 (18.8)	7 (41.2)
Subjects with serious adverse events	0	0	0	0
Subjects with severe adverse events	0	1 (4.8)	0	0
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 (4.8)	0	0	1 (5.9)
Subjects with dose reduced or temporary discontinuation due to adverse events	0	1 (4.8)	1 (3.1)	0

[redacted]

AE=adverse event; BID=twice daily
SAF= Safety Analysis Set: is defined as those participants who received at least one dose of the investigational product according to actual treatment received.
Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.
- Includes all data collected since the first dose of study drug.
- Except for the Number of Adverse Events participants are counted only once per treatment in each row. Serious Adverse Events - according to the investigator's assessment.
(a) Participants who have an AE record that indicates that the AE caused the participant to be discontinued from the study.
(b) Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not cause the participant to be discontinued from study.
N: Number of participants in the analysis set; n: Number of participants with events
MedDRA v23.1 coding dictionary applied.

Assessment of Response:

The Applicant has provided requested data tables for the primary efficacy endpoint Eczema Area and Severity Index (EASI) and adverse events, which showed no apparent differences between the pre-defined age subsets.

As expected due to the small group sizes, large variation is seen across paediatric age subgroups. For EASI Total Score at Day 29 a particularly high mean (and SD) is noted in the vehicle group of participants aged 2-6 years, which could be driven by outlier(s). Nevertheless, subgroup data show that EASI reduced from baseline to day 29 for all treatment groups and similar trends were seen across age subgroups. Unfortunately, it is critically noted that the provided table is mislabelled and displays observed values rather than the requested change from baseline.

Regarding the frequencies of adverse events no apparent differences were observed between pre-defined age subsets.

Conclusion:

Point resolved.

4. No specific paediatric data are shown for time to EASI75 and local tolerability outcomes. The Applicant is asked to present these data for paediatric patients (and according to pre-defined age sub-sets, if feasible) and compare results to adult data, if possible.

Applicant´s Response

The MAH has summarized time to first ≥75% improvement from baseline in Eczema Area and Severity Index (EASI75) by the pre-defined age cohorts.

As described in the Response to Query #2, the reduced sample size posed important challenges for final analysis of the data, and analysis for the paediatric participants as a whole group, rather than by age subsets, was assessed to be the more appropriate way to summarize the limited data.

Because of the smaller-than-originally-planned sample size, further subdividing the population based on age groups renders even smaller sample sizes among the paediatric age groups and makes any meaningful interpretation or conclusions infeasible.

