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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 005

Note

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

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1. Introduction

On June 8th 2021, the MAH submitted a completed paediatric study for Staquis (crisaborole) 20mg/g Ointment, 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 has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study C3291027 "A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants With Mild to Moderate Atopic Dermatitis" is a stand alone study.

The MAH stated that study C3291027 was conducted to support the crisaborole development programme in Japan (Study C3291027) and was not part of the EU PIP for crisaborole (PIP Decision No. P/0276/2020, which was discontinued 20 October 2020).

The study was terminated prematurely (LSLV December 2020) due to the sponsor's business decision and portfolio reprioritisation. This decision was not a result of any safety or efficacy concerns.

CHMP comment

The study under assessment (C3291027) was terminated prematurely. The data from this study are submitted to fulfil the requirements of Article 46 of Regulation (EC) No 1901/2006 (Pediatric Regulation), which is acceptable. However, the submitted safety data are of limited relevance for the European population and the European product label, due to several constraints as outlined in subsequent sections of this report.

2.2. Information on the pharmaceutical formulation used in the study

Crisaborole 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. The activity of crisaborole on PDE-4 gene products is in the range of 55 to 335 nM with less potent binding activity noted on several other PDE forms, ranging from inactive to mid-micromolar potency. It is not known if the limited binding activity on these other PDE isoforms may further enhance the activity of crisaborole in atopic dermatitis (AD), since PDE isoforms like PDE-1 and PDE-7 are involved in immune cell function and their inhibitors have immune-modulatory effects.

As an anti-inflammatory agent, 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 subjects reduces expression of key drivers of atopic inflammation including T-cell derived cytokines IL-13, IL-31, and IFN-γ as well as innate markers of inflammation such as MMP-12. The ability of crisaborole to suppress several types of AD-related cytokines may to its beneficial effects on AD.

The first regulatory approval for crisaborole (containing 0.1% BHT) was received on 14 December 2016 in the US (EUCRISA™). Since then, approvals have been received in Canada, Israel, Australia, Hong Kong, China, Taiwan, UK, EU, and EEA countries Iceland, Liechtenstein and Norway, UAE and Lebanon.

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

In the US, UAE and Lebanon, crisaborole was approved for topical treatment of mild to moderate AD in adult and pediatric patients 3 months of age and older. In Canada, Israel, Australia, Hong Kong, China, and Taiwan, crisaborole is approved for topical treatment of mild to moderate AD in patients 2 years of age and older. In the UK, EU, and EEA countries Iceland, Liechtenstein and Norway, crisaborole is approved for treatment of mild to moderate AD in adults and pediatric patients from 2 years of age with ≤40% BSA affected. Currently, crisaborole is marketed in 6 countries (US, Canada, Israel, Australia, Hong Kong, and China).

The original marketing authorization application for STAQUIS in the EU was based on 1 phase 1/2a dose-escalation study (AN2728-AD-204) and 2 pivotal phase 3 studies (AN2728-AD-301 and AN2728-AD-302'). Additional studies have been performed (see "Annex - Line Listings" at the end of this report).

CHMP comment

The formulation used in this study in Japanese patients is a topical ointment containing crisaborole 2%. The formulation is comparable to Staquis in the EU, but in addition contains the antioxidant BHT at 0.1%.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study C3291027: "A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants With Mild to Moderate Atopic Dermatitis"

2.3.2. Clinical study

Study C3291027: "A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants With Mild to Moderate Atopic Dermatitis"

Study Period:

Date of First Subject First Visit: Sept 14th, 2020

Date of Last Subject Last Visit: Dec 18th, 2020

Description

The purpose of this long-term extension study (C3291027) was to assess the 1-year long-term safety of crisaborole ointment, 2% BID in Japanese AD pediatric and adult participants who completed study intervention in Study C3291032 and Study C3291031.

Study C3291032 is a Phase 3, multicenter, randomized, double-blind, vehicle controlled study to evaluate the efficacy and safety of crisaborole ointment, 2% in Asian pediatric and adult participants (2 years of age and older) with mild to moderate AD, it was estimated 130 Japanese participants in Study C3291032 were expected to enroll into Study C3291027.

Planned Study C3291031 was cancelled due to Sponsor business decision and therefore the Study C3291031 did not enrol into Study C3291027.

This study (C3291027) was terminated prematurely (after three months) due to the Sponsor's business decision and portfolio reprioritization. This decision was not as a result of any safety or efficacy concerns. The study sites were informed of the study termination on 21 October 2020. In addition, Japanese participants in Study C3291032 were informed of Study C3291027 termination at the next scheduled visit, and their willingness to continue participation in Study C3291032 without the possibility of roll over to the long-term extension study were confirmed.

As this study (C3291027) enrolled pediatric participants and is subject to Article 46 of Regulation (EC) No 1901/2006 (Pediatric Regulation), the CSR must be submitted to the regulatory authorities in EU no later than 6 months of LSLV. However, as the parent double-blind Study C3291032 was still ongoing at the time of the termination of this study, analysis and reporting of the PK and efficacy data in this study (C3291027) could result in unblinding of the parent study. In order to keep the blinding intact for the parent study, only the safety analysis was performed and reported in this CSR. The PK and efficacy analyses will be performed and reported in a supplemental CSR after the Study C3291032 is completed.

Methods

Objective(s)

Primary Objective:

- To study the safety of crisaborole ointment, 2% applied BID in Japanese pediatric and adult participants with mild to moderate AD

Tertiary/ Exploratory Objectives:

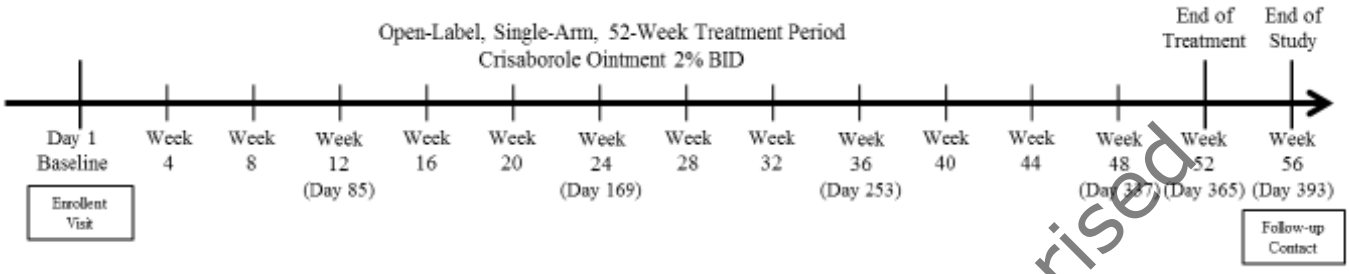
- To characterize the efficacy of long-term administration of crisaborole ointment, 2%
- To characterize the patient/observer reported outcomes for pruritus of long-term administration of crisaborole ointment, 2%
- To assess the PK profile of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment, 2% BID from C3291032 on Day 1

Study design

This study (C3291027) was a Phase 3, multicenter, open-label, long-term safety extension study of Studies C3291032 and C3291031 in Japanese pediatric and adult participants with mild to moderate

AD to support the registration of crisaborole in Japan. After completion of the study intervention period in Studies C3291032 or C3291031 and confirmed Study C3291027 eligibility, participants were offered participation in the study from investigator sites in Japan.

