NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	207695/S-12
Priority or Standard	Standard
Submit Date(s)	June 9, 2022
Received Date(s)	June 9, 2022
PDUFA Goal Date	April 9, 2023
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	April 3, 2023
Established/Proper Name	Crisaborole
(Proposed) Trade Name	EUCRISA (crisaborole) ointment, 2%
Pharmacologic Class	Phosphodiesterase 4 inhibitor
Code name	PF-06930164/ AN2728
Applicant	Anacor Pharmaceuticals, Inc./ Pfizer Inc.
Dosage form	Ointment
Applicant proposed Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	For topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 | Atopic dermatitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	24079001 | Atopic dermatitis (disorder)
Recommended Dosing Regimen	Apply a thin layer twice daily to affected areas. Once clinical effect is achieved, consider reducing application to once daily.

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OPQ=Office of Pharmaceutical Quality
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DPMH=Division of Maternal Health
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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Melinda McCord, MD	OII/DDD	Sections: 1.2, 1.3, 1.4, 2, 3, 4,5,6,7.1,7.2,8.2, 8.4,9.10,11,12,13,16	**Select one:** _X__ Authored ___ Approved
	Signature:			
Clinical Team Leader/ Cross Disciplinary Team Leader	Kevin Clark, MD	OII/DDD	Sections: 1.2, 1.3, 1.4, 2, 3,4,5, 6,7.1,7.2,8.2, 8.4,9.10,11,12,13,16	**Select one:** ___ Authored _X__ Approved
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Division Director for Safety (Clinical)	Tatiana Oussova, MD	OII/DDD	Sections: All	**Select one:** ___ Authored _X_ Approved
Statistical Reviewer	Rabab Elnaiem, PhD	OTS/OB/DBIII	Sections: 1.2, 8.1, 8.3, 8.4	**Select one:** _X_ Authored ___ Approved
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Acting Statistical Team Leader	Kathleen Fritsch, PhD	OTS/OB/DBIII	Sections:1.2, 8.1, 8.3, 8.4	**Select one:** _X__ Authored _X_ Approved
	Signature:			

Glossary

AC	advisory committee
AD	atopic dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DB	double-blind
DDD	Division of Dermatology and Dentistry
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCTD	electronic common technical document
ER	emergency room
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IP	investigational product
IV	intravenous
ISGA	Investigator Static Global Assessment
IND	Investigational New Drug

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	normal range
OCS	Office of Computational Science
OL	open-label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE-4	phosphodiesterase 4
PE	Pediatric Exclusivity
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRAC	Pharmacovigilance Risk Assessment Committee
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
PSUR	Periodic Safety Update report
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SGE	special government employee
SMQ	Standardized MedDRA Query
sNDA	supplemental new drug application
SOC	system organ class
SOL	sleep onset latency
TEAE	treatment emergent adverse event
TEAR	treatment emergent adverse reaction (related to intervention)

TSO	total sleep opportunity
TST	total sleep time
TST/TSO	sleep efficiency (total sleep time/total sleep opportunity)
URI	upper respiratory tract infection
WASO	wake after sleep onset
WRO	written responses only

1 Executive Summary

1.1. Product Introduction

The Applicant, Pfizer Inc., submitted a supplemental new drug application for NDA 207695 (sNDA -012) that provides data to support the addition of a once daily dosing regimen for (b) (4) The proposed labeling for section 2 DOSAGE AND ADMINISTRATION includes the following:

(b) (4)

On December 14, 2016, the FDA approved the original application for crisaborole ointment for the topical treatment of mild-to-moderate atopic dermatitis (AD) in patients 2 years of age and older. The approved dosing regimen is: apply a thin layer of EUCRISA twice daily to affected areas. Approval of sNDA-010 (March 23, 2020) expanded the indication to the topical treatment of mild-to-moderate AD in adult and pediatric patients 3 months of age and older.

Eucrisa (crisaborole) ointment, 2% is a topical phosphodiesterase 4 inhibitor (PDE-4). Inhibition of PDE-4 results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. However, the specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not well defined.

In the Division of Dermatology and Dentistry (DDD), there are no topical products that have received labeling for maintenance treatment at the time of this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from a single randomized, double-blind, vehicle-controlled, phase 3 trial (C3291035) to provide evidence of the effectiveness of crisaborole ointment, 2%, once daily (QD) for maintenance treatment and flare reduction in subjects with mild-to-moderate AD, who responded to twice daily crisaborole ointment, 2%, treatment.

