Amsterdam, 20 August 2020
EMA/591235/2020
Committee for Medicinal Products for Human Use (CHMP)

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

Staquis

International non-proprietary name: crisaborole

Procedure no.: EMA/H/C/004863/P46/003

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 9th, 2020, the MAH submitted a completed paediatric study for Crisaborole ointment 2%, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(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 C3291028, "A Phase 2b, Multi-centre, Randomised, Double-Blind, Vehicle-Controlled, Intra-Participant Study, to Evaluate Efficacy and Safety of Two Regimens of Crisaborole Ointment 2% in Japanese Paediatric and Adult Participants (2 Years and Older) With Mild to Moderate Atopic Dermatitis" is a stand-alone study.

Study C3291028 was conducted to support the crisaborole development program in Japan.

2.2. Information on the pharmaceutical formulation used in the study

STAQUIS (Crisaborole) is presented as an ointment containing 20 mg/g ointment in the EU.

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

Crisaborole is approved under the trade name EUCRISA in the US (14 December 2016) for the topical treatment of mild to moderate AD in patients 2 years of age and older and was approved 23 March 2020 for use in patients down to 3 months of age. EUCRISA is approved in Canada (07 June 2018) for topical treatment of mild to moderate AD in patients 2 years of age and older and under the trade name STAQUIS in Israel (10 February 2019), Australia (15 February 2019), Hong Kong (20 April 2020) and China (29 July 2020) for the same indication. In these regions, the authorised formulation contains 0.1% butylated hydroxytoluene (BHT), an antioxidant excipient.

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.

The original marketing authorisation application for STAQUIS in the EU was based on the results of two identically designed randomised, double-blind, vehicle-controlled, Phase 3 registration studies (AN2728-AD-301 and AN2728-AD-302). AN2728-AD-303 was an open-label, 12 months safety study in patients (2 years and older) with mild to moderate AD who completed Study AN2728-AD-301 or Study AN2728-AD-302. Additional studies have been performed (see "Annex - Line Listings" at the end of this report).

Assessor's 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 C3291028: "A Phase 2b, Multi-centre, Randomised, Double-Blind, Vehicle-Controlled, Intra-Participant Study, to Evaluate Efficacy and Safety of Two Regimens of Crisaborole Ointment 2% in Japanese Paediatric and Adult Participants (2 Years and Older) With Mild to Moderate Atopic Dermatitis".

2.3.2. Clinical study

Study C3291028: "A Phase 2b, Multi-centre, Randomised, Double-Blind, Vehicle-Controlled, Intra-Participant Study, to Evaluate Efficacy and Safety of Two Regimens of Crisaborole Ointment 2% in Japanese Paediatric and Adult Participants (2 Years and Older) With Mild to Moderate Atopic Dermatitis"

Study Period:
Date of First Subject First Visit: June 15th, 2019
Date of Last Subject Last Visit: December 16th, 2019

Description

Study C3291028 was a Phase 2b, multi-centre, randomised, double-blind, vehicle-controlled, intra-participant study to evaluate efficacy and safety of 2 regimens of crisaborole ointment 2% in Japanese paediatric and adult participants (Cohort 1: ≥12 years, Cohort 2: 2 to under 12 years old) with mild to moderate AD. After completing screening activities, including meeting eligibility criteria, 2 target lesions that were moderate in severity were determined by the investigator, participants were randomised to 1 of the 2 regimens, QD (once a day) or BID (twice a day), randomisation ratio; 1:1, and crisaborole ointment 2% or vehicle were randomly assigned to each target lesion at baseline/Day 1. Both target lesions were to be treated at the assigned dosing regimen and dosing regimen was unblinded information to sponsor, investigators/study sites and participants. Participants were treated with investigational products administered for 2 weeks and followed-up 28 days after the end of treatment.

The primary objective of the study was to compare the efficacy of crisaborole ointment 2%, administered QD or BID relative to the corresponding vehicle (QD or BID), on TSS (total severity score) assessment in target lesions, in the treatment of mild to moderate AD in adults & adolescents (Cohort 1) and younger children (Cohort 2).

Secondary objectives (in the same cohorts) were to evaluate efficacy of crisaborole ointment 2% BID relative to crisaborole ointment 2% QD on TSS in target lesions, to evaluate the efficacy of crisaborole

ointment 2%, administered QD or BID on TSS/ ISGA/ pruritus assessments in target lesions and to assess the safety and local tolerability of crisaborole ointment 2%, administered QD or BID.

The exploratory objective (in the same cohorts) was to evaluate the efficacy of crisaborole ointment 2%, administered QD or BID, on ISGA response in target lesions.

Assessor's comment

For the description of cohorts the Applicant uses the term 'adult' for Cohort 1 and 'paediatric' for Cohort 2. It is noted that the cut-offs used are not in line with European standards where paediatric patients include adolescents up to 18 years of age. However, this cut-off between cohorts is not considered problematic and a comparison of the two groups is still of interest. In registrational studies in the EU, there were no relevant differences between adult and adolescent patients in terms of treatment response. However, extent of exposure and tolerability were suspected to be higher/poorer in very young children with high % BSA affected.

Methods

Objective(s)

Primary Objective:

- To compare the efficacy of crisaborole ointment 2%, administered QD or BID relative to the corresponding vehicle (QD or BID), on TSS assessment in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and paediatrics (Cohort 2)

Secondary Objectives:

- To evaluate the efficacy of crisaborole ointment 2% BID relative to crisaborole ointment 2% QD, on TSS assessment in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and paediatrics (Cohort 2)
- To evaluate the efficacy of crisaborole ointment 2%, administered QD or BID, on TSS, ISGA, and pruritus assessments in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and paediatrics (Cohort 2)
- To assess the safety and local tolerability of crisaborole ointment 2%, administered QD or BID, in the treatment of mild to moderate AD in adults (Cohort 1) and paediatrics (Cohort 2)

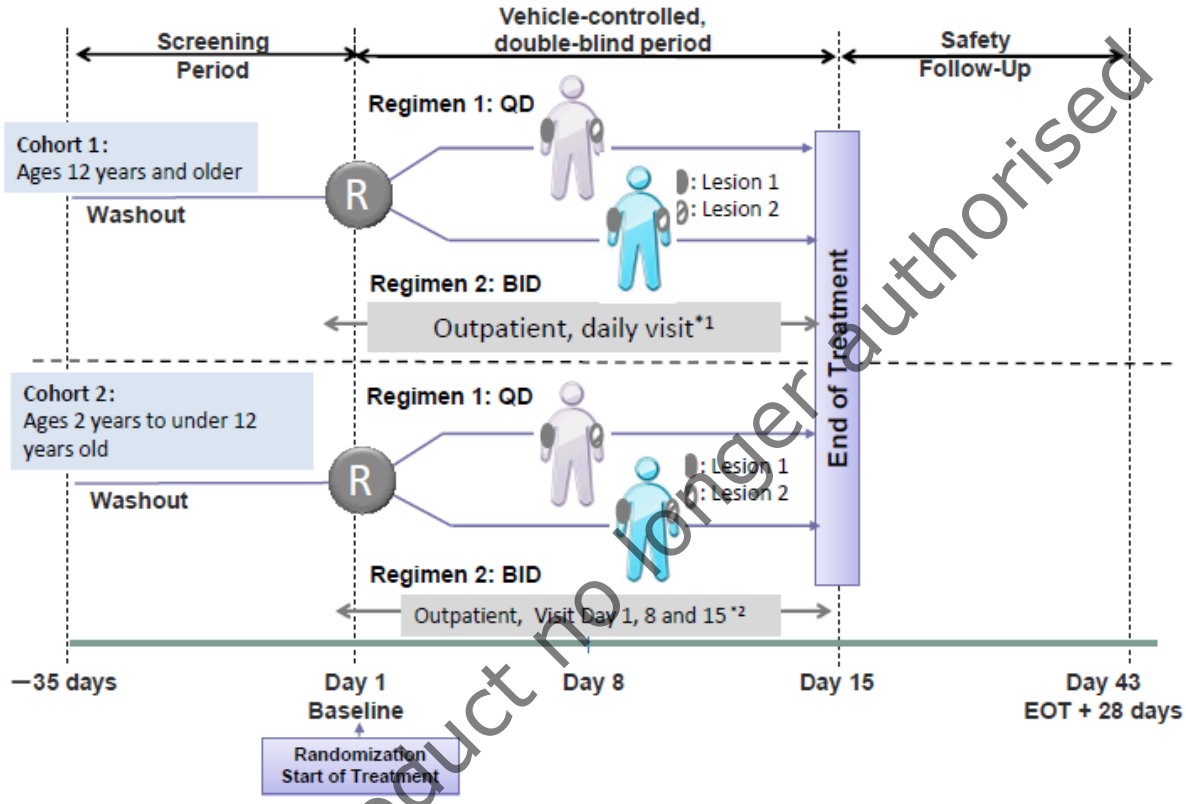
Exploratory Objective:

- To evaluate the efficacy of crisaborole ointment 2%, administered QD or BID, on ISGA response in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and paediatrics (Cohort 2)

Study design

This was a Phase 2b, multi-centre, randomised, double-blind, vehicle-controlled, intra-participant study to evaluate efficacy and safety of 2 regimens of crisaborole ointment 2% in Japanese paediatric and adult participants with mild to moderate AD.

After completing screening activities, including meeting eligibility criteria, 2 target lesions that were moderate in severity were determined by the investigator. Participants were randomised to 1 of the 2 regimens, QD or BID (randomisation ratio; 1:1), and crisaborole ointment 2% or vehicle were randomly assigned to each target lesion at baseline/Day 1. Both target lesions were to be treated at the assigned dosing regimen. The study interventions were applied only to Lesion 1 and Lesion 2, and not applied to other AD affected areas. The dosing regimen (QD or BID) was unblinded information to sponsor, investigators/study sites and participants. Participants were treated for 2 weeks and followed-up 28 days after the end of treatment.



BID: twice daily, QD: once daily
* 1 Visit study site and application by site staff
* 2 Investigational products will be applied by parent/caregiver with site staff check (directly or via live video chat, etc.) and/or by site staff (site staff will visit participant's home as needed).

Study population /Sample size

In Cohort 1 (N=41), 20 participants received crisaborole 2% QD + vehicle and 21 participants received crisaborole 2% BID + vehicle.

In Cohort 2 (N=40), 20 participants received crisaborole 2% QD + vehicle and 20 participants received crisaborole 2% BID + vehicle.

Inclusion Criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female participants ages:
    - Cohort 1: ≥ 12 years at the time of consent

- Cohort 2: 2 years to under 12 years old at the time of consent

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Participants who have confirmed clinical diagnosis of active AD at screening and Baseline/Day 1 according to Hanifin and Rajka criteria and who have at least 6 month history prior to Screening visit and that has been clinically stable for more than 1 month.

4. Participants who have a global ISGA of 2 (mild) or 3 (moderate) at Baseline/Day 1 visit.

5. Participants who have AD lesions on upper limbs, lower limbs or ventral of the body trunk and a body surface area (BSA) covered with AD of at least 1.0% and no more than 30% at Baseline/Day 1, excluding scalp, genitals and groin area. The presence of AD on these areas (scalp, genitals and groin area) is not exclusionary, but will not be included in the calculation for coverage of BSA with AD.

6. Participants who have two lesions of AD at least 3 cm x 3 cm with identical Lesion ISGA = 3 (moderate) for each lesion. These AD lesions must be at least 10 cm apart. The target lesions must not be on the face, neck, scalp, axilla, genitals, groin area, palms, dorsal of the hands, dorsal of the body trunk and soles. In addition, two AD areas on the same limb must not be selected as the Target Lesions. [Note: When possible, AD areas on the bilateral (left/right) area should have been selected as target lesions].

    - Cohort 2: If 0.5%BSA is smaller than 3 cm x 3 cm, 0.5%BSA is acceptable for each of the two AD lesions with identical Lesion ISGA = 3 (moderate) for each lesion.

7. Participants who received any of the following AD treatment regimens are eligible if the following minimum washout criteria are observed:

    At least 28 days prior to Baseline/Day 1:

    - Systemic (oral/injectable) corticosteroids (Note: use of intranasal/inhaled or ophthalmic corticosteroids for stable medical conditions are allowed);
    - Systemic immunosuppressive agents (eg, calcineurin inhibitors, cyclosporine);
    - Sunbathing, tanning bed use, or phototherapy (eg, narrow band ultraviolet B [NbUVB], psoralen plus ultraviolet A [PUVA]).

    At least 14 days prior to Baseline/Day 1:

    - Systemic antimicrobials;
    - Topical corticosteroids (all potencies) and topical calcineurin inhibitors.