PK blood sampling was conducted at study sites for the participants aged between 2-11 years at the time of signing the ICD in Study C3291032.



Study population /Sample size

The sample size of this study (C3291027) was planned for approximately 150 participants but was determined by the number of participants who completed Studies C3291032 or C3291031 treatment period and met eligibility criteria of this study. Scheduled study visits occurred every 4 weeks (1 cycle) with on-treatment or off-treatment cycles to be decided by the investigator based on the ISGA score.

Inclusion criteria:

- Male or female participants who were patients with mild to moderate AD aged 2 years or older and met eligibility criteria for Study C3291032 at the time when entering Study C3291032, and completed treatment period in Study C3291032 without safety issues;

  or

- Male or female participants who were patients with mild to moderate AD aged 1 month to <24 months and met eligibility criteria for Study C3291031 at the time when entering study C3291031, and completed treatment period in Study C3291031 without safety issues.
- Participants who are willing and able to comply with all scheduled visits, treatment plan, lifestyle considerations, and other study procedures.
- The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original copy of each participant's signed consent/assent document.

Exclusion criteria:

- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
- Has an anticipated concomitant use of topical or systemic therapies that might alter the course of AD.
- Participates in other studies involving investigational drug(s) during study participation other than the parent studies C3291032 and C3291031.

- Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
- Experienced a treatment related AE or SAE during participation in Study C3291032 or C3291031, which precludes treatment with investigational product in the judgment of the investigator.
- Early discontinuation from Studies C3291032 or C3291031 treatment, for any reason.
- Had a significant active systemic or localized infection, including known actively infected AD.
- Had a history of significant noncompliance during the Study C3291032 or C3291031 with investigational product dosing, concomitant medication restrictions, or study procedures, in the judgment of the investigator.

See study report for further information on lifestyle considerations for study inclusion.

CHMP comment

The overall design of the planned C3291027 long-term safety study including objectives, endpoints, sample size and study duration would potentially be appropriate to inform on the long-term effects of Staquis.

The study was planned to include only Japanese pediatric and adult patients from 1 month of age with mild to moderate AD who were to be enrolled after completion of one of the two parent studies: C3291032 or C3291031. Patients had to meet eligibility criteria for Study C3291032 (and C3291031) and complete the parent study without safety issues. A certain selection of patient more likely to tolerate treatment well in this long-term study can thus be assumed. As no protocols/reports for C3291031 or C3291032 are provided, no details about the C3291027 populations (e.g. regarding baseline disease criteria including % BSA affected) are known and the treatment duration before enrolment into C3291027 is unclear, limiting the value of study outcomes.

Treatments

Dose selection:

In this study, the participants will apply crisaborole ointment, 2% BID during On-Treatment cycle.

Crisaborole ointment, 2% BID is selected as the highest well-tolerated dose to maximize the potential for efficacy with minimal safety risk based on the results of foreign clinical studies, and 2% was technically the maximum dose for ointment formulation. In addition, the descriptive comparison of BID and QD regimens in Japanese AD patients was conducted in Study C3291028, crisaborole ointment, 2% BID was more effective than crisaborole ointment, 2% QD for Japanese adults and pediatrics participants. Regarding safety, crisaborole ointment, 2% BID was safe and tolerable for both Japanese adults and pediatric participants. Parent study C3291032 is conducted using crisaborole ointment, 2% BID.

This study also has Off-Treatment Cycle to evaluate long term safety and efficacy of crisaborole in a condition close to real world clinical practice.

CHMP comment

The selection of the crisaborole concentration (ointment 2%) and the dosing regimen (BID) for this study are in line with the current European SmPC recommendations.

Dosing procedure, Duration of Treatment and Follow-Up:

For this study, the investigational product is crisaborole ointment, 2%. Crisaborole ointment, 2% is formulated to contain PF-06930164 (2%), white petrolatum, propylene glycol, mono- and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

Ointment should be applied as an even layer of approximately 3 mg/cm^2.

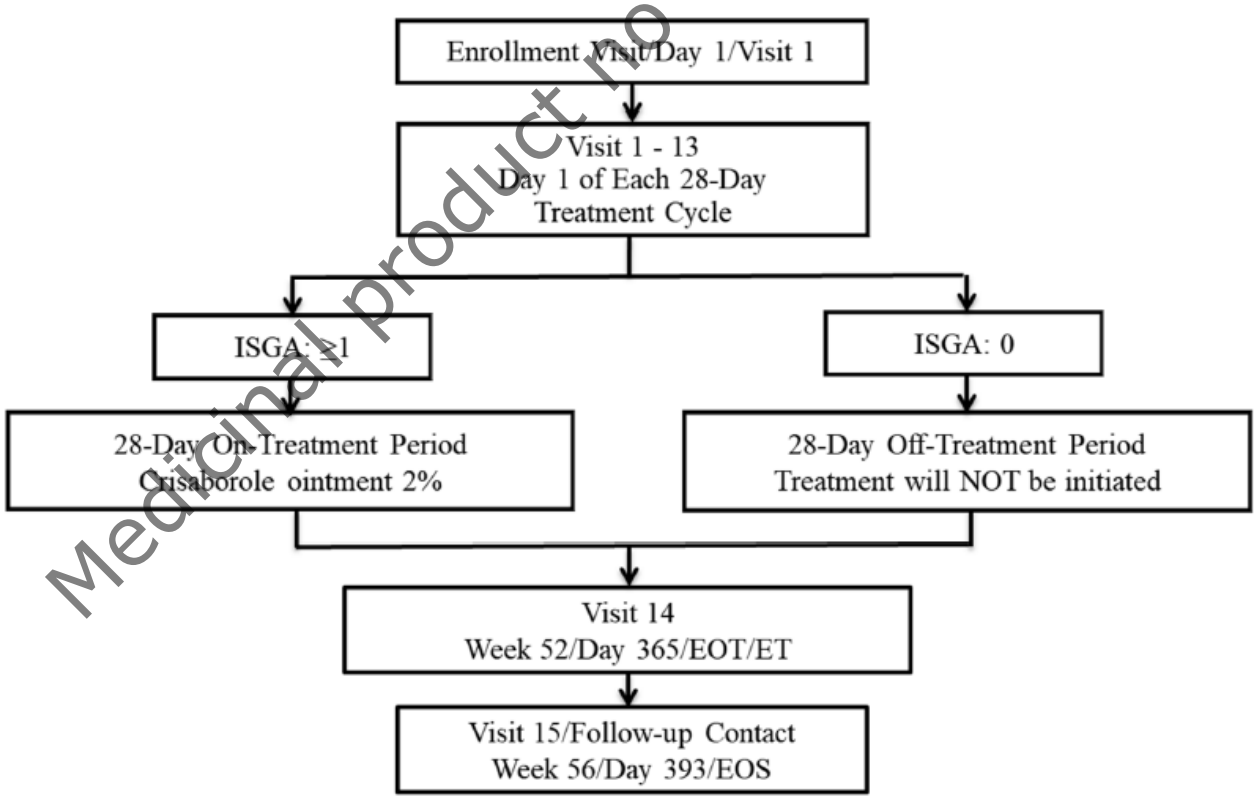
The tool to standardize the calculation of the amount of ointment required for each participant will be provided by the sponsor to the study sites, which is based on each participant's own AD %BSA adjusted by height and weight.