Trial C3291035 enrolled subjects who were 3 month of age and older with a clinical diagnosis of AD according to the criteria of Hanifin and Rajka, ≥5% treatable % body surface area (BSA) (excluding the scalp) affected with AD and an Investigator's Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate). The study design included three periods: an open-label period

of up to 8 weeks, a 52-week randomized double-blind treatment period and a 4 week follow-up period.

The protocol-specified primary efficacy endpoint was the flare-free maintenance until onset of first flare during the 52-week double- blind period. Flare was defined as an ISGA score ≥2. The protocol specified the following secondary efficacy endpoints: flare-free days over 52 weeks, number of flares over 52 weeks and time to first worsening in pruritus for subjects who achieved improvement in pruritus at randomization.

Crisaborole ointment, 2% was statistically superior to vehicle on the primary efficacy endpoint (i.e., time to first flare) and on the first two key secondary efficacy endpoints (i.e., flare-free days and number of flares). However, investigators assessed disease severity and flare during office visits that were conducted every 4 weeks and not daily. Therefore, it is difficult to estimate time to first flare in days, flare free days and number of flares with precision. To convey the results of Trial C3291035, the Agency recommended presenting estimates of proportion of subjects who maintain their response (i.e., ISGA of 0 or 1) over time in labeling. Due to the limitations of the study design and pre-specified endpoints, Section 2 Dosing and Administration (b) (4). However, the data were sufficient to support the addition of a statement regarding the use of crisaborole once daily after clinical effect is achieved.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Eucrisa (crisaborole) ointment, 2% is a phosphodiesterase 4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis (AD) in adult and pediatric patients 3 months of age and older. The benefit-risk profile of crisaborole ointment for the approved indication and dosing regimen (twice daily) in patients 2 years of age and older was established from data in the original application (approved December 14, 2016). Data in a subsequent supplement (S-010) confirmed a similar benefit-risk assessment in the youngest pediatric age group, 3 months to 2 years (S-010 approved April 23, 2020). For a discussion of the benefit-risk profile of crisaborole ointment for the topical treatment of mild to moderate AD, refer to the Clinical Reviews dated November 3, 2016, and March 16, 2020.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that occurs in the pediatric and adult populations. AD is characterized by intense pruritus and xerosis and follows a remitting and relapsing course. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. The onset of AD commonly occurs in children between 3 and 6 months of age. Most patients experience improvement in their disease severity with age. (Kim, 2016).

Most of the FDA-approved therapies that are intended for continuous long-term treatment of AD are systemically administered biologic products or small molecules. Some topical drug products that are indicated for "short-term and non-continuous chronic treatment" of AD include ruxolitinib cream and topical calcineurin inhibitors. Topical drug products with labeling that provides no definitive restriction on the duration of treatment include some formulations of corticosteroids such as desonide foam. However, labeling for corticosteroids generally instructs the user to discontinue treatment when control is achieved. To date, there are no topical products that are specifically indicated for maintenance treatment in the Division of Dermatology and Dentistry (DDD).

The Applicant submitted data from a randomized, double-blind (DB), vehicle-controlled (VC) trial (C3291035). The trial evaluated a new dosing regimen of crisaborole ointment applied once daily for maintenance treatment and "flare reduction" in subjects who achieved treatment success after an open-label (OL), run-in period of up to 8-weeks. During the OL period, subjects applied crisaborole ointment according to the approved dosing regimen of twice daily (BID). Response/treatment success was defined as an Investigator Static Global Assessment (ISGA) score of "clear" [0] or "almost clear" [1] with at least a two-grade improvement from baseline, AND Eczema Area and Severity Index (EASI) of at least 50% improvement from baseline (EASI50). Subjects assessed as responders (n=270) were randomized to receive crisaborole ointment or vehicle once daily (QD) for up to 52 weeks. Subjects who developed a "flare" of AD (ISGA ≥ 2) during the DB period applied crisaborole at the

approved dosing regimen of BID for up to 12 weeks. If the flare resolved, subjects resumed their randomized study product (crisaborole or vehicle) QD; if the flare continued after 12 weeks of twice daily treatment with crisaborole, then subjects withdrew from the trial.

The prespecified primary efficacy endpoint was "flare-free maintenance until onset of the first flare during the 52-week DB period" assessed in days. Key secondary efficacy endpoints during the 52-week DB period were: number of flare-free days, number of flares, and maintenance of pruritus response until onset of first flare. Pruritus response was defined as the maintenance of the improvement of ≥50% from baseline that was obtained at randomization.