    At least 7 days prior to Baseline/Day 1:

    - Topical antimicrobials;
    - Use of antibacterial soaps (for bathing), bleach bath, bath oil, or topical sodium hypochlorite-based products;
    - Topical antihistamines;
    - Systemic sedating antihistamines (eg, hydroxyzine, diphenhydramine or other sedating antihistamines);
    - Systemic and topical traditional Chinese medicine/herbal preparation that might alter the course of AD.

    At least 8 hours prior to 1st dose of investigational products on Baseline/Day 1:

    - Use of emollients and moisturisers.

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
2. History of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of crisaborole ointment 2%.
3. Participants had previous treatment with any topical or systemic PDE-4 inhibitor.
4. Participants who have undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma or carcinoma in situ of the skin, curatively treated with surgical excision only).
5. Participants who are receiving any of the following drugs and have to wash out to participate in this study:
    - Biological drugs;
    - Systemic (oral/injectable) corticosteroids (Note: use of intranasal/inhaled or ophthalmic corticosteroids for stable medical conditions are allowed);
    - Systemic immunosuppressive agents (eg, calcineurin inhibitors, cyclosporine);
    - Phototherapy (eg, NbUVB, PUVA).
6. Participants who require treatment with prohibited concomitant medication(s)
7. Previous administration with an investigational product within 30 days or 5 half-lives preceding the first dose of investigational products used in this study (whichever is longer).
8. Participants who have participated in a clinical study of crisaborole.
9. Participants are not willing to minimise or avoid natural and artificial sunlight exposure during the study.
10. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

Lifestyle considerations:

1. The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct

use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

2. Routine preventative immunisations are permitted during the study; however, it is preferred that immunisations be administered at least 28 days before the start or following the completion of the participation.
3. Participants should refrain from swimming, bathing, sauna or washing the treated areas for at least 4 hours after application.
4. Use of sunscreen is permitted, but only on other areas than target lesions.
5. The participants and/or parents/caregivers should avoid wiping the investigational products off the skin. In the case of any investigational product inadvertently being wiped off, it should not be reapplied to wiped areas until the next scheduled dose.
6. When applying investigational products, the parent/caregiver will not be required to wear gloves when applying investigational products. However, they must be instructed to wash their hands with mild soap and water before and after each application of each investigational product.
7. Participants will be instructed to be dressed in loose-fitting clothing and avoid occluding the treated areas (with dry wraps, for example). Wet wraps are not permitted.
8. Parent/caregiver should be encouraged not to put hands in the mouth to avoid ingestion of investigational products. The parent/caregiver should be instructed for participants who are young children to avoid licking the application site of the investigational product.

Assessor's comment

The study population consisted of two cohorts of Japanese patients (cohort 1: ≥ 12 years; cohort 2: 2 years to < 12 years) with mild to moderate AD. The diagnosis of AD is based on the Hanifin and Rajka criteria (1980) which are well established worldwide and acceptable. Participants were required to have a global ISGA of 2 (mild) or 3 (moderate) and BSA affected between 1-30% at Baseline/Day 1 visit. Target lesions (to which IP or vehicle was applied) were 3 cm x 3 cm with identical Lesion ISGA = 3 (moderate) for each lesion and had to be at least 10 cm apart (on different limbs). The in- and exclusion criteria cover the European target population to a large extent (STAQUIS approved in EU for mild-moderate AD with BSA ≤40%) yet exclude the patient group with a larger body surface area affected (BSA 30-40%).

Treatments

Dose selection:

Crisaborole ointment 2% BID is selected as the highest well-tolerated dose to maximise the potential for efficacy with minimal safety risk based on the results of foreign clinical studies, and 2% was technically the maximum dose for commercial ointment formulation, therefore 2% is selected for dosage of this study. In an earlier single dose phase I study (C3291029), the 2% formulation was evaluated with a BID regimen and considered safe in healthy volunteers (N=20) and AD patients (N=10) with a BSA of at least 25% at baseline.

Dosing procedure:

At Baseline/Day 1, the participants who meet Inclusion/Exclusion Criteria will be randomised to one of the regimens, QD or BID, and for each of two target lesion (Lesion 1 and Lesion 2) meeting the inclusion criteria identified by the investigator, the investigational products (crisaborole ointment 2% or vehicle) will be assigned randomly. The sponsor, investigators/study sites and participants will be blinded with respect to which lesion is receiving the crisaborole ointment 2% or vehicle.

	Regimen 1 (QD)	Regimen 2 (BID)
Morning		
Evening	NA	

BID: twice daily, NA: not applicable, QD: once daily
In case of Regimen 1 (QD), once daily in the evening throughout the treatment period is acceptable as like as once daily in the morning throughout the treatment period.

For cohort 1, the participants will visit the site at every dosing timing [Regimen 1 (QD): once daily in the morning or evening, Regimen 2 (BID): twice daily in the morning and evening] and the investigational products will be applied by the site staff. It may allow that the site staff applies the investigational products at the participant's home as a backup option upon sponsor's agreement when the participant is not able to visit the site. For Regimen 2 (BID), dosing interval should be 12 ±4 hours.

For cohort 2, the parent/caregiver and/or the site staff will apply the investigational products. When the parent/caregiver applies, it will be done with confirmation of the appropriate application by the site staff (directly or via live video chat). When site staff applies, site staff will visit the participant's home as needed. For Regimen 2 (BID), dosing interval should be 12 ±4 hours.

For regimen 1 (QD), participant will be applied investigational products from Day 1 to Day 14. For regimen 2 (BID), when participant will be applied investigational products from AM in Day 1, the last administration will be PM in Day 14. When participant will be applied investigational products from PM in Day 1, the last administration will be AM in Day 15.

In order to better standardise the amount of investigational products applied to the target lesions, the Principal Investigator (PI) will measure the size of each target lesion at Baseline/Day 1 and determine the amount of medication to be applied by using finger-tip unit. The area of the lesion will be determined using the "handprint method", wherein the area represented by the participant's outstretched hand (including all five digits adducted together) equals approximately 1% of the participant's BSA. Parent/caregiver for cohort 2 will receive verbal and written instructions on how much study medication to apply to treatment areas and how the investigational products should be applied. New investigational product tubes will be dispensed at Baseline/Day 1 and Day 8 for parents/caregivers of cohort 2. Parents/caregivers for cohort 2 will be instructed to return the investigational product tubes at Day 8 and Day 15.

Participants should be instructed to wait at least 15 minutes after bathing/showering allowing the skin to dry thoroughly prior to applying medication. Participants should not shower or wash off study medication within 4 hours after application. Crisaborole ointment 2% is for external use on the skin only. Contact with mucous membranes (i.e. inside of nostrils, mouth, vagina, urethra, and rectum), and in the eyes should be avoided. Participants should avoid ingestion of investigational products.

The lesion size and prescribed amount of investigational products will be recorded in the source documentation and marked on the dosing instruction document for the parents/caregivers.

The investigational products will be applied only to Lesion 1 and Lesion 2, and not applied to other AD affected areas.

Duration of Treatment and Follow-Up:

Screening procedures were to be completed between 2 and 28 days (inclusive) prior to the Baseline/Day 1 Visit. The duration of the Investigational Product Application Period was 14 days and included study visits at days 1, 8 and 15 (End of Treatment). The Post-Treatment Follow-Up period included telephone contact between days 28 to 35 (note: amended to 28 to 31 days) from administration of the final dose of investigational products (i.e. between study days 43 to 46).

Assessor's comment

Dose selection: The selection of the crisaborole concentration (ointment 2%) and the dosing regimen (QD or BID) for this study were based on the highest well-tolerated dose and technically feasible dosage. The aim was to maximise the efficacy outcome with minimal safety risk based on the results of foreign clinical studies and study C3291029, in which the safety and tolerability in Japanese patients with AD were confirmed. Dose selection seems adequate.

Dosing procedure: Participants were randomised to one of the regimens, QD or BID, and for each of the two target lesion (Lesion 1 and Lesion 2) meeting the inclusion criteria identified by the investigator, the investigational products (crisaborole ointment 2% or vehicle) were assigned randomly. Crisaborole or vehicle was applied to AD target lesions over a course of 15 days. The application of ointment was always done under supervision (either applied directly or supervised by study personnel) in both cohorts. Standardisation of the process (application method and dose) is considered beneficial for the interpretation of results.

Identifying potential differences between QD or BID regimens is of value for future dosing investigations/ recommendations.

Duration of treatment: The duration of the Investigational Product Application Period was 14 days and included study visits at days 1, 8 and 15 (End of Treatment). The Post-Treatment Follow-Up period included telephone contact between days 43 to 46. While this is acceptable in the context of a Phase 2b study, treatment of only 2 weeks limits conclusions on long-term efficacy and safety (see further comments and discussion below).

Outcomes/endpoints

Primary endpoint (efficacy)

- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (Regimen 1: QD, Regimen 2: BID) for each cohort

Secondary endpoints (efficacy & safety)

- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort
- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 8 in each for each cohort
- Change from baseline in ISGA in target lesions treated with crisaborole ointment or vehicle at each visit up to Day 15 in each regimen for each cohort
- Change from baseline in pruritus assessments in target lesions treated with crisaborole ointment or vehicle at each day up to Day 15 in each regimen using following scales:
    - Cohort 1: Peak pruritus, NRS (Age ≥ 12 years)
    - Cohort 2: Itch severity scale (Age 6-11 years) Self-Report; Caregiver reported itch severity NRS (Age 2-11 years)
- Incidence of TEAEs and each regimen for each cohort

Exploratory endpoint (efficacy)

- ISGA response of clear or almost clear and at least a 2-grade improvement from baseline in target lesions treated with crisaborole ointment or vehicle at each visit up to Day 15 in each regimen for each cohort

Clinical Safety Assessments

The following clinical safety assessments were performed:

- Medical History
- Vital Signs (temperature, pulse rate, blood pressure)
- Physical Examination
- AE and SAE recording

Laboratory Safety Assessments

A pregnancy test is performed at Screening, Day 1 and Day 15. All other safety assessments were performed at screening only.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
At screening only: Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	At screening only: BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	At screening only: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Pregnancy test (β-hCG)[c] At screening only: • FSH[b] • Urine drug screening

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by institutional review board/ethics committee (IRB/EC). For female participants of childbearing potential, if a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

Assessor's comment

The primary study endpoint of success was Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (Regimen 1: QD, Regimen 2: BID) for each cohort (intra-patient). The lesion TSS assesses AD severity in 4 domains, erythema, induration/papulation, excoriation (evidence of scratching), and lichenification (epidermal thickening) by assigning 0-3 points for each domain. The maximum total score is 12 (= most severe AD manifestation). This score employs the same domains (and the same points per domain) as the more commonly used EASI score. The latter further weighs the lesions by multiplying the severity score by area scores and additional multipliers. The choice of the lesion TSS therefore seems reasonable for this study, as the treatment effect on single lesions per patient is evaluated. Comparison to external data (e.g. main phase 3 studies) needs to be done under this prerequisite considering that the endpoints are different (single lesions vs. global disease).

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, although in the study under assessment it was measured at day 15 (compared to day 29) and on the single lesion level (compared to global). This allows for good contextualisation of the data, however.

Secondary endpoints included efficacy evaluations based on TSS (inter-patient) and pruritus assessments in target lesions up to day 15 as well as safety evaluations (adverse event incidence).

Overall, the choice of endpoints is considered adequate.