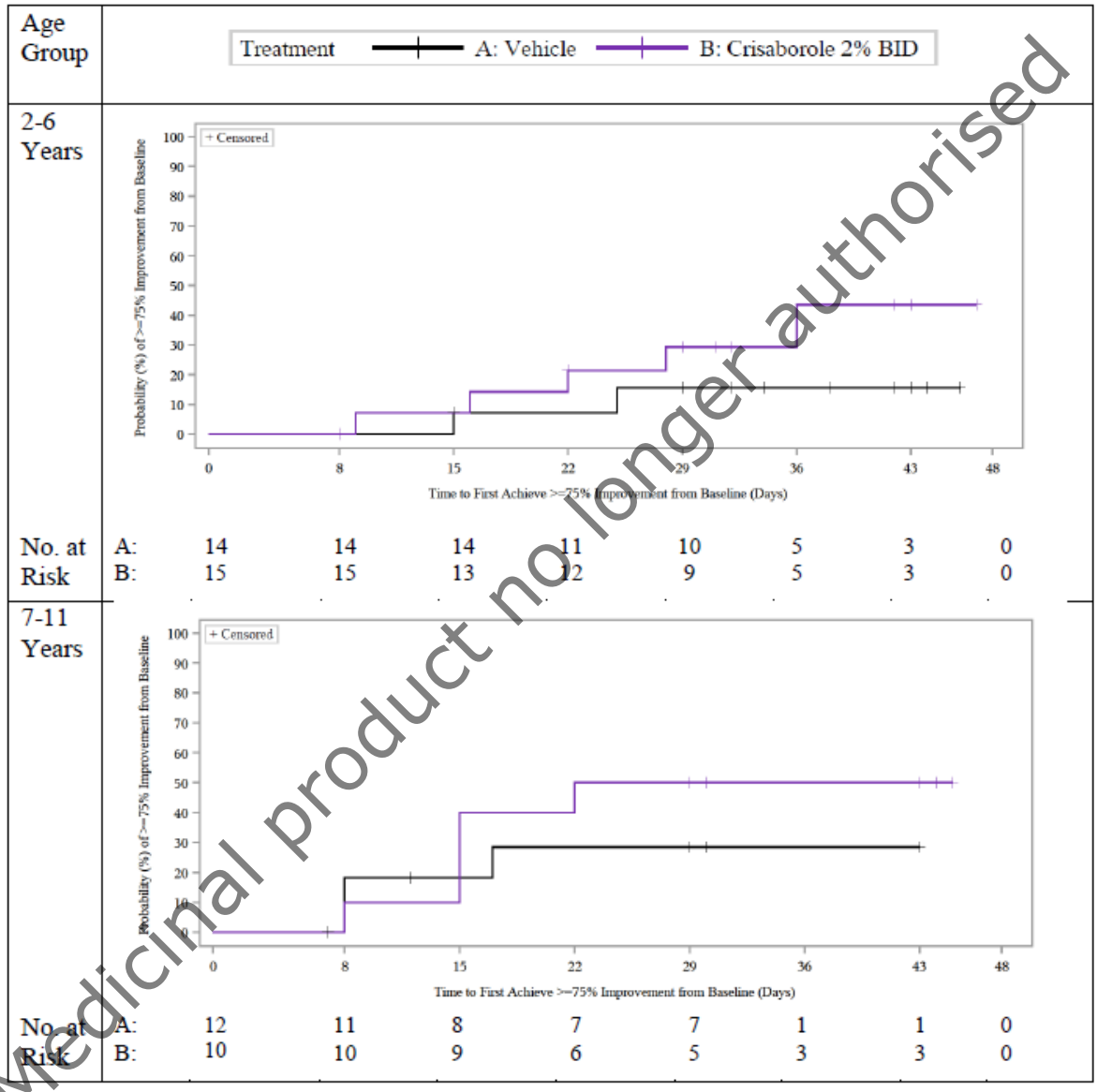
All EASI data collected during the study were included in the summaries. For data up to, and including, Day 29, participants received randomized, blinded treatment; after Day 29, participants no longer received randomized treatment and could initiate other therapies.

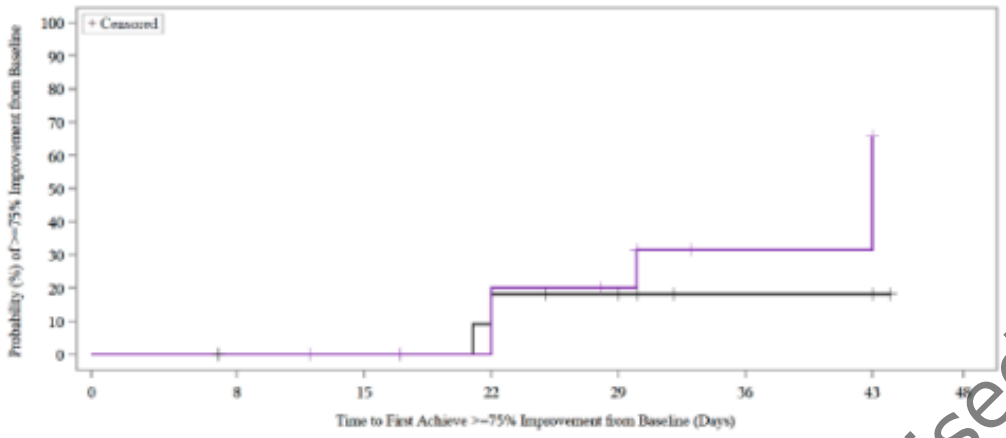
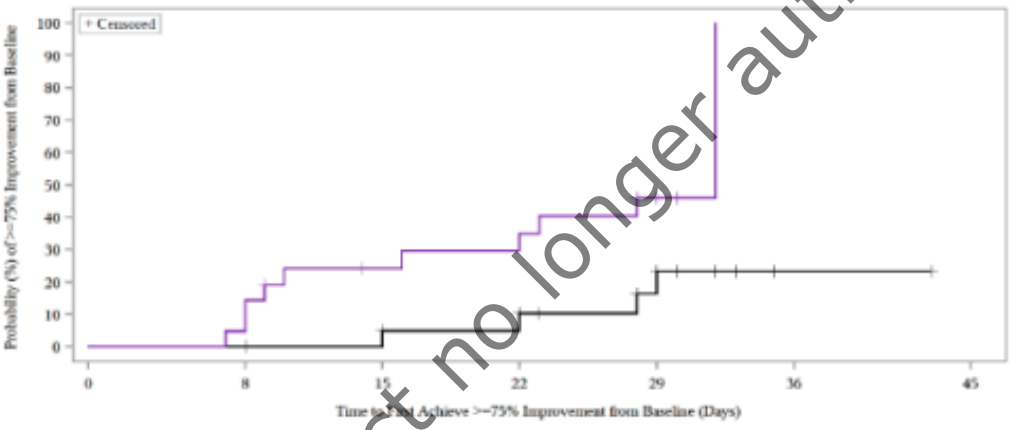
- Kaplan-Meier curves for crisaborole vs vehicle are presented in Figure 1. The plots had similar patterns across age groups. The plot for the pooled crisaborole group and the plot for the pooled vehicle group were separated.
- Kaplan-Meier curves for crisaborole vs active control are presented in Figure 2. The plots had similar patterns across age groups. The plot for the crisaborole cohorts and the plot for the active control groups overlapped.