During the development of crisaborole for maintenance treatment and flare reduction, the FDA conveyed concerns to the Applicant regarding the selection of endpoints to support their new dosing strategy. On the prespecified primary efficacy endpoint and first two key secondary endpoints, the results of Trial C3291035 showed that crisaborole was statistically superior to vehicle. However, the Applicant collected no qualitative data during the trial to support the conclusion that the difference would be clinically meaningful to patients. In addition, the monthly assessments were not sufficiently frequent to support a superiority claim measured in days. During the development program to support this new dosing regimen, the FDA advised the Applicant that treatment benefit should be measured as treatment success/response at a pre-specified timepoint up to Week 52. In a post hoc analysis of the data on the recommended primary efficacy endpoint, crisaborole was numerically superior to vehicle but the difference diminished over the 52 weeks. Because this endpoint was not prespecified, p-values and data regarding statistical superiority are difficult to interpret. However, the benefit of maintenance dosing with QD crisaborole clearly diminished with time.

The safety data from Trial C3291035 included no reports of death. However, one subject in the OL period developed serious adverse events (SAEs) (exacerbation of AD and cutaneous infection) that were considered to be related to crisaborole. The adverse reactions (ARs) observed with twice daily administration of crisaborole were similar to the labeled safety profile; the ARs with QD administration of crisaborole were similar to vehicle. No new safety signals were identified. However, the strategy of applying crisaborole QD as maintenance treatment plus BID for flares of AD rather than applying crisaborole BID for flares and vehicle QD resulted in a substantial increase in the mean total dose of crisaborole used over 52 weeks.

The results of Trial C3291035 were not sufficiently persuasive to establish the benefit of QD use of crisaborole for maintenance rather than episodic use of crisaborole for long- term treatment. The superiority of crisaborole to vehicle in the maintenance of response diminished with time. The absence of qualitative information to establish that that statistically significant treatment effects were also clinically meaningful, the trial design and the endpoint selection limited the utility of the data. Therefore, a description of Trial C3291035 will be included in labeling in Sections 6, 8 and 14 to inform healthcare providers. Section 2 Dosing and Administration (b) (4)