Schedule of activities all subjects

Visit Identifier[a]	Day -35 to Day -1 Screening	Day 1 Baseline	Day 8	Day 15 End of Treatment/ Early Discontinuation[b]	Day 43 Follow-up[c]
Visit Window			**±1 Day**	**±1 Day**	**+3 Days**
Informed consent, including assent	X				
Medical history	X	X			
Vital signs[d]	X				
Physical examination	X			X	
Laboratory					
Hematology	X				
Blood chemistry	X[e]				
Urinalysis	X				
Pregnancy test[f]	X	X		X	
Contraception check[g]	X	X	X	X	X
Identify two target lesions		X			
Randomization		X			
Study treatment					
Cohort 1: Site staff applies the investigational products to the participant at the site.[h]		X	→	X	
Cohort 2: Parent/caregiver and/or the site staff applies the investigational products to the participant.[h]		X	→	X[i]	
Dispense Investigational Products (Cohort 2)		X	X		
Collect Returned Investigational Products (Cohort 2)			X	X	
Weigh Investigational Products		X	X	X	
Compliance confirmation		X	→	X[j]	

Visit Identifier[a]	Day -35 to Day -1 Screening	Day 1 Baseline	Day 8	Day 15 End of Treatment/ Early Discontinuation[b]	Day 43 Follow-up[c]
Visit Window			**±1 Day**	**±1 Day**	**+3 Days**
Assessments					
%BSA for eligibility	X	X			
ISGA for eligibility	X	X			
Lesion ISGA for each target lesion		X	X	X	
Lesion TSS for each target lesion		X	X	X	
Pruritus assessments for each target lesion[k] Cohort 1: Peak Pruritus NRS (age ≥12) Cohort 2: Itch Severity Scale (age 6-11) Cohort 2: Observer Reported Itch Severity NRS (age 2-11)		X	→	X	
Photographs[l]		X	X	X	
Review Prior/Concomitant treatment(s)	X[m]	→	→	→	X
Serious and nonserious adverse event monitoring	X	→	→	→	→

Abbreviations: → = ongoing/continuous event; AD = atopic dermatitis; BID = twice daily; %BSA = percent of body surface area; FSH = follicle stimulating hormone; ISGA = Investigator's Static Global Assessment; NRS = numerical rating scale; QD = once daily; TSS = Total Sign Score.

a. Day relative to start of study treatment (Day 1).
b. If a participant is discontinued, the efficacy evaluation at the timing of the early termination will be conducted as early as possible (the same day is preferable).
c. Follow-up contact will be completed during 28 to 35 days from administration of the final dose of investigational products to capture any potential adverse events and to confirm appropriate contraception usage and concomitant treatments. Visit is planned to occur as a telephone contact.
d. Temperature (tympanic or axillary), pulse rate, and blood pressure taken in the seated or supine position, after the participants have been sitting or lying calmly for a minimum of 5 minutes. Assessment of vital signs should precede blood draw for clinical laboratory tests.
e. Serum FSH concentration will be determined for all females who are amenorrheic only for confirmation postmenopausal status.
f. For females of childbearing potential only. Local urine testing will be standard for the protocol.
g. For females of childbearing potential only. Confirm that contraception is used consistently and correctly.
h. Cohort 1: From Day 1 to Day 15, participants will visit the site once or twice daily to apply investigational products by site staff. If it becomes difficult for the participant to visit the study site, the site staff will visit participant's home and investigational products will be applied by site staff as a backup option upon sponsor's agreement.
Cohort 2: From Day 1 to Day 15, investigational products will be applied once or twice daily by parent/caregiver and/or site staff. When investigational products are applied by parent/caregiver, site staff will check the compliance directly or via live video chat. When investigational products will be applied by site staff, site staff will visit the participant's home as needed.
i. Regimen 1 (QD): Participant will be applied investigational products from Day 1 to Day 14.
Regimen 2 (BID): When participant will be applied investigational products from AM in Day 1, the last administration will be PM in Day 14. When participant will be applied investigational products from PM in Day 1, the last administration will be AM in Day 15.
j. Compliance will be confirmed by parent/caregiver and/or the site staff confirmation.
k. Pruritus assessment will be completed by participants who are ≥6 years old and by observers [parents/caregivers] for the participants (age 2-11) when applicable, once daily from Day 1 to Day 15 before investigational products application preferably at the same time of each day if applicable.
l. Photographs of target lesions will be obtained. Photographs will be taken by local standard procedures.
m. Record all treatments (including medications and non-medication therapies) used for AD 90 days prior to screening and all other medications (including bland [non-medicated] emollients, over the counter drugs, vitamins, and antacids) used within 30 days prior to Screening.

Assessor's comment

Screening activities (day -35 to -1) included medical history, vital signs (temperature, blood pressure, pulse rate), physical examination, laboratory assessments (haematology, blood chemistry, urinalysis) and ISGA/ %BSA evaluation for eligibility. Apart from vital signs and laboratory parameters these parameters were measured throughout the study (at baseline and/or day 8 and/or day 15). A change

in laboratory values after only 14 days of exposure (one lesion only) seems to have been considered unlikely based on data from earlier studies and this might have been the reason for not performing additional measurements.

Statistical Methods

General methodology:

The primary analysis in each regimen for each cohort will be a superiority test to demonstrate crisaborole ointment 2% is more efficacious than vehicle in the target lesion in participants with mild to moderate AD as measured by change from baseline in TSS between crisaborole treated lesion and vehicle treated lesion. The null hypothesis in each regimen for each cohort is that there is no difference between crisaborole ointment 2% and vehicle, and the alternative hypothesis in each regimen for each cohort is that there is difference between crisaborole ointment 2% and vehicle as measured by change from baseline in TSS at Day 15. In each regimen for each cohort the difference between crisaborole and vehicle in TSS change from baseline at Day 15 is statistically significant if p-value<0.05 (two-sided).

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

The binary endpoints will be descriptively summarised using number, percentage and 95% confidence interval (CI) of percentage at each time point.

For the intra-participant comparison of crisaborole vs vehicle in each regimen at each time point, the binary endpoints will be compared using McNemar's test. For the inter-participant comparison of regimen 1 vs regimen 2 at each time point, the binary endpoints will be compared using Chi-squared test.

The continuous endpoints will be descriptively summarised using number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum.

For the intra-participant comparison of crisaborole vs vehicle in each regimen at each time point, a Mixed effect Models for Repeated Measures (MMRM) will be used to derive least- square mean of intra-participant difference and associated 2-sided 95% CI between crisaborole ointment 2% and corresponding vehicle. A MMRM will include the fixed effect of time point (visit or day) and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. If there is convergence issue for unstructured variance and covariance matrix, first order autoregressive (AR(1)) variance and covariance matrix will be used.

For the inter-participant comparison of regimen 1 vs regimen 2 at each time point, a MMRM will be used to derive difference in least-square means and associated 2-sided 95% CI between regimen 1 and regimen 2. A MMRM will include the fixed effects of dosing regimen, time point (visit or day), dosing regimen-by-time point (visit or day) interaction, and baseline value of the corresponding endpoint and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. If there is convergence issue for unstructured variance and covariance matrix, AR(1) variance and covariance matrix will be used.

Categorical endpoints will be descriptively summarised using number and percentage. Shift table from baseline to Day 8 and Day 15 will be provided.

Missing data will not be imputed for efficacy descriptive summary.

For the statistical comparison of continuous endpoints, a MMRM analysis will be conducted including only the observed data in the model under the assumption of the missing at random (MAR) for the missing mechanism.

Non-responder imputation (NRI) will be used for missing values of lesion ISGA response of clear or almost clear and at least a 2 grade improvement from baseline at Day 8 and Day 15.

In addition, missing values for safety endpoints will not be imputed.

Analysis sets:

Full Analysis Set (FAS): All participants randomised and who received ≥1 dose of the study drug.

Per-Protocol Analysis Set (PPAS): All participants randomised and who received ≥1 dose of the study drug, with both baseline and Day 15 primary efficacy data, and without protocol violations that were thought to impact the efficacy evaluation during the treatment period.

Safety Analysis Set: All participants who received ≥1 dose of the study drug.

Assessor's comment

Statistical methods are adequate. Although the overall alpha was not controlled at the (common) 5% level, this can be accepted in the context of a phase 2b study.

Results

Recruitment/ Number analysed

A total of 102 subjects were screened for eligibility, 21 subjects were screen failure and a total of 81 subjects were enrolled.

The *Full Analysis Set*, the *Per-Protocol Analysis Set* (any participant who received ≥1 dose of the study drug, with both baseline and Day 15 primary efficacy data, and without protocol violations that were thought to impact the efficacy evaluation during the treatment period) and the *Safety Analysis Set* (any participant who received ⩾1 dose of investigational product) were the same and had a total of 81 subjects.

Table 6. Subject Evaluation Groups

	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
	n (%)	n (%)	n (%)	n (%)
Screened: 102				
Screened Failure: 21				
Assigned to Treatment	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Treated	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Not Treated	0	0	0	0
Full Analysis Set	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Per Protocol Analysis Set	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Safety Analysis Set	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)

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Table 14.1.1.1 is for Pfizer internal use.

In Cohort 1 (N=41), 20 participants received crisaborole 2% QD + vehicle and 21 participants received crisaborole 2% BID + vehicle.

In Cohort 2 (N=40), 20 participants received crisaborol 2% QD + vehicle and 20 participants received crisaborole 2% BID + vehicle.

All patients enrolled (100.0%) completed both the Treatment Phase and the Follow-Up Phase.

A total of 3 investigational sites in Japan participated in this study.

Protocol deviations

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

All potentially important PDs that occurred during the study are summarised in the table below.

In Cohort 1, 3 participants (15.0%) in QD regimen and 8 participants (38.1%) in BID regimen reported at least 1 potentially important PD. In Cohort 2, 9 participants (45.0%) in QD regimen and 7 participants (35.0%) in BID regimen reported at least 1 potentially important PD.

The most frequently reported potentially important deviation was doses administered outside the allowed dosing window (ie, dosing hours), and that was reported for 3 participants (15.0%) in QD regimen and 7 participants (33.3%) in BID regimen in Cohort 1, and 4 participants (20.0%) in QD regimen and 5 participants (25.0%) in BID regimen in Cohort 2.

Table 5. Summary of Potentially Important Protocol Deviations

Category for Protocol Deviation Subcategory for Protocol Deviation	Cohort 1 Crisaborole 2% QD + Vehicle QD (N=20) n (%)	Cohort 1 Crisaborole 2% BID + Vehicle BID (N=21) n (%)	Cohort 2 Crisaborole 2% QD + Vehicle QD (N=20) n (%)	Cohort 2 Crisaborole 2% BID + Vehicle BID (N=20) n (%)
Number (%) of Subjects With Any Potentially Important Protocol Deviation	3 (15.0)	8 (38.1)	9 (45.0)	7 (35.0)
2: INVESTIGATIONAL PRODUCT	3 (15.0)	7 (33.3)	5 (25.0)	5 (25.0)
Doses administered outside the allowed dosing window (ie. dosing hours).	3 (15.0)	7 (33.3)	4 (20.0)	5 (25.0)
IPs were not prescribed at Day 8 and use the IPs prescribed at Day 1 throughout the study	0	0	1 (5.0)	0
3: CCMEDS	0	1 (4.8)	0	0
Subject used prohibited medications or treatments during the study	0	1 (4.8)	0	0
4: LAB	0	0	2 (10.0)	2 (10.0)
Lab samples not collected according to the schedule of activities.	0	0	2 (10.0)	2 (10.0)
5: VISIT SCHEDULE	0	0	2 (10.0)	1 (5.0)
Visits are performed out of protocol specific window	0	0	2 (10.0)	1 (5.0)
6: PROCEDURES/TESTS	0	3 (14.3)	0	0
Pruritus assessments not performed according to protocol	0	3 (14.3)	0	0

Subjects are only counted once per treatment per deviation.
PFIZER CONFIDENTIAL SDTM Creation: 29JAN2020 (20:27) Source Data: DV Output File: ./csr6/C3291028/addv s001 Date of Generation: 29JAN2020 (20:46)
Table 14.1.5 is for Pfizer internal use.

Assessor's comment

All three analysis sets (Full, Per-Protocol, Safety) were the same and consisted of 81 subjects as all patients enrolled (100.0%) completed both the Treatment Phase and the Follow-Up Phase. An equal number of patients received crisaborole + vehicle in cohort 1 (QD: n=20, BID: n=21) and cohort 2 (QD: n=20, BID: n=20). A total of 3 investigational sites in Japan participated in this study. Most frequent protocol deviations were "IP administered outside the dosing hours", which according to the MAH did not compromise GCP and are unlikely to have substantially affected study outcomes.

Baseline data

In Cohort 1, 11 (55.0%) male and 9 (45.0%) female participants were enrolled in QD regimen, and 17 (81.0%) male and 4 (19.0%) female participants were enrolled in BID regimen. The mean age (standard deviation [SD]) of participants in QD regimen and BID regimen was 33.3 (10.36) years and 33.9 (10.96) years, respectively.

In Cohort 2, 8 (40.0%) male and 12 (60.0%) female participants were enrolled in QD regimen, and 11 (55.0%) male and 9 (45.0%) female participants were enrolled in BID regimen. The mean age (SD) of participants in QD regimen and BID regimen was 7.7 (2.52) years and 7.8 (2.69) years, respectively.

All patients participating in this study were Asian.