Summary data for time to first achievement of EASI75 by paediatric age groups and the ≥18 years age group are presented in Table 1. No inferences can be made for the paediatric age groups and the adult age group due to limited data.

Tolerability is assessed by application site reactions, which are summarized by age groups, in Table 2. Few participants in each group had application site reactions.

Figure 1 Kaplan-Meier Curve for Time to First Achievement of EASI75 - Crisaborole vs. Vehicle by Age Group (FAS, Observed) C3291037



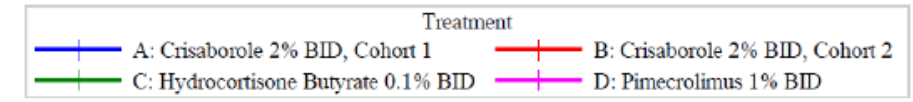
12-17 Years								
No. at Risk	A:	12	11	11	10	8	3	0
	B:	12	12	11	10	7	2	0
≥ 18 Years								
No. at Risk	A:	21	21	20	18	12	1	0
	B:	12	20	14	13	9	0	0

[redacted]

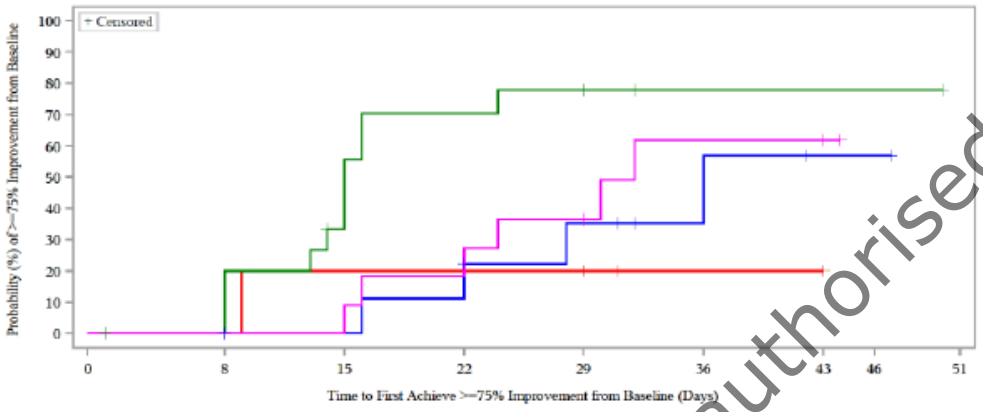
EASI75= Eczema Area and Severity Index ≥75% improvement from Baseline; FAS=Full Analysis Set: is defined as all randomized participants receiving at least one dose of investigational product. Cohorts 1 and 2 data are combined for the analysis of Crisaborole vs. Vehicle.
No. =number
-Baseline is defined as the last evaluation taken before the first dose.
-Participants who complete the study without the event of interest or those who withdrew before experiencing the event of interest had their event times right censored at the last available visit.
-Data reported up to and including Day 29/early termination: participants received randomized, blinded treatment.
-Data reported after Day 29/early termination: participants no longer received randomized treatment and could initiate other therapies.