The investigator will determine whether the participant will receive crisaborole ointment, 2% specified as follows:

- If the participant is assessed as Almost Clear (1) or greater on the ISGA, the participant will begin a 4 week On-Treatment Cycle, with a sufficient quantity of crisaborole ointment, 2% tubes dispensed to the participant or his/her parent/legal guardian to meet anticipated use based on the investigator identified AD-involved areas. The investigator will review the dosing instructions with the participant or his/her parent/legal guardian. Study intervention administration will be performed BID at home.
- If the participant is assessed as Clear (0) on the ISGA, treatment **will NOT** be initiated and the participant will begin a 4-week Off-Treatment Cycle, during which the participant is allowed to use emollient(s)/moisturizer(s) in all areas (AD-involved and uninvolved), as needed.

Any new lesion(s) that develop during an On-Treatment Cycle should also be treated.

Figure 1. Diagram of Study Intervention Allocation by Visit



CHMP comment

Dosing procedure:

Subjects assessed as Almost Clear based on ISGA score ≥ 1 began a 4 week on-treatment cycle to receive crisaborole ointment, 2%. Subjects who were assessed as Clear (ISGA = 0) were started on a 4 week off-treatment cycle (no crisaborole treatment; emollients/moisturizers on AD areas allowed). The proposed protocol could be valuable to inform on intermittent treatment regimens (no information on (the duration of) treatment holidays is given in the European SmPC).

Crisaborole ointment, 2% was applied BID at home to affected AD-involved areas. Participants or their parents/ legal guardians were instructed on how to apply the treatment by the investigator (even layer of approximately 3 mg/cm^2; standardized tool to calculate the amount of ointment / participant based on participant's own AD & BSA affected adjusted by height and weight).

Standardization of the process (application method and dose) is considered beneficial for the interpretation of results.

Duration of treatment & Follow-Up:

The duration of the Investigational Product Application Period was planned to be 365 days (= 13 treatment cycles of 28 days) including study visits at the beginning of each treatment cycle (i.e. every 28 days) until week 52/day 365 (End of Treatment) with a planned post-treatment follow up-contact at week 56/ day 393 (End of Study).

The planned duration of treatment and follow-up are considered adequate to inform on long-term safety (and exploratory efficacy).

Outcomes/endpoints

Primary endpoint (safety):

- Incidence of treatment emergent AEs and SAEs

Tertiary/ Exploratory endpoints (efficacy):

- Percentage change from baseline in EASI over time
- Achievement of EASI50 (≥50% improvement from baseline) over time
- Achievement of EASI75 (≥75% improvement from baseline) over time
- Change from baseline in treatable percent BSA over time
- Achievement of success in ISGA (defined as an ISGA score of clear [0] or almost clear [1] with at least a 2-grade improvement from baseline) over time
- Achievement of improvement in ISGA (defined as an ISGA score of clear [0] or almost clear [1]) over time
- Achievement of success in regional ISGA-face (defined as a regional ISGA-face score of clear [0] or almost clear [1] with at least a 2-grade improvement from baseline) over time

- Achievement of improvement in regional ISGA-face (defined as a regional ISGA-face score of clear [0] or almost clear [1]) over time
- Incidence of the use of rescue medication (topical corticosteroids or topical calcineurin inhibitors)

Tertiary/ Exploratory endpoints (Patient/Observer Reported Outcomes):

- Change from baseline in peak pruritus NRS over time – for participants ≥12 years
- Changes from baseline in patient reported itch severity scale over time - for participants ≥6 years and <12 years
- Change from baseline in observer reported itch severity scale over time - for participants <6 years

Tertiary/ Exploratory endpoints (Pharmacokinetics):

- Plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) on Day 1

CHMP comment

The primary study endpoint was Incidence of treatment emergent AEs and SAEs and, together with the description of the quality of the AEs and the relation to treatment, this is appropriate for the characterisation of long-term safety.

Tertiary/ exploratory endpoints relate to efficacy (evaluated via EASI, ISGA, %BSA and incidence of rescue medication), patient/ observer reported outcomes (evaluating pruritus/itching) and pharmacokinetics (PK of crisaborole and main metabolites). The exploratory endpoint (ISGA response of (almost) clear with ≥ 2 grade improvement) was used as primary endpoint in the main clinical phase 3 studies for Staquis in Europe, which is expected to allow for contextualisation of results, once the efficacy data from C3291027 (and C3291032) are submitted.

Safety assessments:

Unscheduled ***clinical laboratory measurements*** may be obtained at any time during the study to assess any perceived safety issues.

A ***complete physical examination*** will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. In addition, an assessment will be made of the condition of all AD-involved skin. Weight for participants aged 18 years old or older and height and weight for participants aged under 18 years old will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the

study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

Adverse Events (AEs) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention.

Each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up.

Table 1 Schedule of activities:

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 6.	Enrollment Visit	Intervention Period				Follow-up Contact[b]
	Visit 1	Visit 2-13		Unplanned Visit to initiate study intervention during Off-Treatment Cycle	Visit 14	Visit 15
	Day 1[c]	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337			Week 52/ EOT/ET Day 365/ EOT/ET	Week 56/EOS Day 393/EOS At least 28 days after last study dose
		Start Day of On-Treatment Cycle[c]	Start Day of Off-Treatment Cycle[c]			
Visit Window		±7 days based on Day 1			±7 days based on Day 1	+7 days based on Week 52/EOT/ET
Informed consent, including assent	X[d]					
Registration	X					
Demographics and medical history including AD history/prior AD treatment (including reasons of stop)	X[e]					
Current/prior treatments for current/prior medical history other than AD	X[e]					
Inclusion/exclusion criteria	X					
Physical examination	X[e]	X (Week 24 only)	X (Week 24 only)		X	
Weight (age ≥18)	X				X	
Height and Weight (age <18)	X[e]	X (Weeks 12, 24, 36, 48 only)	X (Weeks 12, 24, 36, 48 only)		X	
Laboratory						
Pregnancy test[f]	X[e]	X	X		X	
Contraception check[g]	X	X	X		X	X
Study intervention						
Body Site Checklist of AD lesions	X	X		X	X	
Record treatable AD areas	X	X		X		
Study Intervention Dispensing[h]	X[i]	X		X		
Instruction for dosing and dispense dosing diary	X[i]	X		X		
Weigh the investigational product tube(s) and dispense	X[i]	X		X		
Study intervention administration	X[i]	BID, throughout On-Treatment Cycle[j,k]		BID, for the remainder of a treatment cycle[j,k]		
Review dosing diary; assess compliance		X[l]	X[l]		X[l]	
Collect and weigh returned investigational product tubes, including empty, partially used and unused tubes		X[l]	X[l]		X[l]	
Assessments						
Calculate and record treatable %BSA	X[e]	X	X	X	X	
ISGA[m]	X[e]	X	X	X	X	
Regional ISGA-face[m,o]	X[e]	X	X		X	
EASI[m]	X[e]	X	X		X	
Peak Pruritus NRS/Patient Reported Itch Severity Scale/ Observer Reported Itch Severity Scale[n]	X[e]	X	X		X	
Concomitant treatment(s)	X[e]	→	→	→	→	X
Serious and nonserious adverse event monitoring	X[e]	→	→	→	→	→
Review lifestyle considerations	X	X	X		X	X
Schedule/reconfirm next study visit or contact	X	X	X		X	
Remind to bring all investigational product tubes and the dosing diary to the next visit	X[i]	X	X[p]	X		
Blood sampling to obtain plasma for crisaborole and metabolites PK	X[q]					