Demographic, disease and lesion baseline characteristics are summarised below:

Table 7. Demographic and Disease Baseline Characteristics - Full Analysis Set

	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Age (years)				
2 - 6	0	0	6 (30.0)	6 (30.0)
7 - 11	0	0	14 (70.0)	14 (70.0)
12 - 17	0	0	0	0
18 - 64	20 (100.0)	21 (100.0)	0	0
>=65	0	0	0	0
n	20	21	20	20
Mean (SD)	33.3 (10.36)	33.9 (10.96)	7.7 (2.52)	7.8 (2.69)
Median	33.5	33.0	7.5	8.5
Range (min, max)	(18, 52)	(21, 55)	(3, 11)	(2, 11)
Gender				
Male	11 (55.0)	17 (81.0)	8 (40.0)	11 (55.0)
Female	9 (45.0)	4 (19.0)	12 (60.0)	9 (45.0)
Race				
Asian	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Ethnicity				
Not Hispanic or Latino	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Treatable Percent BSA (Global) (%)				
n	20	21	20	20
Mean (SD)	18.54 (7.368)	18.33 (7.217)	4.80 (2.263)	9.19 (7.610)
Median	21.25	18.00	4.40	6.90
Range (min, max)	(3.3, 30.0)	(6.5, 30.0)	(1.7, 10.5)	(2.9, 29.3)
Investigator's Static Global Assessment (ISGA) (Global)				
0: Clear	0	0	0	0
1: Almost Clear	0	0	0	0
2: Mild	12 (60.0)	7 (33.3)	16 (80.0)	5 (25.0)
3: Moderate	8 (40.0)	14 (66.7)	4 (20.0)	15 (75.0)
4: Severe	0	0	0	0
n	20	21	20	20
Mean (SD)	2.4 (0.50)	2.7 (0.48)	2.2 (0.41)	2.8 (0.44)
Median	2.0	3.0	2.0	3.0
Range (min, max)	(2, 3)	(2, 3)	(2, 3)	(2, 3)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment and regimen group.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:14) Source Data: adsl Output File: ./csr6/C3291028/adsl_s001 Date of Generation: 21JAN2020 (13:24)
Table 14.1.2.1.1 is for Pfizer internal use.

Table 8. Lesion Baseline Characteristics - Full Analysis Set

	Cohort 1				Cohort 2			
	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=21)		Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=20)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=21)	Vehicle BID (N=21)	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=20)	Vehicle BID (N=20)
Investigator's Static Global Assessment (ISGA)								
0: Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1: Almost Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2: Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3: Moderate	20 (100.0)	20 (100.0)	21 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)	20 (100.0)
4: Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n	20	20	21	21	20	20	20	20
Mean (SD)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)	3.0 (0.00)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Range (min, max)	(3, 3)	(3, 3)	(3, 3)	(3, 3)	(3, 3)	(3, 3)	(3, 3)	(3, 3)
Total Sign Score (TSS)								
n	20	20	21	21	20	20	20	20
Mean (SD)	7.7 (1.59)	7.5 (2.01)	7.1 (2.13)	7.4 (2.18)	6.2 (1.70)	6.5 (1.67)	7.1 (2.00)	7.3 (1.97)
Median	8.0	7.5	6.0	7.0	6.0	6.0	8.0	7.5
Range (min, max)	(4, 11)	(4, 12)	(3, 11)	(4, 11)	(4, 9)	(4, 9)	(4, 10)	(3, 10)
Peak Pruritus Numerical Rating Scale (NRS)								
n	20	20	21	21	-	-	-	-
Mean (SD)	5.3 (2.65)	5.3 (2.53)	5.1 (2.14)	5.3 (1.95)	-	-	-	-
Median	6.0	5.5	5.0	5.0	-	-	-	-
Range (min, max)	(1, 9)	(2, 9)	(1, 9)	(2, 9)	-	-	-	-
Itch Severity Scale								
n	-	-	-	-	16	16	14	14
Mean (SD)	-	-	-	-	1.6 (1.31)	1.8 (1.29)	1.9 (1.23)	1.6 (1.28)
Median	-	-	-	-	1.0	2.0	2.0	1.5
Range (min, max)	-	-	-	-	(0, 4)	(0, 4)	(0, 3)	(0, 4)
Caregiver Reported Itch Severity Numerical Rating Scale (NRS)								
n	-	-	-	-	20	20	20	20
Mean (SD)	-	-	-	-	4.7 (2.52)	5.0 (2.24)	5.5 (2.52)	5.1 (2.49)
Median	-	-	-	-	4.5	5.0	5.5	5.0
Range (min, max)	-	-	-	-	(1, 10)	(1, 9)	(1, 9)	(0, 9)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
- = Not applicable.
PFIZER CONFIDENTIAL SDTM Creation: 21JAN2020 (17:04) Source Data: adsl Output File: ./csr6/C3291028/adsl_s901 Date of Generation: 21JAN2020 (17:04)
Table 14.1.2.1.2 is for Pfizer internal use.

Assessor´s comment:

The study included a total of 81 patients (41 in cohort 1 and 40 in cohort 2). All patients were Asian. For unknown reasons no paediatric patients were enrolled into cohort 1 (all patients were ≥ 18 years of age), although patients > 12 years were targeted according to the inclusion/exclusion criteria. Thus, the focus with regard to this P46 procedure are based on cohort 2. While data from Japanese patients > 12 to < 18 years of age would have been of interest, prior experience with crisaborole ointment 2% (e.g. main EU registrational studies) does not suggest that efficacy/safety in this age group would substantially differ from adults.

In cohort 2, the mean (SD) Global Treatable Percent BSA at Baseline in the QD regimen was 4.80 (2.26) as opposed to 9.19 (7.61) in the BID regimen. (Cohort 1 mean of approx. 18.5 in both QD and BID). Likewise, based on global ISGA, 16/20 (80%) patients in the QD regimen had mild AD and 4/20 (20%) had moderate AD. In contrast, 5/20 (25%) patients in the BID regimen had mild AD and 15/20 (75%) had moderate AD (comparable, yet less pronounced imbalance in cohort 1). This suggests comparably higher global AD disease activity at baseline in patients in the BID regimen. However,

characteristics of lesions treated (lesion ISGA, lesion itch severity) were similar between QD and BID regimens and the randomisation procedure seems adequate. Thus, it is unlikely that study outcomes have been affected by baseline differences in treatable BSA in different regimens.

Efficacy results

Primary endpoint results:

Change From Baseline in TSS in Target Lesions at Day 15 for Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle

Cohort 1 (Age ≥12 Years):

For the QD regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% QD treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle QD treated lesions (Table 9 and Figure 1). The least square means (LSM) of intra-participant difference of TSS change from baseline was -1.6 with a p-value of 0.0071 (Table 9).

In the BID regimen, the primary efficacy endpoint was also achieved. The crisaborole ointment 2% BID treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle BID treated lesions (Table 9 and Figure 2). The LSM of intra-participant difference of TSS change from baseline was -2.0 with a p-value of 0.0029 (Table 9).

Table 9. Change From Baseline in Total Sign Score (TSS) on Day 15 for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set

Summary Statistics at Day 15	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=21)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=21)	Vehicle BID (N=21)
Change from baseline				
n	20	20	21	21
Mean (standard error)	-4.5 (0.60)	-2.9 (0.51)	-4.8 (0.53)	-2.7 (0.47)
Median (range)	-4.5 (-10, -1)	-3.5 (-7, 1)	-5.0 (-11, -1)	-3.0 (-7, 1)
Least squares mean of intra-participant difference of change from baseline (Crisaborole 2% - Vehicle)	-1.6	-	-2.0	-
95% Confidence interval	(-2.7, -0.5)	-	(-3.3, -0.8)	-
p-Value	0.0071	-	0.0029	-

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effect of visit, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
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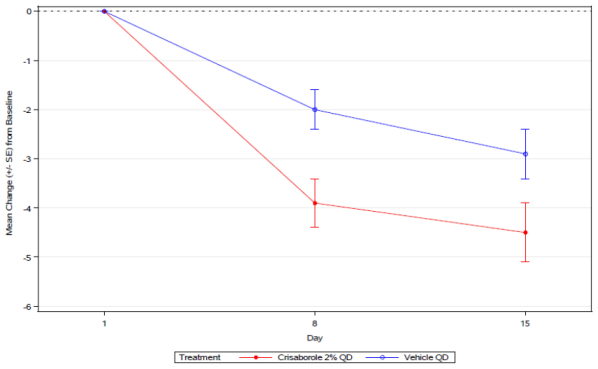
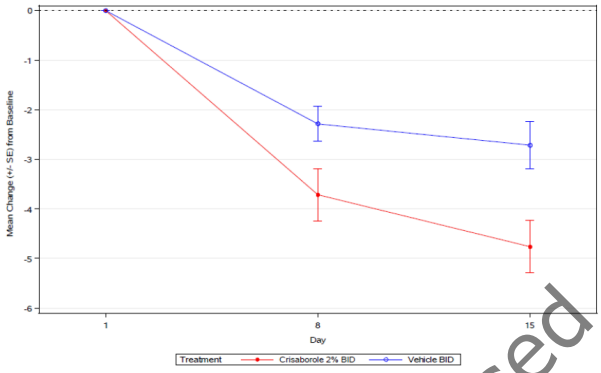
File: ./csr6/C3291028/adface_s910_1 Date of Generation: 29JAN2020 (14:04)
Table 14.2.2.1.1 is for Pfizer internal use.

Figure 1. Line Plots of Mean Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set, QD Regimen



Source: Figure 14.2.2.9
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Figure 2. Line Plots of Mean Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set, BID Regimen



Source: Figure 14.2.2.9
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Cohort 2, (Age 2-11 Years):

For the QD regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% QD treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle QD treated lesions (Table 10 and Figure 3). The LSM of intra-participant difference of TSS change from baseline was -1.5 with a p-value of 0.0250 (Table 10).

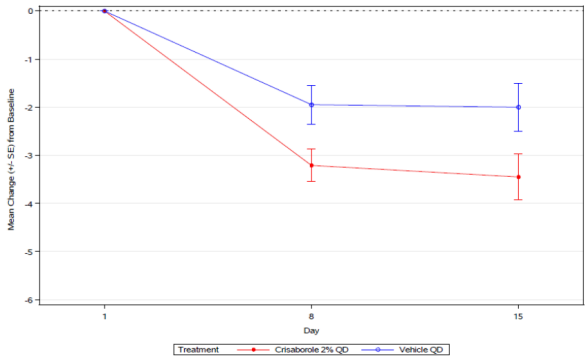
For the BID regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% BID treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle BID treated lesions (Table 10 and Figure 4). The LSM of intra-participant difference of TSS change from baseline was -2.1 with a p-value of 0.0014 (Table 10).

Table 10. Change From Baseline in Total Sign Score (TSS) on Day 15 for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 2 - Full Analysis Set

Summary Statistics at Day 15	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=20)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=20)	Vehicle BID (N=20)
Change from baseline				
n	20	20	20	20
Mean (standard error)	-3.5 (0.47)	-2.0 (0.50)	-4.7 (0.50)	-2.6 (0.54)
Median (range)	-4.0 (-8, 0)	-1.5 (-7, 1)	-5.0 (-8, 1)	-3.0 (-6, 2)
Least squares mean of intra-participant difference of change from baseline (Crisaborole 2% - Vehicle)	-1.5	-	-2.1	-
95% Confidence interval	(-2.7, -0.2)	-	(-3.3, -0.9)	-
p-Value	0.0250	-	0.0014	-

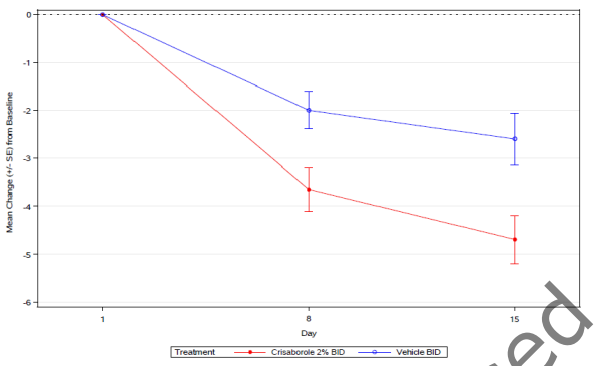
Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effect of visit, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:15) Source Data: adceso Output
File: ./csr6/C3291028/adface s910 2 Date of Generation: 29JAN2020 (14:12)
Table 14.2.2.1.2 is for Pfizer internal use.

Figure 3. Line Plots of Mean Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 2 - Full Analysis Set, QD Regimen



Source: Figure 14.2.2.9
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Figure 4. Line Plots of Mean Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 2 - Full Analysis Set, BID Regimen



Source: Figure 14.2.2.9
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Assessor´s comment:

Both QD and BID regimens were superior to vehicle in treatment of single AD target lesions over a course of 15 days in either age cohort. The effect size seems comparable across cohorts and regimen groups.

Described results are mainly relevant for the description of the study population, but these results need to be interpreted with caution in terms of the risk for false positive conclusions and generalisation to a broader population.

Secondary endpoint results:

Change From Baseline in TSS in Target Lesions at Day 15 for Inter-Participant Versus Crisaborole Ointment 2% QD

<u>Cohort 1 (Age ≥12 Years):</u>

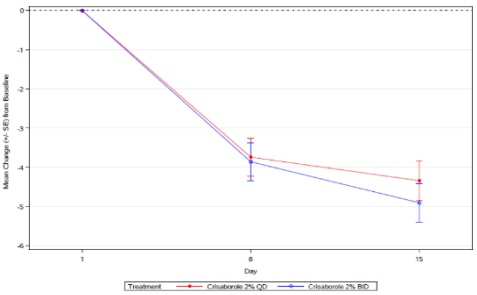
For the comparison of the BID and QD regimens, the reduction in TSS at Day 15 in the crisaborole ointment 2% BID treated lesions was larger than the reduction observed in crisaborole ointment 2% QD treated lesions. Inter-participant LSM difference of TSS change from baseline was -0.6 (Table 11 and Figure 5).