Figure 2 Kaplan-Meier Curve for Time to First Achievement of EASI75 - Crisaborole vs. Active Control by Age Group (FAS, Observed) C3291037

Age Group

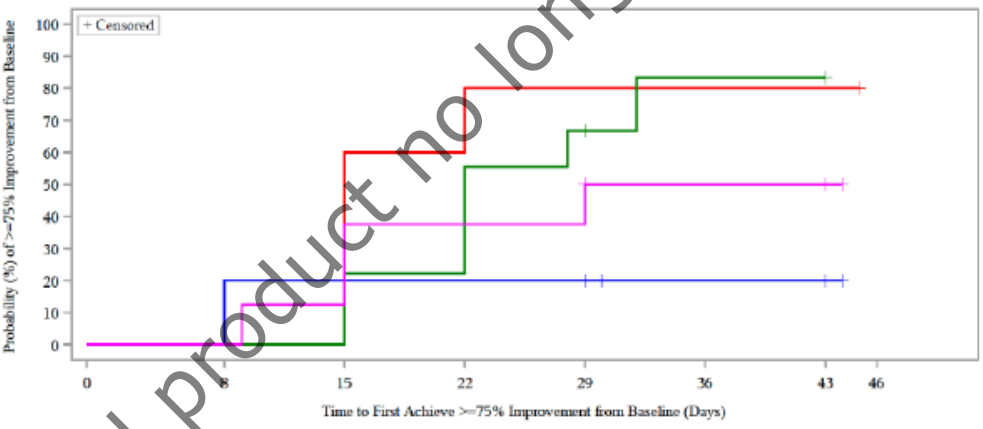


2-6 Years

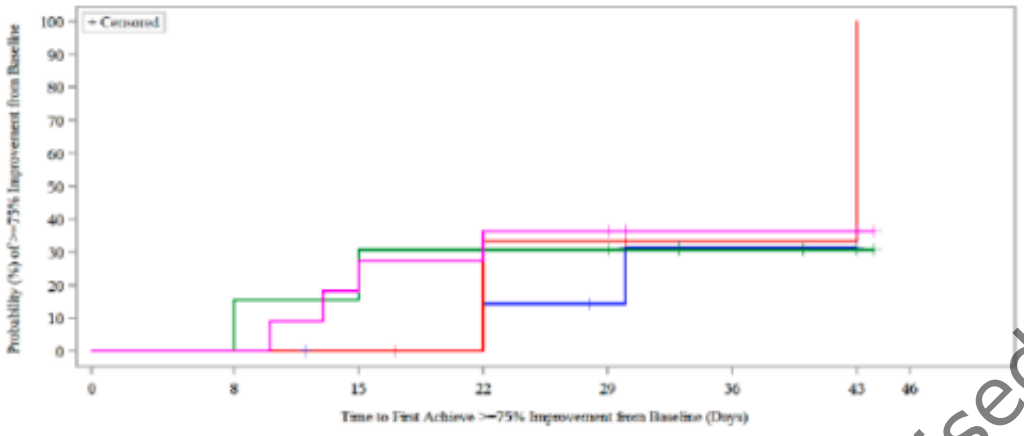
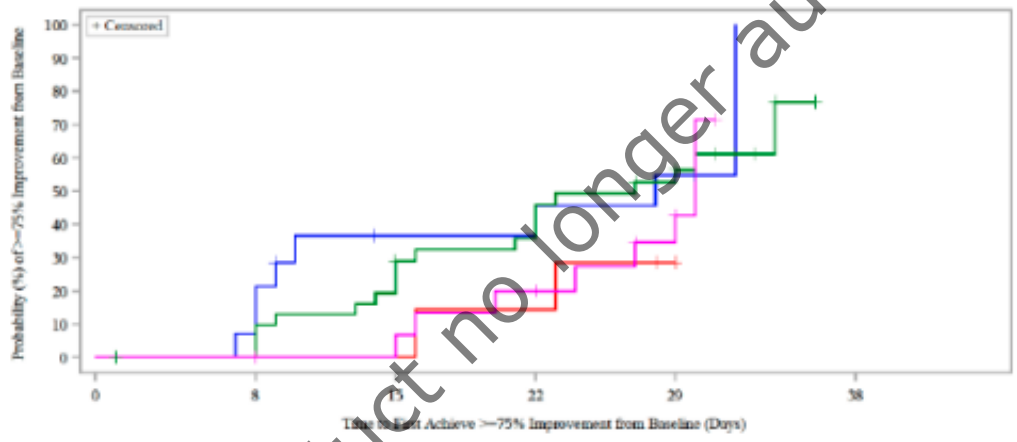