a. Day relative to start of study intervention (Day 1).
b. Contact may occur via telephone contact and must occur 28 to 35 days from Week 52/EOT/ET Visit.
c. Day 1 will be the same day as EOT visit of Study C3291032 or C3291031. Procedure done at Day 1 Visit of next treatment cycle. Depending upon ISGA score and investigator's judgment, participant will initiate an "On-treatment Cycle" or "Off-treatment Cycle".
d. Obtain written informed consent (from adult participant or parent/legal guardian of pediatric participant) and assent (from pediatric participant, as applicable) before any study procedures are performed.
e. Procedure done at Day 29 (concomitant treatment, physical examination, %BSA, ISGA, Regional ISGA-face, EASI, Peak Pruritus NRS/Patient Reported Itch Severity Scale/ Observer Reported Itch Severity Scale, urine pregnancy test and AE/SAE) and Screening (medical history including AD history/prior AD treatment) of Study C3291032 or procedure done at Week 24 (concomitant medications/therapies, physical examination, height/length and weight, %BSA, EASI, ISGA, Observer Reported Itch Severity Scale, and AE/SAE) and Screening (medical history including AD history/prior AD treatment) of Study C3291031 will serve as Enrollment Visit data for Study C3291027.
f. For all female participants biologically capable of having children (refer to Section 10.4.2 for definition of a female of childbearing potential). The participant and his/her parent/legal guardian will be instructed regarding the contraception method requirement and informed of the requirement to conduct a urine pregnancy test. Pediatric female participant who has not experienced menarche is not required to perform pregnancy testing. If the pediatric female participant starts menarche during the study, pregnancy testing will be performed.
g. For studies enrolling pediatric participants, it is the opportunity to assess changing potential to father/bear children and allows for implementing contraception and pregnancy testing as children mature physically and behaviorally during conduct of the study.
h. Study coordinator or specified designee will contact IRT to register the visit and, if applicable, obtain the next investigational product tube(s) assignment.
i. Participant who will start "On-treatment Cycle" from Enrollment Visit.
j. At home dosing by participant or his/her parent/legal guardian. Investigational product application BID through the evening before the day of visit. After the procedure/assessment of the visit, the participant or his/her parent/legal guardian can apply the investigational product, if applicable.
k. In the event the scheduled Start Day of the next treatment cycle visit does not fall exactly on the scheduled date, the participant or his/her parent/legal guardian will be instructed to continue investigational product application BID through the evening before the actual visit date.
l. Performed only for those participants completing a previous On-Treatment Cycle (e.g., Previous "On-treatment" and continue "On-treatment", or previous "On-treatment" and initiate "Off-treatment").
m. The ISGA should be completed prior to Regional ISGA-face and EASI assessments, whenever possible.
n. Peak Pruritus NRS will be completed by participants ≥12 years of age at the time of signing the ICD in the prior study, Patient Reported Itch Severity Scale will be completed by participants ≥6 years and <12 years at the time of signing the ICD in the prior study, and Observer Reported Itch Severity Scale will be completed by the observers (caregivers of participants) for participants <6 years of age at the time of signing the ICD in the prior study.
o. Only for participants who completed study intervention for Study C3291032 and had AD in face at Day 1 Visit of Study C3291032.
p. Performed to remind the participants initiating "Off-treatment Cycle" to bring back dosing diary which records concomitant medication usage.
q. PK blood sampling will be conducted at the selected study sites in participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032. The date and time for most recent dose (last dose in C3291032 study) will be collected.

CHMP comment

The Schedule of Activities includes physical examination (cardiovascular, respiratory, gastrointestinal, and neurological systems at a minimum), examination of height and weight at day 1, week 24 and week 52 (EOT), laboratory pregnancy test at start of each treatment cycle and week 52 (EOT), Study Intervention related to e.g. administration, weighing of product tube, instruction for dosing at beginning of treatment cycle and unplanned visits, assessment of BSA, ISGA, regional ISGA face, EASI, Peak Pruritus at each beginning of treatment cycle and EOT as well as blood sampling for PK at day 1. Evaluation of these parameters and timing thereof is considered reasonable for the intended study purpose.

Vital signs (e.g. temperature, blood pressure, pulse rate) and laboratory assessments (e.g. hematology, blood chemistry, urinalysis) were not conducted. This is considered a shortcoming, as subclinical changes in terms will not be evaluated which might, however, provide important information for long-term safety. However, as this study was prematurely terminated preventing collection of longer-term data (see results), no further issue is made.

Statistical Methods

The primary endpoint of incidence of safety events will be analyzed using descriptive measures such as percentages and exposure-adjusted incidence rates along with confidence intervals. No statistical hypotheses will be tested.

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.

Efficacy analyses will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported.

For purposes of analysis, the following analysis sets are defined:

- Full Analysis Set: All participants who take at least one dose of study intervention.
- Safety: All participants who take at least one dose of study intervention.
- PK Analysis Set: All participants who take at least one dose of study intervention in Study C3291032 and who have at least one concentration value.

CHMP comment

Safety (and efficacy) endpoints will be analysed descriptively without formal hypothesis testing, which is acceptable for the intended purpose.

The Full Analysis Set is identical to the Safety Set defined as all participants who take at least one dose of study intervention. The PK analysis set includes all participants who take at least one dose of study intervention in Study C3291032 and who have at least one concentration value.

Analysis sets are considered adequately defined.

Results

Recruitment/ Number analysed

The disposition events summary is provided in Table 2. A total of 40 participants were assigned to study intervention period, and 37 participants received crisaborole ointment 2% BID. Three participants started the study with off-treatment cycle and discontinued without treatment. Of the 40 participants, 30 participants were in <18 years of age group, and 10 participants were in ≥18 years of age group. All 40 participants discontinued the study (39 participants due to study terminated by the Sponsor and 1 participant due to AE) and were included in the safety analysis set (all participants who took at least 1 dose of study intervention, and also who entered the first off-treatment cycle).

Table 2. Disposition Events Summary (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	>= 18 years (N=10)	Total (N=40)
Number (%) of Subjects	n (%)	n (%)	n (%)
Disposition phase: Treatment			
Subjects Entered:	30 (100.0)	10 (100.0)	40 (100.0)
Discontinued	30 (100.0)	10 (100.0)	40 (100.0)
Reason for discontinuation			
Adverse Event	1 (3.3)	0	1 (2.5)
Study Terminated By Sponsor	29 (96.7)	10 (100.0)	39 (97.5)
Completed	0	0	0
Disposition phase: Follow-Up			
Subjects Entered:	30 (100.0)	10 (100.0)	40 (100.0)
Discontinued	0	0	0
Completed	30 (100.0)	10 (100.0)	40 (100.0)

PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adds Table Generation: 26JAN2021 (15:22)
Output File: ./csr6/C3291027/adds_s001
Table 14.1.1.2 Crisaborole is for Pfizer internal use.