Table 11. Change From Baseline in Total Sign Score (TSS) on Day 15 for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 1 - Full Analysis Set

Summary Statistics at Day 15	Crisaborole 2% QD (N=20)	Crisaborole 2% BID (N=21)
Least squares mean of change from baseline	-4.3	-4.9
95% Confidence interval	(-5.4, -3.3)	(-5.9, -3.9)
Difference of least squares mean of change from baseline (Crisaborole 2% BID - Crisaborole 2% QD)	-	-0.6
95% Confidence interval	-	(-2.0, 0.9)

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:15) Source Data: adceso Output
File: ./csr6/C3291028/adface s911 1 Date of Generation: 29JAN2020 (15:08)
Table 14.2.2.1.3 is for Pfizer internal use.

Figure 5. Line Plots of Least Squares Mean of Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 1 - Full Analysis Set



Source: Figure 14.2.3.1.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Cohort 2 (Age 2-11 Years):

For the comparison of the BID and QD regimens, the reduction in TSS at Day 15 in the crisaborole ointment 2% BID treated lesions was larger than the reduction observed in the crisaborole ointment 2% QD treated lesions. Inter-participant LSM difference of TSS change from baseline was -0.8 (Table 12 and Figure 6).

Table 12. Change From Baseline in Total Sign Score (TSS) on Day 15 for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 2 - Full Analysis Set

Summary Statistics at Day 15	Crisaborole 2% QD (N=20)	Crisaborole 2% BID (N=20)
Least squares mean of change from baseline	-3.7	-4.5
95% Confidence interval	(-4.5, -2.8)	(-5.4, -3.6)
Difference of least squares mean of change from baseline (Crisaborole 2% BID - Crisaborole 2% QD)	-	-0.8
95% Confidence interval	-	(-2.1, 0.4)

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:15) Source Data: adceso Output
File: ./csr6/C3291028/adface s911 2 Date of Generation: 29JAN2020 (15:09)
Table 14.2.2.1.4 is for Pfizer internal use.

Figure 6. Line Plots of Least Squares Mean of Change (±Standard Error) From Baseline to Day 8 and Day 15 in Total Sign Score for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 2 - Full Analysis Set

Source: Figure 14.2.3.1.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Assessor´s comment:

A tendency towards stronger lesion TSS reduction was seen in the BID compared to QD regimens at day 15 in both cohorts.

Change From Baseline in TSS in Target Lesions at Day 8:

Cohort 1 (Age ≥12 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 8, in QD regimen, the LSM of intra-participant difference of TSS change from baseline was -1.9 with a p-value of 0.0029, where as in BID regimen, the LSM of intra-participant difference of TSS change from baseline was -1.4 with a p-value of 0.0282.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

At Day 8, inter-participant LSM difference of TSS change from baseline of crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

Cohort 2 (Age 2-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 8, in QD regimen, the LSM of intra-participant difference of TSS change from baseline was -1.2 with a p-value of 0.0237, where as in BID regimen, the LSM of intra-participant difference of TSS change from baseline was -1.7 with a p-value of 0.0077.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

At Day 8, inter-participant LSM difference of TSS change from baseline of crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

Assessor´s comment:

Results comparable to day 15 were obtained for TSS assessments at day 8 for intra- and inter-patient comparisons in both cohorts (i.e. reduction in TSS in crisaborole vs. vehicle in either regimen, but no marked difference between regimens), indicating an early onset of effect with either regimen in all age groups.

Change From Baseline in ISGA in Target Lesions:

Cohort 1 (Age ≥12 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.9 with a p-value of 0.0005, and in BID regimen, the LSM of intra-participant difference of change from baseline was -0.7 with a p-value of 0.0098 (Table 13).

At Day 8, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.5 with a p-value of 0.0084 and in BID regimen, the LSM of intra-participant difference of change from baseline was -0.4 with a p-value of 0.0584.

Table 13. Change From Baseline in Investigator's Static Global Assessment (ISGA) on Day 15 for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set

Summary Statistics at Day 15	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=21)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=21)	Vehicle BID (N=21)
Change from baseline				
n	20	20	21	21
Mean (standard error)	-1.9 (0.19)	-1.0 (0.15)	-1.9 (0.19)	-1.1 (0.19)
Median (range)	-2.0 (-3, 0)	-1.0 (-2, 0)	-2.0 (-3, 0)	-1.0 (-3, 0)
Least squares mean of intra-participant difference of change from baseline (Crisaborole 2% - Vehicle)	-0.9	-	-0.7	-
95% Confidence interval	(-1.4, -0.4)	-	(-1.2, -0.2)	-
p-Value	0.0005	-	0.0098	-

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effect of visit, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:15) Source Data: adqsad Output
File: ./csr6/C3291028/adqsad s910 1 Date of Generation: 29JAN2020 (14:13)
Table 14.2.3.2.1.1 is for Pfizer internal use.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

At Day 15, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.0 (Table 14).

At Day 8, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.1.

Table 14. Change From Baseline in Investigator's Static Global Assessment (ISGA) on Day 15 for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 1 - Full Analysis Set

Summary Statistics at Day 15	Crisaborole 2% QD (N=20)	Crisaborole 2% BID (N=21)
Least squares mean of change from baseline	-1.9	-1.9
95% Confidence interval	(-2.3, -1.5)	(-2.2, -1.5)
Difference of least squares mean of change from baseline (Crisaborole 2% BID - Crisaborole 2% QD)	-	0.0
95% Confidence interval	-	(-0.5, 0.6)

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (15:15) Source Data: adqsad Output
File: ./csr6/C3291028/adqsad_s911_1 Date of Generation: 29JAN2020 (17:33)
Table 14.2.3.2.1.3 is for Pfizer internal use.

Cohort 2 (Age 2-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.7 with a p-value of 0.0093. In BID regimen, the LSM of intra-participant difference of change from baseline was -1.0 with a p-value of 0.0001.

At Day 8, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.3 with a p-value of 0.1435. In BID regimen, the LSM of intra-participant difference of change from baseline was -0.4 with a p-value of 0.0569.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

At Day 15, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

At Day 8, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.2.

Assessor´s comment:

LSM (least square mean) reductions in ISGA in lesions treated with crisaborole ointment 2% compared to vehicle (intra-patient) were observed in both cohorts for both regimes at day 15 (cohort 1: -0.9 in QD and -0.7 in BID; cohort 2: -0.7 in QD and -1.0 in BID). Also, no inter-patient differences between the treatment regimens were seen. Thus no regimen was superior to the other. This is underlined by the findings that ISGA Response of Clear or Almost Clear and at least a 2 Grade Improvement from Baseline in Target Lesions at Day 15 was seen in ≥ 66.7% of patients in either cohort receiving crisaborole ointment 2% irrespective of dose regimen, compared to approx. 20.0-30.0% of patients receiving vehicle (see "exploratory endpoint results" below).

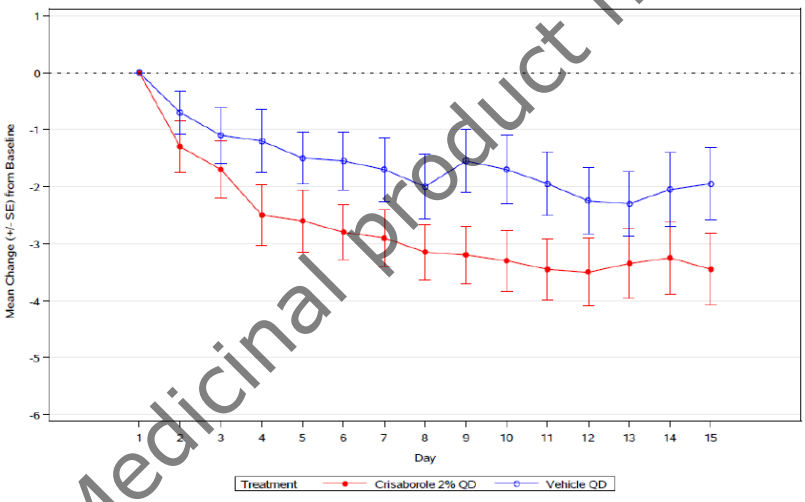
Peak Pruitus NRS (only Cohort 1, Age ≥ 12 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

In QD regimen (Figure 7), a greater improvement in pruritus NRS was observed for the crisaborole treated versus the vehicle treated lesions 1 day after the first application (-1.3 versus -0.7), and the improvement was maintained through Day 15 (-3.5 versus -2.0). Crisaborole ointment 2% was superior to vehicle at each time point up to Day 15 with p-values <0.05, except at Day 3.

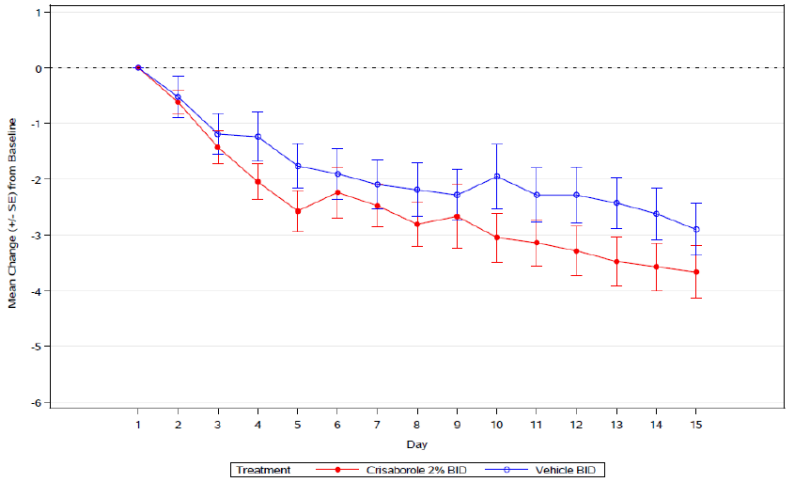
In BID regimen (Figure 8), a slightly greater improvement in pruritus NRS was observed for the crisaborole treated versus the vehicle treated lesions 1 day after the first application (-0.6 versus -0.5), and the improvement was maintained through Day 15 (-3.7 versus -2.9). Crisaborole ointment 2% was superior to vehicle at several time points but not at all days, with p-values <0.05 up to Day 15.

Figure 7. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Peak Pruritus NRS (Age ≥12 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set, QD Regimen



Source: Figure 14.2.3.3.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Figure 8. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Peak Pruritus NRS (Age ≥12 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set, BID Regimen

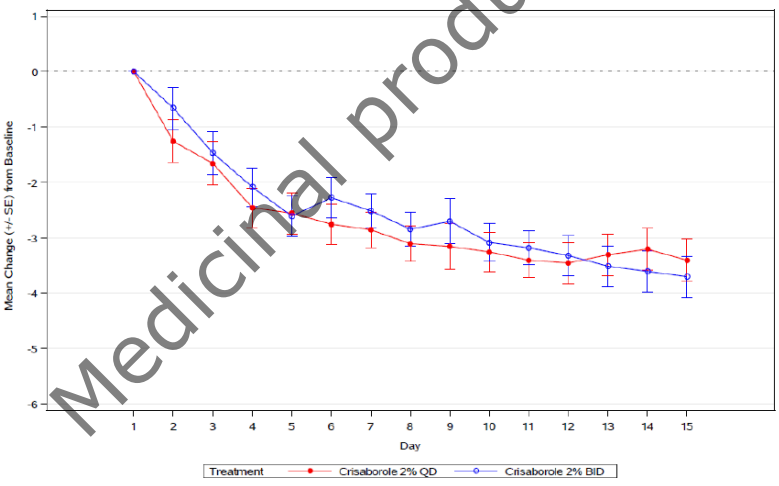


Source: Figure 14.2.3.3.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

The LSM was generally greater in crisaborole ointment 2% QD than crisaborole ointment 2% BID from Day 2 to Day 12, but after Day 13, the LSM in crisaborole ointment 2% BID was greater than crisaborole ointment 2% QD (Figure 9).