No. at Risk									
A:	10	10	9	8	5	3	1	1	0
B:	5	5	4	4	4	2	2	0	0
C:	16	15	9	4	3	1	1	1	0
D:	11	11	11	9	7	3	3	0	0

7-11 Years



No. at Risk								
A:	5	5	4	4	4	2	2	0
B:	5	5	5	2	1	1	1	0
C:	9	9	9	7	3	1	1	0
D:	8	8	7	5	5	2	2	0

12-17 Years								
No. at Risk	A:	8	8	7	7	5	1	1	0
	B:	4	4	4	3	2	1	1	0
	C:	13	13	11	9	9	6	3	0
	D:	11	11	9	8	7	4	4	0
≥18 Years								
No. at Risk	A:	14	13	7	7	5	0	
	B:	7	7	7	6	4	0	
	C:	32	31	25	19	13	0	
	D:	17	17	15	12	8	0	

[redacted]

EASI75= Eczema Area and Severity Index ≥75% improvement from Baseline; FAS= Full Analysis Set is defined as all randomized participants receiving at least one dose of investigational product. Cohort 1 data is included for analysis of Crisaborole vs. Hydrocortisone Butyrate. Cohort 2 data is included for analysis of Crisaborole vs. Pimecrolimus.
No. =number
-Baseline is defined as the last evaluation taken before the first dose.
-Participants who complete the study without the event of interest or those who withdraw before experiencing the event of interest will have their event times right censored at the last available visit.
-Data reported up to and including Day 29/early termination: participants received randomized, blinded treatment
-Data reported after Day 29/early termination: participants no longer received randomized treatment and could initiate other therapies.

Table 1. Time to First Achievement of EASI75 by Treatment and Age Groups (FAS, Observed) (C3291037)

Age Group		Vehicle	Crisaborole 2%			Hydrocortisone Butyrate 0.1% BID	Pimecrolimus 1% BID
			Cohort 1	Cohort 2	Total		
2-6 Years	**Number of Participants with data**	**14**	**10**	**5**	**15**	**16**	**11**
	Participants with event, n (%)	2 (14.3)	4 (40.0)	1 (20.0)	5 (33.3)	11 (68.8)	6 (54.5)
	Participants censored, n (%)	12 (85.7)	6 (60.0)	4 (80.0)	10 (66.7)	5 (31.3)	5 (45.5)
	Median time to event-days (95% CI)	NE (NE, NE)	36.0 (16.0, NE)	NE (9.0, NE)	NE (22.0, NE)	15.0 (8.0, 24.0)	32.0 (16.0, NE)
7-11 Years	**Number of Participants with data**	**12**	**5**	**5**	**10**	**9**	**8**
	Participants with event, n (%)	3 (25.0)	1 (20.0)	4 (80.0)	5 (50.0)	7 (77.8)	4 (50.0)
	Participants censored, n (%)	9 (75.0)	4 (80.0)	1 (20.0)	5 (50.0)	2 (22.2)	4 (50.0)
	Median time to event-days (95% CI)	NE (8.0, NE)	NE (8.0, NE)	15.0 (15.0, NE)	NE (8.0, NE)	22.0 (15.0, 32.0)	NE (9.0, NE)
12-17 Years	**Number of Participants with data**	**12**	**8**	**4**	**12**	**13**	**11**
	Participants with event, n (%)	2 (16.7)	2 (25.0)	2 (50.0)	4 (33.3)	4 (30.8)	4 (36.4)
	Participants censored, n (%)	10 (83.3)	6 (75.0)	2 (50.0)	8 (66.7)	9 (69.2)	7 (63.6)
	Median time to event-days (95% CI)	NE (22.0, NE)	NE (22.0, NE)	43.0 (22.0, 43.0)	43.0 (22.0, NE)	NE (15.0, NE)	NE (13.0, NE)
≥18 Years	**Number of Participants with data**	**21**	**14**	**7**	**21**	**32**	**17**
	Participants with event, n (%)	4 (19.0)	8 (57.1)	2 (28.6)	10 (47.6)	20 (62.5)	7 (41.2)
	Participants censored, n (%)	17 (81.0)	6 (42.9)	5 (71.4)	11 (52.4)	12 (37.5)	10 (58.8)
	Median time to event-days(95% CI)	NE (29.0, NE)	28.0 (8.0, 32.0)	NE (16.0, NE)	32.0 (16.0, 32.0)	27.0 (16.0, 34.0)	30.0 (20.0, NE)