The subject evaluation groups are provided in Table 3.

A total of 40 participants were screened and enrolled into the study intervention period. A total of 37 out of 40 participants (92.5%) were treated with crisaborole ointment 2% BID, of which 27 participants (90.0%) in <18 years of age group and 10 participants (100.0%) in ≥18 years of age group. Three participants (10.0%) in <18 years of age group discontinued without treatment with crisaborole ointment 2% BID.

Table 3. Subject Evaluation Groups (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	>= 18 years (N=10)	Total (N=40)
	n (%)	n (%)	n (%)
Screened: 40			
Screened Failure: 0			
Assigned to Treatment	30 (100.0)	10 (100.0)	40 (100.0)
Treated	27 (90.0)	10 (100.0)	37 (92.5)
Not Treated	3 (10.0)	0	3 (7.5)
Safety Analysis Set	30 (100.0)	10 (100.0)	40 (100.0)
Full Analysis Set	30 (100.0)	10 (100.0)	40 (100.0)

Table 3. Subject Evaluation Groups (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30) n (%)	>= 18 years (N=10) n (%)	Total (N=40) n (%)

These participants started off-treatment from cycle 1 and discontinued without treatment
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adsl Table Generation: 26JAN2021 (15:22)
Output File: ./csr6/C3291027/adsl_s002
Table 14.1.1.1 Crisaborole is for Pfizer internal use.

CHMP comment

Among the total of 40 subjects enrolled into the study, 27 participants in the <18 years of age group (and 10 in the ≥18 years of age group) were treated with crisaborole ointment 2% BID (3 subjects <18 years of age discontinued without treatment) for a maximum of three months in this extension study (total exposure unknown as no details from parent study available).

Except one participant who discontinued the study due to an AE, all participants discontinued the study due to termination by the Sponsor.

Protocol deviations

The following was compiled by the clinical assessor based on the submitted document "Protocol deviations":

Potentially important protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being were reported in 22/40 (55.5 %) subjects.

The majority of these deviations (15/22; 68.2%) were described as "PK blood sampling time was not within 1 hour away from 12 hours after the last dose of C3291032 study drug". Other deviations were due to visit occurring outside of allowable window (4/22; 18,2 %), use of prohibited medication (2/22; 9.1 %) and IP not returned (1/22; 4.5 %).

The MAH states that a formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

CHMP comment

Potentially important protocol deviations were reported in 22/40 (55.5 %) subjects. However, as the majority of these (15/22) were related to inappropriate PK blood sampling time (which is not assessed during this procedure as no PK results are submitted), no impact on interpretability of safety results is expected. No issue is raised.

Baseline data

Table 4. Demographic Characteristics (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	>= 18 years (N=10)	Total (N=40)
Age (years), n (%)			
<=1	0	0	0
2-11	22 (73.3)	0	22 (55.0)
12-17	8 (26.7)	0	8 (20.0)
18-64	0	10 (100.0)	10 (25.0)
>=65	0	0	0
n[a]	30	10	40
Mean(SD)	9.3 (3.99)	31.8 (7.97)	15.0 (11.11)
Median	9.0	32.0	10.5
Range (min, max)	(4, 16)	(19, 45)	(4, 45)
Gender, n (%)			
Male	15 (50.0)	6 (60.0)	21 (52.5)
Female	15 (50.0)	4 (40.0)	19 (47.5)
Race, n (%)			
Asian	30 (100.0)	10 (100.0)	40 (100.0)
Ethnicity, n (%)			
Not Hispanic or Latino	30 (100.0)	10 (100.0)	40 (100.0)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set.
Age is at baseline.
a. n is the number of subjects with non-missing age.
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adsl Table Generation: 28JAN2021 (09:23)
Output File: ./csr6/C3291027/adsl_s001
Table 14.1.2.1 Crisaborole is for Pfizer internal use.

CHMP comment

The study population consisted of a total of 40 participants, all Asian, 10/40 ≥ 18 years of age, and 30/40 between 2-17 years of age. Within the paediatric cohort 22/30 (73.3%) were between 2-11 yoa and 8/30 (26.7%) were between 12-17 yoa. As no patients from the prematurely terminated parent study C3291031 are recruited, no patients 1 month-<2 years are included.

Efficacy results

No efficacy results were submitted.

CHMP comment

Efficacy results (exploratory) were not submitted due to potential unblinding of the still ongoing Phase 3 study (C3291032) from which subjects were enrolled into this study. This is acceptable. Results from both studies are expected to be submitted to EMA after trial completion.

Safety results

Brief Summary of Adverse Events

Extent of exposure:

Table 2. Summary of Study Treatment Exposure (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	**>= 18 years (N=10)**	**Total (N=40)**
Duration of treatment (days)[a]			
N	30	10	40
Mean (SD)	25.0 (11.7)	31.5 (10.6)	26.6 (11.7)
Median (range)	29.0 (0, 51)	29.0 (14, 56)	29.0 (0, 56)
Category (days)[a], n (%)			
0	3 (10.0)	0	3 (7.5)
1-28	11 (36.7)	5 (50.0)	16 (40.0)
29-	16 (53.3)	5 (50.0)	21 (52.5)
Total number of applications			
N	30	10	40
Mean (SD)	49.4 (22.8)	62.4 (19.9)	52.7 (22.6)
Median (range)	56.5 (0, 92)	58.0 (28, 107)	56.5 (0, 107)
Number of participants by total number of applications, n (%)			
0	3 (10.0)	0	3 (7.5)
1-56	12 (40.0)	5 (50.0)	17 (42.5)
57-	15 (50.0)	5 (50.0)	20 (50.0)
Amount of drugs used			
N[b]	29	10	39
Mean (SD)	175.1 (213.3)	296.3 (257.2)	206.2 (228.2)
Median (range)	93.3 (0, 865)	200.9 (72, 789)	114.1 (0, 865)
Total number of treatment cycles started per participant			
N	30	10	40
Mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Median (range)	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)

Table 2. Summary of Study Treatment Exposure (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	>= 18 years (N=10)	Total (N=40)
Number of participants started, n (%)			
1 cycle	27 (90.0)	9 (90.0)	36 (90.0)
2 cycles	3 (10.0)	1 (10.0)	4 (10.0)
Total number of off-treatment cycles started per participant			
N	30	10	40
Mean (SD)	0.1 (0.3)	0.0 (0.0)	0.1 (0.3)
Median (range)	0.0 (0, 1)	0.0 (0, 0)	0.0 (0, 1)
Number of participants started off-treatment, n (%)			
1 cycle	4 (13.3)	0	4 (10.0)
2 cycles	0	0	0
Number of participants with off-Treatment, n (%)			
cycle 1	4 (13.3)	0	4 (10.0)
cycle 2	0	0	0
all treatment cycles	4 (13.3)	0	4 (10.0)

a. The Total Number of Dosing Days on which study drug was actually administered
b. Actual total dose & unit of one subject who is less than 18 years old is unknown
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adex Table Generation: 26JAN2021 (15:45)
Output File: ./csr6/C3291027/adex_s001
Table 14.4.1.1 Crisaborole is for Pfizer internal use

CHMP comment

In both the <18 years of age group (n=30) and the ≥18 years of age group (n=10) the median duration of crisaborole ointment 2% BID treatment was 29.0 days (ranges of 0 to 51 and 14 to 56 days, respectively). Due to the early study discontinuation the majority of subjects were only treated over the course of one treatment cycle.