Figure 9. Line Plot of Least Square Mean of Change (±Standard Error) From Baseline up to Day 15 in Peak Pruritus NRS (Age ≥12 Years) for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD in Cohort 1 - Full Analysis Set



Source: Figure 14.2.3.3.6
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

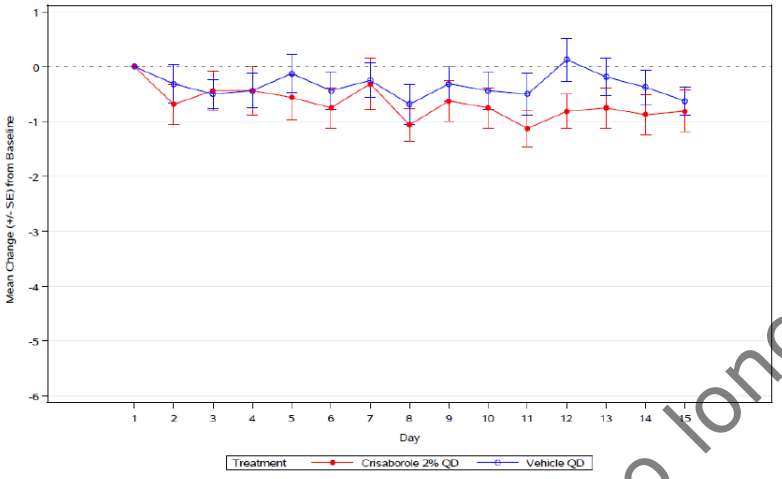
Itch Severity Scale (only Cohort 2, Age 6-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

In QD regimen (Figure 10), the improvement in itch severity scale was observed more in the crisaborole treated lesions than the vehicle treated lesions 1 day after the first application (-0.7 versus -0.3), and was -0.8 versus -0.6 at Day 15.

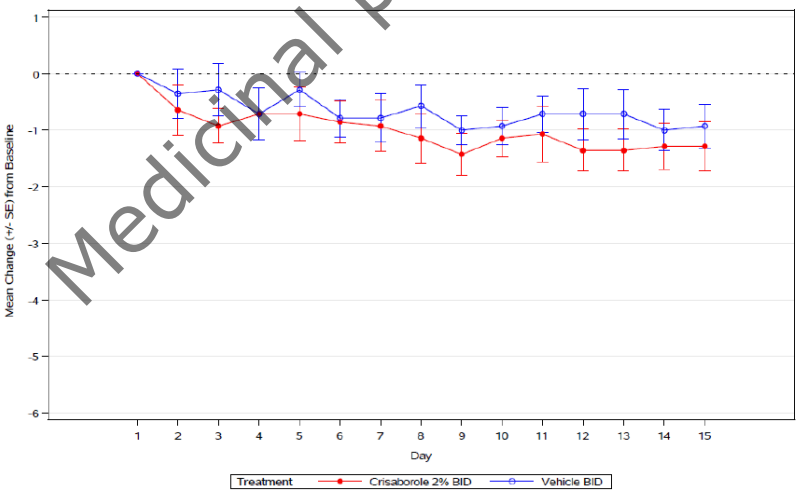
In BID regimen (Figure 11), the improvement in itch severity scale was observed more in the crisaborole treated lesions than the vehicle treated lesions 1 day after the first application (-0.6 versus -0.4), and was -1.3 versus -0.9 at Day 15.

Figure 10. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Itch Severity Scale (Age 6-11 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle for Cohort 2, QD Regimen - Full Analysis Set



Source: Figure 14.2.3.4.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Figure 11. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Itch Severity Scale (Age 6-11 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle for Cohort 2, BID Regimen - Full Analysis Set

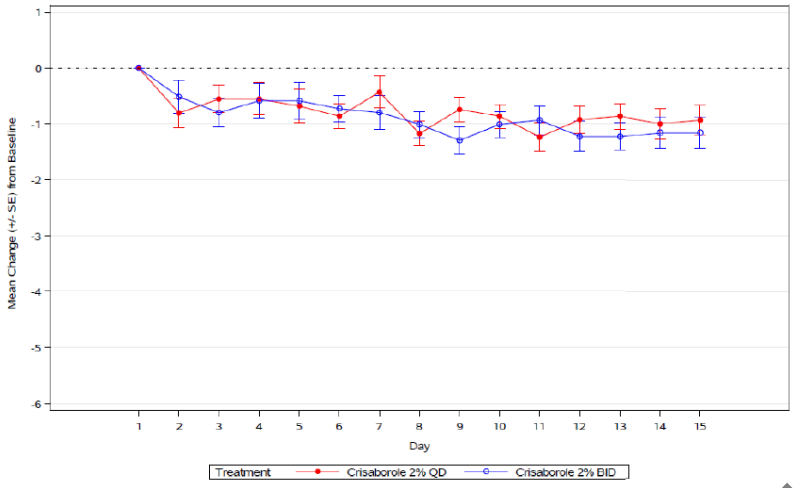


Source: Figure 14.2.3.4.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

The LSM of change from baseline of crisaborole ointment 2% BID versus crisaborole ointment 2% QD was generally similar from Day 2 to Day 15 (Figure 12).

Figure 12. Line Plot of Least Squares Mean of Change (±Standard Error) From Baseline up to Day 15 in Itch Severity Scale (Age 6-11 Years) for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD for Cohort 2 - Full Analysis Set



Source: Figure 14.2.3.4.6
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Caregiver Reported Itch Severity Numerical Rating Scale (only Cohort 2, Age 2-11 Years):

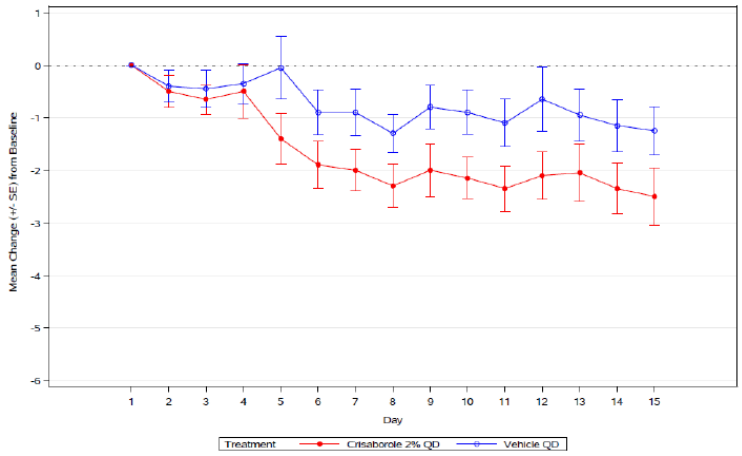
Intra Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

A larger reduction was observed in crisaborole compared to the vehicle in both regimens.

In QD regimen (Figure 13), improvement in itch severity scale observed for the crisaborole treated was more versus the vehicle treated lesions 1 day after the first application (-0.5 versus -0.4), and the improvement was maintained through Day 15 (-2.5 versus -1.3).

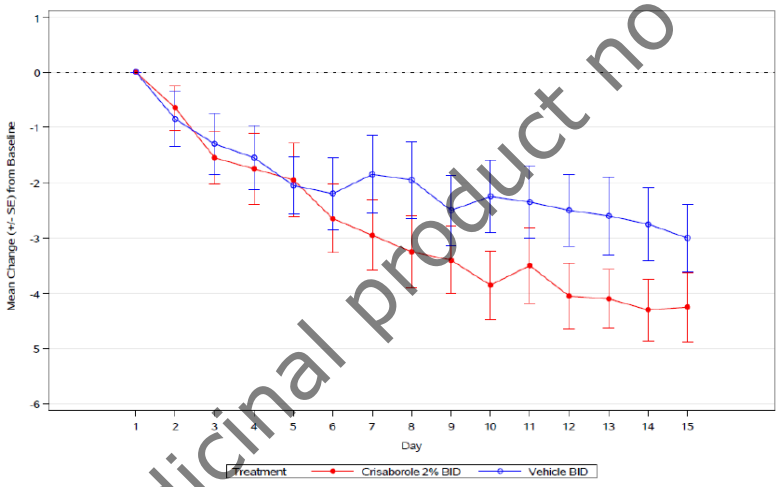
In BID regimen (Figure 14), improvement in itch severity scale observed for the crisaborole treated was less versus the vehicle treated lesions 1 day after the first application (-0.7 versus -0.9), but the improvement was more in crisaborole treated versus the vehicle treated lesions at Day 15 (-4.3 versus -3.0).

Figure 13. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Caregiver Reported Itch Severity NRS (Age 2-11 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle for Cohort 2, QD Regimen - Full Analysis Set



Source: Figure 14.2.3.5.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Figure 14. Line Plots of Mean Change (±Standard Error) From Baseline up to Day 15 in Caregiver Reported Itch Severity NRS (Age 2-11 Years) for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle for Cohort 2, BID Regimen - Full Analysis Set

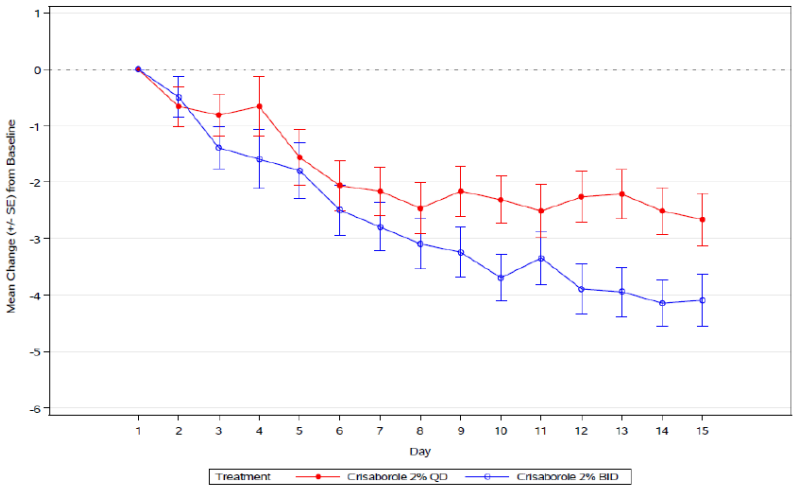


Source: Figure 14.2.3.5.4
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

The LSM of change from baseline of crisaborole ointment 2% BID was generally more when compared to the crisaborole ointment 2% QD from Day 2 to Day 15.

Figure 15. Line Plots of Least Squares Mean of Change (±Standard Error) From Baseline up to Day 15 in Caregiver Reported Itch Severity NRS (Age 2-11 Years) for Inter-Participant Comparison of Crisaborole 2% BID Versus Crisaborole 2% QD - Cohort 2, Full Analysis Set



Source: Figure 14.2.3.5.6
Refer to Section 4 for the list of abbreviations.
Baseline was defined as the last observation up to and including first dosing date.
Bars denote standard error.
The full analysis set included all participants who were randomized and received at least 1 dose of investigational product.

Assessor´s comment:

Results for pruritus assessments indicate no clear favourable effect of IP vs. vehicle in either cohort and also no impact of regimen. It seems challenging to evaluate pruritus based on one distinct lesion only on a patient with a larger BSA affected.

Exploratory endpoint results:

ISGA Response of Clear or Almost Clear and at least a 2 Grade Improvement from Baseline in Target Lesions up to Day 15:

Cohort 1 (Age ≥12 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, 14 participants (70.0%) treated with crisaborole ointment 2% and 4 participants (20.0%) treated with vehicle showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

At Day 15, in BID regimen, 14 participants (66.7%) treated with crisaborole ointment 2% and 5 participants (23.8%) treated with vehicle showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

For Cohort 1, 14 participants (66.7%) in crisaborole ointment 2% BID regimen versus 14 participants (70.0%) in crisaborole ointment 2% QD regimen showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

Cohort 2 (Age 2-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, 12 participants (60.0%) treated with crisaborole ointment 2% and 6 participants (30.0%) treated with vehicle showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

At Day 15, in BID regimen, 14 participants (70.0%) treated with crisaborole ointment 2% and 5 participants (25.0%) treated with vehicle showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus QD:

For Cohort 2, 14 participants (70.0%) in crisaborole ointment 2% BID regimen versus 12 participants (60.0%) in crisaborole ointment 2% QD regimen showed a response of clear or almost clear and at least a 2-grade improvement from baseline to Day 15.

Assessor´s comment:

Overall, efficacy results support a favourable effect of Crisaborole compared to vehicle in a single target lesion in Japanese adults and paediatric patients over a 15-day treatment course. No regimen (BID or QD) was superior to the other.

Safety results

All safety endpoints were considered secondary endpoints in this study.

Compliance

Cohort 1 (Age ≥12 Years):

In QD regimen, all 20 participants received the study treatment. The median duration of crisaborole/vehicle treatment was 14.0 days, with a range of 14 to 15 days. The median (range) number of crisaborole/vehicle applications was 14.0 (14 to 15).

In BID regimen, all 21 participants received the study treatment. The median duration of crisaborole/vehicle treatment was 14.0 days, with a range of 14 to 15 days. The median (range) number of crisaborole/vehicle applications was 28.0 (28 to 30).

All applications were conducted by study site staff at the study sites every day and all participants in both regimens were considered compliant for the treatment (100.0%).