[redacted]

BID=twice daily; CI=confidence interval; EASI75= Eczema Area and Severity Index improvement ≥75%; NE: Not Evaluable
FAS=Full Analysis Set is defined as all randomized participants receiving at least one dose of investigational product. Cohorts 1 and 2 data are combined for the analysis of Crisaborole vs. Vehicle.
NE=not evaluable
-Baseline is defined as the last evaluation taken before the first dose.
-Participants who complete the study without the event of interest or those who withdraw before experiencing the event of interest will have their event times right censored at the last available visit.
N: Number of participants in the analysis set. n (%): number (Percentage) of participants.

Table 2. Summary of Application Site Reactions by Treatment and Age Groups (SAF) C3291037

Age Group	High Level Term Preferred Term	Vehicle n (%)	Crisaborole 2% BID n (%)	Hydrocortisone Butyrate 0.1% BID n (%)	Pimecrolimus 1% BID n (%)
2-6 Years	N	14	15	16	11
	Application and instillation site reactions	2 (14.3)	4 (26.7)	0	0
	Application site pain	1 (7.1)	4 (26.7)	0	0
	Application site pruritus	1 (7.1)	0	0	0
7-11 Years	N	12	10	10	8
	Application and instillation site reactions	0	1 (10.0)	0	0
	Application site pain	0	1 (10.0)	0	0
12-17 Years	N	12	12	13	11
	Application and instillation site reactions	0	1 (8.3)	0	0
	Application site pain	0	1 (8.3)	0	0
	Application site pruritis	0	1 (8.3)	0	0
≥18 Years	N	21	21	32	17
	Application and instillation site reactions	0	3 (14.3)	0	2 (11.8)
	Application site discharge	0	0	0	1 (5.9)
	Application site erythema	0	0	0	1 (5.9)
	Application site exfoliation	0	1 (4.8)	0	0
	Application site pain	0	2 (9.5)	0	2 (11.8)
	Application site pruritus	0	0	0	1 (5.9)
	Application site swelling	0	0	0	1 (5.9)

[redacted]

SAF=Safety Analysis Set is defined as those participants who received at least one dose of the investigational product according to actual treatment received. Cohort 1 included hydrocortisone butyrate cream 0.1% as an active comparator. Cohort 2 included Pimecrolimus 1% cream as an active comparator.
N=the number of participants evaluable for AEs; n=number of participants with events
- If the same participant in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
- Participants are counted only once per treatment per event. For the TESS algorithm any missing severities have been imputed as severe unless the participant 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 v23.1 coding dictionary applied.