As it is not known how long patients were treated in the parent trial (C3291032) it is also unknown how long the overall treatment duration was. Due to the short treatment duration in this trial, the study is likely not appropriate to allow assessment of crisaborole long-term effects.

Treatment-Emergent Adverse Events (All-Causalities):

A total of 14 participants (35.0%) experienced a total of 15 all-causality TEAEs. In <18 years of age group, 11 participants (36.7%) experienced 12 all-causality TEAEs. In ≥18 years of age group, 3 participants (30.0%) experienced 3 all-causality TEAEs (Table 6).

There were no deaths, SAEs or severe AEs reported in either age group in the study. All TEAEs were mild in severity. The permanent discontinuation from the study and the dose reduction or temporary

discontinuations due to TEAEs were each reported in 1 participant in <18 years of age group in the study (Table 6).

Table 6. Treatment-Emergent Adverse Events (All Causalities) (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
	< 18 years (N=30)	>= 18 years (N=10)	Total (N=40)
Number (%) of Subjects	n (%)	n (%)	n (%)
Subjects evaluable for adverse events	30	10	40
Number of adverse events	12	3	15
Subjects with adverse events	11 (36.7)	3 (30.0)	14 (35.0)
Subjects with serious adverse events	0	0	0
Subjects with severe adverse events	0	0	0
Subjects with adverse events on treatment area	2 (6.7)	0	2 (5.0)
Subjects with adverse events on treatment area (eyelid)	1 (3.3)	0	1 (2.5)
Subjects with adverse events on treatment area (face)	1 (3.3)	0	1 (2.5)
Subjects with adverse events on treatment area (popliteal fossa)	1 (3.3)	0	1 (2.5)
Subjects with adverse events on treatment area (periorbital area)	1 (3.3)	0	1 (2.5)
Subjects with adverse events on treatment area (perioral area)	1 (3.3)	0	1 (2.5)
Subjects discontinued from study due to adverse events[a]	1 (3.3)	0	1 (2.5)
Subjects discontinued study drug due to AE and continue Study[b]	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (3.3)	0	1 (2.5)

Includes data up to lag days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Subjects who had an AE record that indicates that the AE caused the subject to be discontinued from the study
b. Subjects who had an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adae Table Generation: 26JAN2021 (19:58)
Output File: ./csr6/C3291027/adae_t010
Table 14.3.1.2.1 Crisaborole is for Pfizer internal use.

Treatment-Related Adverse Events:

One participant (2.5%) experienced a TEAE which was considered as treatment-related (Table 7). This participant (in <18 years of age group) experienced a TEAE of application site pain and discontinued from the study after 13 days of study treatment. The TEAE was observed on the following treatment areas: eyelid, face, periorbital area, and perioral area and was mild in severity.

Table 7. Treatment-Emergent Adverse Events (Treatment Related) (Safety Analysis Set) (Protocol C3291027)

Number (%) of Subjects	Crisaborole 2% (N=40) n (%)
Subjects evaluable for adverse events	40
Number of adverse events	1
Subjects with adverse events	1 (2.5)
Subjects with serious adverse events	0
Subjects with severe adverse events	0
Subjects with adverse events on treatment area	1 (2.5)
Subjects with adverse events on treatment area (eyelid)	1 (2.5)
Subjects with adverse events on treatment area (face)	1 (2.5)
Subjects with adverse events on treatment area (periorbital area)	1 (2.5)
Subjects with adverse events on treatment area (perioral area)	1 (2.5)
Subjects discontinued from study due to adverse events[a]	1 (2.5)
Subjects discontinued study drug due to AE and continue Study[b]	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0

Includes data up to lag days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Subjects who had an AE record that indicates that the AE caused the subject to be discontinued from the study
b. Subjects who had an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be discontinued from Study
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adae Table Generation: 26JAN2021 (19:58)
Output File: ./csr6/C3291027/adae_s011
Table 14.3.1.3.1 Crisaborole is for Pfizer internal use.

Incidence of Adverse Events:

The all-causality TEAEs reported in the study are presented by SOC and PT in Table 8.

Table 8. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) (Safety Analysis Set) (Protocol C3291027)

Number (%) of Subjects: by System Organ Class and Preferred Term	Crisaborole 2% < 18 years (N=30) n (%)	Crisaborole 2% >= 18 years (N=10) n (%)	Crisaborole 2% Total (N=40) n (%)
With Any adverse event	11 (36.7)	3 (30.0)	14 (35.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.3)	0	1 (2.5)
Application site pain	1 (3.3)	0	1 (2.5)
INFECTIONS AND INFESTATIONS	7 (23.3)	1 (10.0)	8 (20.0)
Bronchitis	1 (3.3)	0	1 (2.5)
Gastroenteritis	0	1 (10.0)	1 (2.5)
Molluscum contagiosum	1 (3.3)	0	1 (2.5)
Nasopharyngitis	3 (10.0)	0	3 (7.5)
Otitis media acute	1 (3.3)	0	1 (2.5)
Rhinitis	1 (3.3)	0	1 (2.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (10.0)	1 (2.5)
Wound	0	1 (10.0)	1 (2.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (10.0)	1 (2.5)
Joint effusion	0	1 (10.0)	1 (2.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (13.3)	0	4 (10.0)
Acne	1 (3.3)	0	1 (2.5)
Dermatitis atopic	2 (6.7)	0	2 (5.0)
Dermatitis contact	1 (3.3)	0	1 (2.5)

Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes data up to lag days after last dose of study drug.
MedDRA v23.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 22JAN2021 (15:20) Source Data: adae Table Generation: 26JAN2021 (15:23)
Output File: ./csr6/C3291027/adae_s0311
Table 14.3.1.2.2 Crisaborole is for Pfizer internal use.

Analysis of Adverse Events:

The most frequently reported all-causality TEAEs by PT were nasopharyngitis (3 participants) and dermatitis atopic (2 participants). Neither of these TEAEs were determined by the investigator to be related to study treatment. Only 2 TEAEs occurring in the treatment area were reported, of which 1 TEAE, application site pain, was considered treatment-related and it resolved by the end of the study.

Information on the location affected by AEs occurring in the treatment area was collected. Application site pain was observed on eyelid, face, periorbital area, perioral area, and dermatitis atopic was observed on popliteal fossa. Because of the small number of reported AEs in the treatment area, the study could not identify the most frequently reported location.

No deaths, SAEs, or moderate/severe AEs were reported in the study. All the TEAEs (all-causalities) reported in the study were mild in severity.

TEAEs potentially attributable to systemic PDE-4 inhibition (diarrhea, vomiting, and weight decreased) were not reported. No other TEAEs potentially associated with systemic PDE-4 inhibition (e.g., insomnia, nausea, serious infections, malignancy) were observed in this study.