Cohort 2 (Age 2-11 Years):

In QD regimen, all 20 participants received study treatment. The median duration of crisaborole/vehicle treatment was 14.0 days, with a range of 14 to 16 days. The median (range) number of crisaborole/vehicle applications was 14.0 (14 to 16).

In BID regimen, all 20 participants received study treatment. The median duration of crisaborole/vehicle treatment was 14.0 days, with a range of 14 to 17 days. The median (range) number of crisaborole/vehicle applications was 28.0 (28 to 34).

All applications were confirmed by site staff via live video chat for Cohort 2 except during the schedule visits. In QD regimen, all participants were compliant for treatment (100.0%). In BID

regimen, almost all participants were compliant for treatment (19 participants, 95.0%) and 1 participant was non-compliant for treatment because Day 15 visit was out of window and total number of applications were 34.

Assessor´s comment:

In cohort 1, 41/41 (100.0%) and in cohort 2, 39/40 (97.5%) completed both treatment and follow-up phase, indicating good compliance with treatment recommendations and also acceptable tolerability of the study drug.

Incidence of Adverse Events

The all-causality TEAEs reported in the study are presented by SOC and PT in Tables 19 & 20.

Table 19. Treatment-Emergent Adverse Events (All Causalities)

	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects evaluable for adverse events	20	21	20	20
Number of adverse events	9	12	2	3
Subjects with adverse events	6 (30.0)	6 (28.6)	2 (10.0)	2 (10.0)
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]	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	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 v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (22:37) Source Data: adae Output
File: ./csr6/C3291028/adae s010 2 Date of Generation: 30JAN2020 (15:05)
Table 14.3.1.2.1.2 is for Pfizer internal use.

Table 20. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)
With any adverse event	6 (30.0)	6 (28.6)	2 (10.0)	2 (10.0)
Gastrointestinal Disorders	1 (5.0)	0	0	0
Dental caries	1 (5.0)	0	0	0
General Disorders And Administration Site Conditions	5 (25.0)	5 (23.8)	0	1 (5.0)
Application site coldness	0	1 (4.8)	0	0
Application site irritation	3 (15.0)	4 (19.0)	0	0
Application site pain	1 (5.0)	1 (4.8)	0	1 (5.0)
Application site pruritus	3 (15.0)	2 (9.5)	0	1 (5.0)
Infections And Infestations	1 (5.0)	1 (4.8)	1 (5.0)	1 (5.0)
Application site folliculitis	1 (5.0)	1 (4.8)	0	0
Hand-foot-and-mouth disease	0	0	1 (5.0)	1 (5.0)
Musculoskeletal And Connective Tissue Disorders	0	0	1 (5.0)	0
Arthralgia	0	0	1 (5.0)	0
Respiratory, Thoracic And Mediastinal Disorders	0	3 (14.3)	0	0
Oropharyngeal pain	0	3 (14.3)	0	0

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 v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (22:37) Source Data: adae Output
File: ./csr6/C3291028/adae s0311 2 Date of Generation: 30JAN2020 (15:07)
Table 14.3.1.2.2.2 is for Pfizer internal use.

Cohort 1: All-Causality and Treatment-Related:

For the QD regimen, 6 participants (30.0%) experienced a total of 9 all-causality TEAEs of which 8 were considered as treatment-related. The most frequently reported all-causality TEAEs by PT were application site irritation and application site pruritus (3 participants each), all of which were considered to be treatment-related.

For the BID regimen, 6 participants (28.6%) experienced a total of 12 all-causality TEAEs of which 8 were considered as treatment-related. The most frequently reported all-causality TEAEs by PT were application site irritation (4 participants) and oropharyngeal pain (3 participants). All events of

application site irritation were considered to be treatment-related, and none of the events of oropharyngeal pain were considered to be treatment-related.

Cohort 2: All-Causality and Treatment-Related:

For the QD regimen, 2 participants (10.0%) experienced a total of 2 all-causality TEAEs, neither of which were considered as treatment-related. The reported all-causality TEAEs by PT were arthralgia and hand-foot-and-mouth disease (1 participant each).

For the BID regimen, 2 participants (10.0%) experienced a total of 3 all-causality TEAEs of which 2 were considered as treatment-related. The reported all-causality TEAEs by PT were application site pruritus, application site pain and hand-foot-and-mouth disease (1 participant each). Of these events, application site pruritus and application site pain were considered to be treatment-related.

Cohort 1: Adverse Events in the Target Lesions:

The all-causality TEAEs in cohort 1 in the target lesions are shown in Table 21. For the QD regimen, 5 participants (25.0%) experienced a total of 6 TEAEs in crisaborole ointment 2% treated lesion: Application site irritation and application site pruritus were each reported in 2 participants (10.0%), and application site pain and application site folliculitis were each reported in 1 participant (5.0%). In vehicle treated lesion 2 participants (10.0%) experienced a total of 3 TEAEs: Application site pruritus was reported in 2 participants (10.0%), and application site irritation was reported in 1 participant (5.0%). All of the TEAEs in both target lesions were considered treatment-related but were mild in severity.

For the BID regimen, 4 participants (19.0%) experienced a total of 7 TEAEs in crisaborole ointment 2% treated lesion: Application site irritation was reported in 4 participants (19.0%), and application site pain, application site pruritus, and application site folliculitis were reported in 1 participant (4.8%) each. In vehicle treated lesions 2 participants (9.5%) experienced a total of 3 TEAEs: application site coldness, application site irritation, and application site pruritus were reported in 1 participant (4.8%) each. All of the TEAEs in both target lesions, except for the application site folliculitis in the crisaborole treated lesions, were considered treatment-related but were mild in severity.

Table 21. Treatment-Emergent Adverse Events Which Occurred in the Target Lesions by System Organ Class and Preferred Term (All Causalities) Cohort 1

Number of Subjects Evaluable for AEs	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=21)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=21)	Vehicle BID (N=21)
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)
With any adverse event	5 (25.0)	2 (10.0)	4 (19.0)	2 (9.5)
General Disorders And Administration Site Conditions	4 (20.0)	2 (10.0)	4 (19.0)	2 (9.5)
Application site coldness	0	0	0	1 (4.8)
Application site irritation	2 (10.0)	1 (5.0)	4 (19.0)	1 (4.8)
Application site pain	1 (5.0)	0	1 (4.8)	0
Application site pruritus	2 (10.0)	2 (10.0)	1 (4.8)	1 (4.8)
Infections And Infestations	1 (5.0)	0	1 (4.8)	0
Application site folliculitis	1 (5.0)	0	1 (4.8)	0

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 v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (22:37) Source Data: adae Output
File: ./csr6/C3291028/adae_s0311_1 Date of Generation: 30JAN2020 (15:06)
Table 14.3.1.2.2.1 is for Pfizer internal use.

Cohort 2: Adverse Events in the Target Lesions:

The all-causality TEAEs in cohort 2 in the target lesions are shown in Table 22. For the QD regimen, no participant experienced TEAEs in the target lesions. In BID regimen, in the crisaborole treated lesions, 2 TEAEs of application site pain and application site pruritus were reported in 1 participant (5.0%) each. No participant experienced TEAEs in vehicle treated lesions. All of the TEAEs in the crisaborole treated lesions were considered treatment-related but were mild in severity.

Table 22. Treatment-Emergent Adverse Events Which Occurred in the Target Lesions by System Organ Class and Preferred Term (All Causalities) Cohort 2

Number of Subjects Evaluable for AEs	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=20)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=20)	Vehicle BID (N=20)
Number (%) of Subjects: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)
With any adverse event	0	0	1 (5.0)	0
General Disorders And Administration Site Conditions	0	0	1 (5.0)	0
Application site coldness	0	0	0	0
Application site irritation	0	0	0	0
Application site pain	0	0	1 (5.0)	0
Application site pruritus	0	0	1 (5.0)	0
Infections And Infestations	0	0	0	0
Application site folliculitis	0	0	0	0

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 v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 16JAN2020 (22:37) Source Data: adae Output File: ./csr6/C3291028/adae s0311 1 Date of Generation: 30JAN2020 (15:06)
Table 14.3.1.2.2.1 is for Pfizer internal use.

Analysis of Adverse Events

Only the TEAEs that occurred in the target lesion were considered treatment-related. The TEAEs in the target lesion, including application site coldness, application site irritation, application site pain, application site pruritus, and application site folliculitis, were all reported as mild in severity.

Permanent Discontinuations Due to Adverse Events

There were no cases of permanent discontinuations reported in the study.

Dose Reductions or Temporary Discontinuations Due to Adverse Events

There were no cases of dose reductions or temporary discontinuations due to AEs reported in the study.

Other Serious or Significant Adverse Events

There were no SAEs or significant AEs reported in the study.

Deaths

There were no cases of death reported in the study.

Clinical Laboratory Results

Data was collected only at screening for eligibility but not during the study.

Vital Signs, Electrocardiogram, Physical Findings, and Other Observations Related to Safety

Vital signs were assessed only at screening for eligibility, ECG measurements were not performed, Physical Examinations (pre-specified in the study protocol as “at a minimum assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems”) were performed at screening and at the end of treatment, yet no results could be found in the study report.

Assessor´s comment:

Cohort 1: For the QD regimen, 6 participants (30.0%) experienced a total of 9 all-causality TEAEs of which 8 were considered as treatment-related (most frequent: application site irritation and application site pruritus in 3 participants each). For the BID regimen, 6 participants (28.6%) experienced a total of 12 all-causality TEAEs of which 8 were considered as treatment-related (most frequent: application site irritation in 4 participants).

Cohort 2: A total of 5 mild, all-causality TEAEs were reported in 4/40 (10%) participants (QD: arthralgia and hand-foot-mouth disease- neither treatment related nor in target lesion; BID: application site pruritus (treatment-related in target lesion), application site pain (treatment-related in target lesion) and hand-foot-and-mouth disease).

Overall, fewer TEAEs were noted in cohort 2 compared to cohort 1 which is reassuring for the assessment of safety in children. However, it is not reported whether the target lesions in children were smaller compared to adults (as per the inclusion criteria it is possible that lesions of patients in cohort 2 smaller than 3x3 cm were treated, yet details on size of target lesions were not reported). This could explain fewer local side effects. No differences between the QD and the BID regimen were observed.

No serious or severe TEAEs, or deaths occurred in either cohort.

Clinical laboratory data was obtained only at screening, but not thereafter and no data on physical examination at the end of treatment could be found in the study report. While it cannot be excluded that sub-clinical changes were missed, this is considered very unlikely, as treatment was limited to single AD lesions and two weeks only. Thus the exposure was much below what had been recorded in prior studies investigating crisaborole safety in adults and children where no clinical laboratory anomalies of concern had been reported.

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

2.3.3. Discussion on clinical aspects

The MAH submitted the final clinical study report of the crisaborole ointment 2% Study C3291028 performed in Japanese patients ≥ 2 years of age with atopic dermatitis (AD). This Phase 2b,

randomised, double-blind, vehicle-controlled, intra-participant study was conducted at 3 investigational sites in Japan. This submission is done to meet the requirement of Art. 46 to submit paediatric data within 6 months from end of study. The study was not part of the key binding elements of the EMA PIP (EMEA-002065-PIP01) in Europe. No changes to the product information (SmPC or PIL) are proposed within this procedure based on results from study C3291028, which is deemed acceptable.

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

Study design and methods

In the study under revision (study C3291028) efficacy and safety of Crisaborole ointment 2% (EUCRISA) were investigated over a 15 day treatment period. The target population was Japanese paediatric and adult patients (≥ 2 years of age) with mild to moderate AD, which is in line with the currently approved indication in EU and US. Patients with BSA (body surface area) affected ≤ 30% at Baseline/Day 1 (excluding scalp, genitals and groin area) were included.

Inclusion/exclusion criteria were comparable with other studies submitted for the MAA of STAQUIS in Europe and cover the European target population to a large extent (STAQUIS approved in the EU for mild-moderate AD with BSA ≤40%), yet exclude the patient group with a larger body surface area affected (BSA > 30-40%). Still, this is a good prerequisite for comparison of data and study results are considered of interest for the European target population ≥ 2 years of age.

Crisaborole ointment 2% or vehicle was applied to predefined AD target lesions with ISGA = 3 (= moderate; two lesions per patient on opposite limbs, at least 3 cm x 3 cm lesion size). The drug was applied always by or under supervision of study personnel which minimises the risk of non-compliance. Per patient one lesion was treated with IP and one with vehicle, thus this study did not evaluate the effect of crisaborole ointment 2% on global AD. QD or BID applications were performed over a course of 15 days (Treatment Phase), patients were then followed-up for 28 to 31 days until study days 43 to 46 (End of Study).

Two AD cohorts were studied, cohort 1 targeted patients ≥12 years of age as per the inclusion criteria and cohort 2 targeted patients 2 to <12 years of age.