Assessment of Response:

As requested, the Applicant has provided time to EASI75 data for all age subgroups. Median time to first achieve EASI75 was not evaluable in most subgroups, since Kaplan-Meier (KM) estimators were above 50% throughout the observation period. Yet, KM curves for crisaborole vs vehicle show similar results across age groups. Overall, from visual assessment, time to response seemed to be achieved earlier in the crisaborole group than in the vehicle group. In contrast, KM curves for crisaborole vs active controls overlapped and varied across age subgroups. Crisaborole groups (cohort 1 and cohort 2) showed partially opposing trends, which should not be over-interpreted due to very small sample sizes. Of note, in the age subgroup of 2-6 years TCS treatment showed earliest and highest response

rates. Overall, no clear trend could be observed across age subgroups comparing crisaborole and active controls.

The Applicant also provided the requested summary of application site reactions by treatment for all age subgroups. In the treatment area, application and instillation site reactions were experienced most frequently in the crisaborole treatment group (9 participants, 15.5%) and observed in all age subgroups with highest frequency in the crisaborole group for the age subgroup of 2-6 years (26.7%; vs 10% for 7-11 years, 8.3% for 12-17 years and 14.3% for ≥18 years).

Conclusion:

Point resolved.

5. The Applicant should explain why certain PRO data were not analysed or presented in the study report and how the choice was made on which analyses to conduct/present and which not. Data for all pre-defined secondary PRO endpoints and all age groups, including time to ≥2 and ≥ 3 point improvement from baseline should be presented, if feasible.

Applicant´s Response

As previously described (see Response to Query #1), the MAH made the decision to terminate this study in October 2020, before its completion. The rationale for early termination was due to business reasons only and not related to any safety or efficacy concerns regarding crisaborole.

At the time of study termination, only 39% (235/600) of planned participants were enrolled. Of these, a total of 96 enrolled participants were 2 to 11 years old. There were only approximately 12 participants (range 8 to 16) in each age and treatment group (ie, 2 age groups [2-6 and 7-11 years] and 4 treatment groups). Because of the inherent variability associated with such small sample sizes, robust statistical or clinically meaningful conclusions could not be drawn.

The statistical analysis plan (SAP) was updated before randomization code release and database release including the selection of endpoints for the final summary, which were based on available sample size and investigator-assessed measures (see Response to Query #1 and #2). All safety data were summarized as planned. Efficacy endpoints based on assessments performed by trained investigators, such as Eczema Area and Severity Index (EASI), Investigator's Static Global Assessment (ISGA), and percent body surface area (%BSA), were descriptively summarized.

Patient-reported outcomes (PRO) endpoints Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), and Dermatitis Family Impact Questionnaire (DFI) were summarized for age groups with larger sample sizes.

Pruritus-related PRO endpoints used different instruments in each of 3 age groups as described below. As a result, the sample sizes were even smaller for each age group and therefore, some endpoints were not summarized.

To assess pruritus, 3 instruments were used to collect data during the study:

- Peak Pruritus Numerical Rating Scale (NRS) for ≥ 12 years old participants;
- Patient Reported Itch Severity Scale for 6-11 years old participants;

- Observer Reported Itch Severity Scale for 2-5 years old participants.

For 2 to 5 years and 6 to 11 years: Because of the smaller-than-originally-planned sample size, further subdividing the population based on age groups renders even smaller sample sizes among the paediatric age groups, and makes any meaningful interpretation or conclusions infeasible. The use of different instruments in these 2 age groups precluded pooling of the data. Therefore, given the small number of participants and the fact that this was a secondary endpoint not based on assessments by trained investigators, pruritus-related secondary endpoints for paediatric participants in the 2 age groups 2-5 and 6-11 years were not summarized in the final analysis.

For 12 years and older: The MAH decided not to summarize the Time to ≥2-point improvement from Baseline in Peak Pruritus NRS and Time to ≥3-point improvement from Baseline in Peak Pruritus NRS for 12 years and older participants, because the median time to event would not be estimable due to the small sample sizes. Nonetheless, summaries, at each time point, for the change from Baseline for Peak Pruritus NRS, achievement of ≥2- point improvement from Baseline in Peak Pruritus NRS and achievement of ≥3-point improvement from Baseline in Peak Pruritus NRS were developed for this response.

Considering the small sample size, endpoints that included data from assessments performed by trained investigators, such as the EASI and ISGA, were included in the SAP. This decision was made as part of the updates to the protocol and the SAP due to the early termination of the study and before randomization code release and database release (see response to Query #1).