Permanent Discontinuations Due to Adverse Events:

One participant in <18 years of age group discontinued the study due to a TEAE of application site pain on multiple treatment areas of the face which was mild in severity and considered as treatment-related. This event of application site pain is consistent with the known safety profile of crisaborole. The TEAE resolved after permanent discontinuation of the study treatment.

Dose Reductions or Temporary Discontinuations Due to Adverse Events:

One participant in <18 years of age group had a TEAE of dermatitis atopic that led to drug interruption. It was not related to study treatment.

CHMP comment

Frequencies of all-causality TEAEs (all mild in severity) were comparable between paediatric and adult subjects (paediatric group: 11 participants (36.7%) with 12 all-causality TEAEs; adult group: 3 participants (30.0%) with 3 all-causality TEAEs). In the paediatric group, the most frequently reported all-causality TEAEs by PT were nasopharyngitis (3 participants) and dermatitis atopic (2 participants).

2 TEAEs occurring in the treatment area were reported, of which 1 TEAE, application site pain, was considered treatment-related and it resolved by the end of the study.

Skin and application site reactions seem the most common adverse reactions observed in the paediatric population (observed in one patient <18yoa). TEAE incidence in paediatric subjects appears comparable to what has been reported during the clinical studies included in the application to obtain initial marketing authorisation for Staquis in the EU (AN2728-AD-301 and AN2728-AD-302). This provides reassurance, particularly given that the used formulation in this study contains the potentially irritating agent BHT (which has been removed from the formulation used in the EU).

Permanent study discontinuation due to AEs was reported in a single paediatric patient (TEAE of application site pain on multiple treatment areas of the face; treatment related, mild severity) which resolved after discontinuation.

Notably, no TEAEs which may be related to/ associated with systemic PDE-4 inhibition (diarrhea, vomiting, and weight decreased; insomnia, nausea, serious infections, malignancy) were reported.

No SAEs, severe AEs or deaths occurred.

The safety monitoring seems adequate from the information provided. No safety issues could be identified.

It is re-emphasized that all of the above refers to short-term treatment (approx. 1 month for the majority of subjects) in study C3291027 (with unknown duration of prior exposure in the parent study C3291032) and the study does not allow to draw any conclusions on longer-term safety.

2.3.3. Discussion on clinical aspects

The MAH submitted a clinical study report of Study C3291027, a Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants With Mild to Moderate Atopic Dermatitis. This study was conducted to support the crisaborole development programme in Japan and was not part of the EU PIP for crisaborole (PIP Decision No. P/0276/2020).

The study was terminated prematurely due to the sponsor's business decision and portfolio reprioritisation. According to the MAH, this decision was not a result of any safety or efficacy concerns.

This submission is done to meet the requirement of Art. 46 to submit paediatric data within 6 months from end of study.

Only safety data were reported from this trial. The submitted safety data are of limited value for the European label, due to several constraints as outlined below, above all the size and treatment duration of the study sample are inadequate.

No changes to the product information (SmPC or PIL) are proposed or indicated based on results from study C3291027.

This study was conducted with a Crisaborole formulation containing 0.1% Butylhydroxytoluole, BHT (approved in US, Canada, Israel, and Australia, but not EU). The formulation approved in the EU (trade name Staquis) does not contain BHT.

Study design and methods

Study C3291027 intended to assess long-term safety (1 year) of crisaborole ointment, 2% BID in Japanese AD pediatric and adult participants. Participants who completed study intervention in two other MAH conducted studies, C3291032 and Study C3291031, were planned to be enrolled into this study. However, the latter was terminated and did not enrol patients into C3291027. All participants in study C3291027 were enrolled from study C3291032 (Phase 3, multicenter, randomized, double-blind, vehicle controlled; efficacy and safety of crisaborole ointment, 2% in Asian subjects ≥ 2 years of age) which was still ongoing at the time of this P46 procedure.

The **duration** of the Investigational Product Application Period was intended to be 365 days (= 13 treatment cycles of 28 days). This included study visits at the beginning of each treatment cycle (i.e. every 28 days) until week 52/day 365 (End of Treatment) with post-treatment follow up-contact at week 56/ day 393 (End of Study).

The duration of treatment and follow-up would have been considered adequate to inform on long-term safety and exploratory efficacy (as noted above, the study was terminated earlier).

The study was planned to include only Japanese pediatric and adult patients from 1 month of age with mild to moderate AD who were to be enrolled after completion of one of the two parent studies. Patients had to meet eligibility criteria for Study C3291032 (and C3291031) and complete the parent study without safety issues. A certain selection of patient more likely to tolerate treatment well in this long-term study can thus be assumed. As no protocols/reports for C3291031 or C3291032 are provided no details about the C3291027 populations (e.g. regarding baseline disease criteria including % BSA affected) are known and the treatment duration before enrolment into C3291027 is unclear, limiting the value of study outcomes.

The **primary study endpoint** was Incidence of treatment emergent AEs and SAEs. Together with the description of the quality of the AEs and the relation to treatment, this is appropriate for the characterisation of long-term safety.

Tertiary/ exploratory endpoints planned relate to efficacy and PK (not reported).

Vital sign (e.g. temperature, blood pressure, pulse rate) and laboratory assessments (e.g. hematology, blood chemistry, urinalysis) were not evaluated. This is considered a shortcoming, as subclinical changes will not be detected which might, however, provide important information for long-term safety. However, as this study was prematurely terminated preventing collection of longer-term data (see results), no further issue is raised.

As regards the **dosing procedure**, subjects assessed as Almost Clear based on ISGA score ≥ 1 began a 4 week on-treatment cycle to receive crisaborole ointment, 2%. Subjects who were assessed as Clear (ISGA = 0) were started on a 4 week off-treatment cycle (no crisaborole treatment; emollients/moisturizers on AD areas allowed). Crisaborole ointment, 2% was applied BID at home to affected AD-involved areas using a standardised process, which is considered beneficial for the interpretation of results. The proposed protocol could have been valuable to inform on intermittent treatment regimens (no information on (the duration of) treatment holidays is given in the European SmPC).

In terms of **statistical methods**, safety (and efficacy) endpoints were analysed descriptively without formal hypothesis testing, which is acceptable for the intended purpose.

Results

It was expected that the C3291027 **study population** would consist of approx. 130 Japanese subjects who had completed study C3291032. Eventually only 40 participants were enrolled into study C3291027.

All participants were Asian, 10/40 ≥ 18 years of age, and 30/40 between 2-17 years of age. Within the paediatric cohort 22/30 (73.3%) were between 2-11 yoa and 8/30 (26.7%) were between 12-17 yoa.

Among the total of 40 subjects, 27 participants in the < 18 years of age group (and 10 in the ≥18 years of age group) were treated with crisaborole ointment 2% BID (3 subjects in <18 years of age group discontinued without treatment with crisaborole ointment 2% BID). In both the <18 years of age group (n=30) and the ≥18 years of age group (n=10) the median duration of crisaborole ointment 2% BID treatment was 29.0 days (ranges of 0 to 51 and 14 to 56 days, respectively). Due to the early study discontinuation the majority of subjects were only treated over the course of one treatment cycle, which does not permit to draw any conclusions on long-term safety of crisaborole ointment 2% in the population under investigation. As it is not known how long patients were treated in the parent trial (C3291032) it is also unknown how long the overall treatment duration is.