The primary study endpoint of success was change from baseline in TSS (total sign score) in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (Regimen 1: QD, Regimen 2: BID) for each cohort (intra-patient comparison). The lesion TSS assesses AD severity in 4 domains, erythema, induration/papulation, excoriation (evidence of scratching), and lichenification (epidermal thickening) by assigning 0-3 points for each domain. The maximum total score is 12 (= most severe AD manifestation). This score employs the same domains (and the same points per domain) as the more commonly used EASI score and appears overall reasonable and an established tool for the purpose of evaluating the treatment effect on single lesions per patient. Comparison to external data (e.g. registrational phase 3 studies) needs to be done under the prerequisite that the endpoints are different (single lesions vs. global disease). 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 and this allows for good contextualisation of the data. It needs to be noted, that in the study now under assessment ISGA response was measured at day 15 (compared to day 29 in phase III) and on the single lesion level (compared to global in phase III).

Secondary endpoints included efficacy evaluations based on TSS (inter-patient) and pruritus assessments in target lesions up to day 15 as well as safety evaluations (adverse event incidence).

Overall, the choice of endpoints is considered adequate as relevant disease parameters are covered. Notably, as single lesions per patient are evaluated, this strategy does not allow to conclude on global impact of crisaborole ointment 2% in treatment of mild to moderate AD in the target population. As AD is a chronic condition and patients are likely treated for longer periods of time/more than one 2-week course in clinical practice, the study is furthermore not appropriate to assess long-term efficacy or delayed safety events or effects associated with chronic use. However, this was not the objective of this trial.

Results

Randomisation and blinding procedures appear adequate. Statistical methods are considered appropriate for the given purpose. Although the overall alpha was not controlled at the (common) 5% level, this approach is not unusual in the context of such phase 2b studies. Missing values were not imputed for efficacy and safety endpoints, however, there were hardly any drop-outs, missing data problems or loss to follow-up, therefore no relevant impact on observed results is expected. Still, the results have to be interpreted keeping in mind the descriptive nature of the trial.

The study included a total of 81 patients (41 in cohort 1 and 40 in cohort 2). All patients were Asian. No paediatric patients were enrolled into cohort 1 (all patients were $\geqslant$ 18 years of age), although patients > 12 years were targeted according to the inclusion/exclusion criteria. Thus, the focus with regard to this P46 procedure is on cohort 2. While data from Japanese patients > 12 to < 18 years of age would have been of interest, prior experience with crisaborole ointment 2% (e.g. main EU registrational studies) does not suggest that efficacy/safety in this age group would substantially differ from adults.

In cohort 2, 8 (40.0%) male and 12 (60.0%) female participants were enrolled in QD regimen, and 11 (55.0%) male and 9 (45.0%) female participants were enrolled in BID regimen, which seems sufficiently balanced. The mean age (SD) of participants in QD regimen and BID regimen was 7.7 (2.52) years and 7.8 (2.69) years, respectively. Six patients ≤ 4 years of age were enrolled (3 in each regimen), the youngest patient was 2 years old. In cohort 2 the mean (SD) Global Treatable Percent BSA at Baseline in the QD regimen was 4.80 (2.26) as opposed to 9.19 (7.61) in the BID regimen (Cohort 1: mean %BSA of approx. 18.5 in both QD and BID). Thus, the BSA affected was rather small in this cohort. Based on global ISGA, 16/20 (80%) patients in the QD regimen had mild AD and 4/20 (20%) had moderate AD. In contrast, 5/20 (25%) patients in the BID regimen had mild AD and 15/20 (75%) had moderate AD (comparable, yet less pronounced imbalance in cohort 1). These imbalances seem, however, negligible for study outcomes as characteristics of lesions treated (ISGA, itch severity) were similar in both groups. An underlying cause for the baseline (global) ISGA and % BSA imbalances is not known, but as the randomisation procedure seems adequate, no questions are asked. It is unlikely that study outcomes have been affected by baseline differences in % treatable BSA in different regimens.

Over the 15-day treatment duration in cohort 2, all 20 (100.0%) participants in the QD arm and 19/20 (95.0%) were compliant with study treatment (100% compliance in cohort 1 for both arms). All patients (in both cohorts) completed both treatment and follow-up phase, showing good compliance with treatment recommendations, which is an indicator for acceptable tolerability of the study drug.

Efficacy:

Cohort 2: In the QD and BID regimens, the least square means (LSM) of intra-participant difference of lesion TSS change from baseline at day 15 (IP vs. vehicle) were -1.5 (p= 0.0250) and -2.1 (p= 0.0014), respectively. (Results in Cohort 1 were comparable.)

Thus, both QD and BID regimens were superior to vehicle in treatment of single AD target lesions over a course of 15 days (in either age cohort). The effect size seems comparable across cohorts and regimens.

When comparing the inter-participant differences between QD and BID regimens in either cohort, a tendency towards stronger lesion TSS reduction was seen in the BID regimens at day 15.

Results comparable to day 15 were obtained for TSS assessments at day 8 for inter- and intra-patient comparisons in both cohorts (i.e. reduction in TSS in crisaborole vs. vehicle in either regimen, but no marked difference between regimens), indicating an early onset of effect with either regimen (in both cohorts).

Likewise, LSM reductions in ISGA in lesions treated with crisaborole ointment 2% compared to vehicle (intra-patient) were observed for both regimes at day 15 in both cohorts (cohort 2: -0.7 in QD; - 1.0 in BID). ISGA Response (Clear or Almost Clear and at least a 2 Grade Improvement from Baseline in Target Lesions at Day 15) was seen in ≥ 66.7% of patients in either cohort receiving crisaborole ointment 2% irrespective of treatment regimen, compared to approx. 20.0- 30.0% of patients receiving vehicle. No inter-patient differences between the treatment regimens (for neither ISGA-based evaluation) were seen, thus no regimen was superior to the other.

It is critically noted, that while crisaborole ointment 2% was superior to vehicle in reducing lesion TSS/ ISGA, the clinical relevance of the effect size is not discussed by the MAH and it is unclear what threshold of improvement (response) would be considered as a meaningful patient benefit.

Results for pruritus assessments indicate no clear favourable effect of IP vs. vehicle in either cohort and also no impact of regimen. It seems challenging to evaluate pruritus based on one distinct lesion only on a patient with a larger BSA affected.

Overall, it can be concluded that over a course of 15 days, crisaborole ointment 2% improved AD target lesions- based on lesion TSS and ISGA- when applied either QD or BID in Japanese patients ≥ 2 years of age. Neither pronounced differences in efficacy between the treatment regimens nor between the age cohorts were observed. While no data was generated in paediatric patients > 12 to < 18 years of age, prior experience with crisaborole ointment 2% does not suggest that efficacy in this age group would substantially differ from adults.

Safety:

Cohort 2: A total of 5 mild, all-causality TEAEs were reported in 4/40 (10%) participants (QD: arthralgia and hand-foot-mouth disease- neither treatment related nor in target lesion; BID: application site pruritus (treatment-related in target lesion), application site pain (treatment-related in target lesion) and hand-foot-and-mouth disease).

AE rates were higher in cohort 1 (For QD regimen: 6 participants (30.0%) experienced a total of 9 all-causality TEAEs of which 8 were considered as treatment-related (most frequent: application site irritation and application site pruritus in 3 participants each). For the BID regimen, 6 participants (28.6%) experienced a total of 12 all-causality TEAEs of which 8 were considered as treatment-related (most frequent: application site irritation in 4 participants).

Overall, TEAE incidence and severity (in both cohorts) were much lower in this study compared to other studies investigating crisaborole ointment 2% treatment in patients with AD (e.g. main phase 3 studies in adults and recently submitted phase 4 study C3291002 in children between 3 to ≤ 24 months of age which is currently under assessment), likely due to the much shorter observational period. Younger patients reported fewer AEs compared to adults. No serious or severe TEAEs, or deaths were reported in either cohort. Application site reactions (that occurred in this study as AEs) are reflected in the product information as common side effect.

While these findings do not give rise to safety concerns- particularly given that the used formulation contains the potentially irritating agent BHT (which was removed from the EU formulation)- it is emphasised that conclusions can only be made for short term treatment (treatment phase of only 2 weeks) on a restricted treatment area (one lesion). While no PK analysis was performed, it is reasonable to assume that systemic levels of crisaborole or propylene glycol or BHT (including metabolites thereof) in this study were much below what was achieved in prior studies or what would be achieved in clinical practise.

Clinical laboratory data was obtained only at screening, but not thereafter and no data on physical examination at the end of treatment could be found in the study report. While it cannot be excluded that sub-clinical changes were missed, this is considered very unlikely, taking the abovementioned aspects and prior experience with the IP (no clinical laboratory anomalies of concern despite higher exposure in children and adults) into account.

Final remark:

As this study was conducted to support the crisaborole development program in Japan, it is understood that all patients included in this study were Japanese. The data are not fully applicable to the European population, particularly when considering ethnical differences in AD genotypes and phenotypes and unfortunately no discussion on the applicability of results for the EU population use is included in the submission. Nonetheless, this study provides some further insight in the performance of crisaborole in paediatric (and adult) AD patients.

3. Rapporteur's overall conclusion and recommendation

Overall, this phase 2b study demonstrates that crisaborole ointment 2% is more efficacious than vehicle in the treatment of a single AD lesion in Japanese patients over a treatment course of 2 weeks. This was seen irrespective of regimen (QD or BID) or age cohort (2 to < 12 years of age and ≥ 18 years of age). Crisaborole ointment 2% was comparably better tolerated in the younger age cohort (fewer side effects), yet all adverse events in both cohorts were of mild severity and mainly application site reactions (frequencies irrespective of regimen). As only single lesions per patient were treated, generalisability of results for global AD should be done with caution. There is no requirement to change the SmPC.

☒ Fulfilled:

No regulatory action required.

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

Non clinical studies

Product Name: Staquis Active substance: Crisaborole

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

Clinical studies

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/0162/2020
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/0162/2020
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/0162/2020
Study C3291028: A Phase 2b, Multi center, Randomized, Double-blind, vehicle-controlled, intra-participant study, to evaluate efficacy and safety of two regimens of crisaborole ointment 2% in japanese pediatric and adult participants (2 years and older) with mild to moderate atopic dermatitis.	C3291028	LSLV December 2019	Article 46 submission by June 2020 (09 June 2020 submission deadline)
Study C3291032: A Phase 3, Multicenter, Randomized, Double blind, Vehicle Controlled Study of the Efficacy and Safety of Crisaborole Ointment, 2% in Asian Pediatric and Adult Subjects (ages 2 years and older) with Mild to Moderate Atopic Dermatitis.	C3291032	LSLV November 2021	Article 46 submission by May 2022
PIP Study 8: C3291037 - Assessor-blind, randomised, active- and vehicle -controlled study to evaluate efficacy and safety of crisaborole ointment, 2% compared to topical corticosteroid (TCS), topical calcineurin inhibitor (TCI) and vehicle in children from 2 to less than 18 years of age (and adults) with mild to moderate atopic dermatitis.	C3291037	LSLV May 2021 (EMA PIP decision: P/0162/2020)	Latest PIP decision: P/0162/2020 The Article 46 submission of Study C3291037 will be planned to be submitted by November 2022.
PIP Study 7: C3291031 - Double-blind, randomised, vehicle-controlled trial to evaluate safety and efficacy of crisaborole ointment, 2% compared to vehicle in children from 1 month to less than 24 months of age with mild-to-moderate atopic dermatitis.	C3291031	Date of completion (LSLV) in current agreed PIP (P/0162/2020) is August 2021. Ongoing PIP modification to request a change in the LSLV to October 2022 (Procedure number: EMEA-002065-PIP01-16-M03).	Latest PIP decision: P/0162/2020 Based on PDCO agreement on the ongoing PIP modification procedure (Procedure number: EMEA-002065-PIP01-16-M03) which includes a request to change the LSLV for PIP Study 7, the Article 46 submission of Study C3291031 will be planned to be submitted by April 2023.
Study C3291035: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Maintenance Treatment and Flare Reduction with Crisaborole Ointment, 2%, Once Daily Over 52 Weeks in Pediatric and Adult Participants (Ages 2 Years and Older) with Mild-to-Moderate Atopic Dermatitis, who Responded to Twice Daily Crisaborole Ointment, 2%, Treatment.	C3291035	LSLV July 2022	Article 46 submission by January 2023.
Study C3291034: A Phase 3, Multicenter, Open-label Study of the Long-term Safety of Crisaborole Ointment 2% in Chinese Pediatric and Adult Subjects (ages 2 years and older) with Mild to Moderate Atopic Dermatitis.	C3291034	LSLV September 2022	Article 46 submission by March 2023
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	C3291027	LSLV July 2023	Article 46 submission by January 2024