Due to the short timeline allowed to respond to this query, table generation for PRO endpoints is not possible.

Assessment of Response:

It is acknowledged that the use of different instruments in the two age groups 2-6 and 7-11 years precluded pooling of the data and that the group sizes are very small. However, no sound justification is provided why no data tables could be generated for PRO endpoints, although the data seem to be available. PRO data are relevant to complement the pivotal sign/symptom scores. However, earlier studies indicate that the relationship between QoL measures and ISGA seems to be linear, and thus the lack of these data could be less relevant for the current assessment. Although the lack of proper documentation is critically noted, the issue is thus not further pursued.

Conclusion:

Point not further pursued.

6. The number of paediatric subjects with <5% treatable %BSA at baseline should be provided and the aberrance to the inclusion criteria as well as potential impact on clinical outcomes should be commented on.

Applicant´s Response

The mean treatable percent body surface area (%BSA) at Baseline reported in Study C3291037 was 15.45, as presented in Table 14.1.2.1 of the CSR. From the total 144 paediatric participants enrolled,

only one paediatric participant entered the study with treatable BSA < 5%. This participant was under 10 years old with a reported 2.5% treatable BSA at Baseline.

This participant was enrolled to Cohort 2 and was assigned to the crisaborole group. The affected BSA reduced to 2% at Day 29. The Eczema Area and Severity Index (EASI) total score changed from 1.6 at Baseline to 1.4 at Day 29. No change for Investigator's Static Global Assessment (ISGA) was reported throughout the study; the ISGA was reported as mild for all study visits. The individual study data corresponding to this participant is presented in Table 1 below. The overall study outcomes were not impacted by this single participant with %BSA <5%.

Table 1. One Paediatric Participant with Baseline %BSA < 5 (Study C3291037)

Cohort	Collection Date	Study Day*	Nominal Visit	Analysis Visit	EASI	%BSA	ISGA
2	2020-09-16	-7	SCREENING	Screening			MILD
	2020-09-23	1	DAY1	Baseline	1.6	2.5	MILD
	2020-09-30	8	DAY8	Day 8	0.6	1	MILD
	2020-10-07	15	DAY15	Day 15	0.6	1	MILD
	2020-10-14	22	DAY22	Day 22	1.5	2	MILD
	2020-10-21	29	DAY29_EOT_ET	Day 29	1.4	2	MILD
	2020-11-04	43	DAY43	Day 43	3.2	5	MILD

%BSA=percent body surface area; EASI= Eczema Area and Severity Index; EOT=end of treatment; ET=early termination; ISGA=Investigator's Static Global Assessment
*Day relative to start of study treatment (Day1)
Baseline is defined as the last evaluation taken before the first dose.

Assessment of Response:

As requested, the Applicant provided information on participants with baseline %BSA <5. One single paediatric participant with baseline %BSA <5 was enrolled. This is considered unlikely to have an impact on the outcome, in particular since no change for Investigator's Static Global Assessment (ISGA) was reported for this patient throughout the study.

Conclusion:

Point resolved.

5. CHMP discussion

The CHMP discussed the applicant request and considered that the data available even if from an early terminated study are relevant for the prescriber. In line with Regulation (EC) No 1901/2006 and the SmPC guideline providing instruction on how reflecting paediatric data, the information should be added to the SmPC.

A wording along the lines of:

'Limited data from a prematurely terminated comparative phase IIIb/IV study in children (and adults) from 2 years of age investigating comparative efficacy and safety of crisaborole compared to vehicle, and compared to two active treatments (TCI and TCS) support a larger effect of crisaborole compared to vehicle in patients with mild to moderate atopic dermatitis. Crisaborole showed a smaller effect size compared to moderate potency TCS and a similar to smaller effect compared to TCI. Local reactions were most often reported in the crisaborole groups over the 29-day treatment period.'

should be proposed.

The Applicant is asked to submit a type II variation to include a statement in section 5.1 of the SmPC (and the respective section in the PIL, if applicable) to reflect the relevant results from the early terminated phase III/IV trial within 2 months of receipt of this opinion.