Potentially important protocol deviations were reported in 22/40 (55.5 %) subjects. However, as the majority of these (15/22) were related to inappropriate PK blood sampling time (which is not assessed during this procedure, no PK data are submitted), no impact on interpretability of safety results is suspected. No further issue is raised

Safety

Frequencies of all-causality TEAEs (all mild in severity) were comparable between paediatric and adult subjects (paediatric group: 11 participants (36.7%) with 12 all-causality TEAEs; adult group: 3

participants (30.0%) with 3 all-causality TEAEs). In the paediatric group, the most frequently reported all-causality TEAEs by PT were nasopharyngitis (3 participants) and dermatitis atopic (2 participants).

2 TEAEs occurring in the treatment area were reported, of which 1 TEAE, application site pain, was considered treatment-related. This reaction lead to permanent study discontinuation but resolved by the EOS.

TEAE incidence in paediatric subjects appears comparable to what has been reported during the clinical studies included in the application to obtain initial marketing authorisation for Staquis in the EU (AN2728-AD-301 and AN2728-AD-302). This provides reassurance, particularly given that the used formulation in this study contains the potentially irritating agent BHT (which has been removed from the formulation used in the EU).

Notably, no TEAEs which may be related to/ associated with systemic PDE-4 inhibition (diarrhea, vomiting, and weight decreased; insomnia, nausea, serious infections, malignancy) were reported.

No SAEs, severe AEs or deaths occurred.

The safety monitoring seems adequate from the information provided. No safety issues could be identified.

Efficacy and PK

No efficacy and PK data were submitted, due to the potential of unblinding of study C3291032 which was still ongoing at the time of assessment of this P46 procedure. This is acceptable. Results are expected to be submitted to EMA after trial completion.

3. CHMP overall conclusion and recommendation

The limited data from the prematurely terminated study C3291027 do not allow a better characterisation of crisaborole long-term effects in paediatric patients with mild to moderate atopic dermatitis. Uncertainties pertain to the short study duration (only one 28 day treatment cycle in most patients), the small paediatric sample (only 27 paediatric patients were treated in the course of the study) but also to the characterisation of the patients included (no inclusion/exclusion criteria from parent studies available).

Available limited results overall support a benign short-time safety profile of Crisaborole ointment, 2% in the paediatric population >2 years of age. No SmPC changes are proposed or indicated.

☒ **Fulfilled:**

No regulatory action required.

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

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Staquis Active substance: Crisaborole

Study title	Study number	Date of completion	Date of submission of final study report
PIP Study 1: 4-week definitive juvenile toxicity study in rats with a 1-week recovery period to evaluate food consumption, sexual maturation, functional observational battery, motor activity, acoustic startle response, clinical pathology, necropsy findings, organ weights and histopathology.	003-NCL TX-055-01	17/10/2012 (Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020
PIP Study 2: 4-week definitive juvenile dermal toxicity study in Gottingen minipigs with a 1-week recovery period to evaluate clinical signs, bodyweight, food consumption, growth rate, clinical pathology, ECG and ophthalmoscopy.	003-NCL TX-054-01 AN2728 TOPICAL OINTMENT	08/11/2012 (Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020
PIP Study 3: 4-week definitive juvenile toxicity study in rats with a 2-week recovery period to evaluate systemic safety, body weight, food consumption, motor activity, acoustic startle habituation, clinical pathology, including haematology and clinical chemistry, macroscopic and microscopic pathology.	20093673 (16GR400)	04/08/2017(Final study report signed)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020

Clinical studies

Product Name: Staquis Active substance: Crisaborole

Study title	Study number	Date of completion	Date of submission of final study report
PIP Study 5: Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 2 to less than 18 years of age (and adults) with mild to-moderate atopic dermatitis.	AN2728-AD-302	27/04/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020
PIP Study 4: Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 2 to less than 18 years of age (and adults) with mild to-moderate atopic dermatitis.	AN2728-AD-301	29/04/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020

Staquis (crisaborole) Article 46 (Study C3291027) June 2021

Study title	Study number	Date of completion	Date of submission of final study report
PIP Study 6: Open-label, uncontrolled, extension study to evaluate long-term safety of crisaborole ointment, 2% in children from 2 to less than 18 years of age (and adults) with mild-to-moderate atopic dermatitis.	AN2728-AD-303	27/10/2015 (LSLV)	Staquis EU MAA Procedure No. EMEA/H/C/004863/0000 Latest PIP decision: P/0276/2020
A Phase 2b, Multi center, Randomized, Double-blind, vehicle-controlled, intra-participant study, to evaluate efficacy and safety of two regimens of crisaborole ointment 2% in japanese pediatric and adult participants (2 years and older) with mild to moderate atopic dermatitis.	C3291028	LSLV 16 December 2019	Article 46 submission by June 2020 (09 June 2020 submission deadline) This procedure is complete (EMA/H/C/004863/P46/003)
A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants with Mild to Moderate Atopic Dermatitis	C3291027	LSLV 18 December 2020 Study C3291027 was terminated prematurely. This decision was based solely on business reasons and was not related to any safety issues regarding crisaborole.	Article 46 submission by June 2021
PIP Study 8: Assessor-blind, randomised, active- and vehicle -controlled study to evaluate efficacy and safety of crisaborole ointment, 2% compared to topical corticosteroid (TCS), topical calcineurin inhibitor (TCI) and vehicle in children from 2 to less than 18 years of age (and adults) with mild to moderate atopic dermatitis.	C3291037	LSLV May 2021 (EMA PIP decision: P/0276/2020 In October 2020 Pfizer took the decision to terminate the ongoing global EU PIP Study C3291037. This decision was based solely on business reasons and was not related to any safety issues regarding crisaborole.	Latest PIP decision: P/0276/2020
A Phase 3, Multicenter, Randomized, Double-blind, Vehicle Controlled Study of the Efficacy and Safety of Crisaborole Ointment, 2% in Asian Pediatric and Adult Subjects (ages 2 years and older) with Mild to Moderate Atopic Dermatitis.	C3291032	LSLV September 2021	Article 46 submission by March 2022

Staquis (crisaborole) Article 46 (Study C3291027) June 2021

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Maintenance Treatment and Flare Reduction with Crisaborole Ointment, 2%, Once Daily Over 52 Weeks in Pediatric and Adult Participants (Ages 2 Years and Older) with Mild-to-Moderate Atopic Dermatitis, who Responded to Twice Daily Crisaborole Ointment, 2%, Treatment.	C3291035	LSLV April 2022	Article 46 submission by October 2022.
PIP Study 7: Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 1 month to less than 24 months of age with mild-to-moderate atopic dermatitis.	C3291031	Date of completion (LSLV) in current agreed PIP P/0276/2020is October 2022. In October 2020 Pfizer took the decision to cancel the planned EU PIP Study C3291031. This decision was based solely on business reasons and was not related to any safety issues regarding crisaborole.	Latest PIP decision: P/0276/2020.