(b) (4) However, the data were sufficient to support the addition of a statement regarding the use of crisaborole QD after clinical effect is achieved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atopic dermatitis (AD) is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. The diagnosis is based on clinical information and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). • Although the disorder may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For most patients, the disease resolves by adulthood. One meta-analysis indicated that 80% of patients do not have persistent disease by age 8 and less than 5% had persistent disease 20 years after diagnosis (Kim, 2016). Risk factors for persistent, refractory disease include severe disease at diagnosis and late onset of AD. • Subjects with severe persistent AD carry a higher risk of comorbidities. Comorbidities may include asthma, allergic rhinoconjunctivitis, food allergies, mood disorders such as anxiety and depression, metabolic disorders, and obesity. The combination of these comorbidities and lifestyle choices such as smoking increases the risk for cardiovascular disease, stroke, and hypertension.	AD, as a chronic inflammatory disease, significantly impacts the quality of life of patients and their families. The primary and secondary disease-related skin changes may alter the appearance of the skin. Patients with disease in visible locations may experience depression/anxiety and feelings of social isolation. In addition, subjects with severe persistent AD carry a higher risk of comorbidities. The major symptom of AD, pruritus, may disrupt sleep, and result in fatigue and irritability during the day. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• T-helper 2 (Th2) cells figure prominently in the complex pathogenesis of atopic dermatitis (AD), and lesional skin includes increased levels of Th2 cytokines (IL-4, IL-13, IL-31).	
Current Treatment Options	• Topical corticosteroids (TCS) are the first-line pharmacologic therapy for patients with AD of all severities. Local adverse reactions from TCS may include atrophy, striae, telangiectasias, burning, hypo-pigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible. TCS carry the risk of hypothalamic pituitary- adrenal (HPA) axis suppression, with the potential for glucocorticosteroid insufficiency. • For AD of mild to moderate severity, there are a limited number of nonsteroidal topical treatment options. Tacrolimus ointment and pimecrolimus cream are topical calcineurin inhibitors that are approved for treatment of AD. The labeling specifies that these products are second-line therapy for AD and are for "short-term and non-continuous chronic treatment…" The labeling includes Boxed Warnings that describe rare cases of malignancy (e.g., skin and lymphoma) that have been reported in patients treated with topical calcineurin inhibitors. • Ruxolitinib 1.5% cream (approved September 21, 2021), a Janus kinase (JAK) 1 and JAK2 inhibitor, mediates the signaling of several cytokines and growth factors that are important for hematopoiesis and immune function. Ruxolitinib cream is indicated for the short-term and non-continuous chronic treatment of mild to moderate AD in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Because	There is a medical need for additional topical treatment options for long-term use in patients with mild to moderate AD. Long term use of corticosteroids and other topical therapies are limited by potential adverse reactions. In order to minimize the potential for adverse reactions, health care providers generally rotate therapies or implement modified dosing regimens. The Applicant seeks labeling for an alternate dosing regimen after subjects achieve treatment success on the approved dosing regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, labeling includes a boxed warning for serious infections, all-cause mortality, lymphoma and other malignancies, major adverse cardiovascular events (MACE), and thrombosis. In addition, there are warnings for hematologic effects (thrombocytopenia, anemia and neutropenia) and lipid elevations.	
Benefit	• Crisaborole ointment, 2% was statistically superior to vehicle on the primary efficacy endpoint (i.e., time to first flare:) and on the first two key secondary efficacy endpoints (i.e., flare-free days: 234 vs 199 days] and number of flares [0.95 vs 1.36 days]). On the Agency recommended efficacy endpoint (i.e., the proportion of subjects who maintain their response (i.e., ISGA of 0 or 1 up to Week 52), crisaborole was numerically superior to vehicle. However, the difference from vehicle diminished over time to Week 52.	A dosing strategy that would allow patients with mild to moderate AD to maintain remission for a longer duration, minimize the potential for adverse reactions by less frequent dosing and promote compliance would represent a substantial treatment benefit. However, the study design and endpoints used to assess the treatment benefit were not sufficient. Investigators conducted assessments every 4 weeks and instructed subjects to provide daily assessments in an electronic diary. However, because investigator assessments were not conducted daily, it is more difficult to provide estimates of time to first flare, flare free days and number of flares with precision. The addition of a treatment arm with the approved BID dosing for 52 weeks may have identified the proportion of subjects who could reduce the dose and still maintain treatment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		success.
Risk and Risk Management	• There were no deaths. One subject in the OL period developed serious adverse events (SAEs) (exacerbation of AD and cutaneous infection) that were considered to be related to crisaborole. During the OL, a total of 109 subjects (22%) developed 166 AEs with BID application of crisaborole. When related terms were grouped together, the TEAEs that occurred with the greatest frequency were application site pain (6%), upper respiratory tract infection (6%) and dermatitis atopic (5%). During the DB period, a total of 36 subjects (27%) who received crisaborole once daily developed 83 TEAEs and 49 subjects (36%) who received vehicle once daily developed 76 TEAEs. The TEAEs that occurred with the greatest frequency after pooling related terms included upper respiratory tract infection (9%) dermatitis atopic (3%) and application site pain (2%). Two subjects developed severe TEAEs with the preferred term (PT) of dermatitis contact. • No additional serious safety concerns were identified that warranted consideration of a Risk Evaluation and Mitigation Strategy (REMS). The Prescribing Information and Patient Information adequately addresses the known risks associated with the moiety. • The Applicant evaluated the relevant pediatric age groups during Trial C3291035. There were no meaningful differences in safety between the adult and pediatric populations. The Agency agrees with a partial waiver of assessments in the pediatric population 0 to 3 months of age because studies are impossible or highly impractical.	The size of the safety database and the scope of the safety analyses were sufficient to evaluate the safety profile of crisaborole applied with reduced frequency, once daily. There is an unmet need for topical product that is both safe and effective for long term use. The data confirmed the safety of crisaborole for long term use. However, the efficacy results were not sufficiently persuasive to support the proposed strategy to recommend the use of crisaborole once daily for maintenance. The absence of qualitative information to establish that that statistically significant treatment effects were also clinically meaningful, the trial design and the endpoint selection limited the utility of the data. However, the data were sufficient to support the addition of a statement regarding the consideration of once daily dosing after disease control is achieved. The safety of the product used twice daily is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The entry criteria excluded pregnant and breastfeeding females, and females planning to become pregnant and breastfeed during the trial. However, post marketing safety data as reviewed by Division of Pediatric and Maternal Health (DPMH) does not identify effects on the developing fetus or a new safety signal in this population.	well established; therefore, additional safety findings with once daily dosing were not anticipated. No post-marketing requirements (PMRs) are indicated in response to this submission.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.2
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that occurs in the pediatric and adult populations. The presence of AD is frequently associated with elevated serum immunoglobulin E (IgE) levels, an atopic diathesis, and the predisposition to develop asthma, hay fever, allergic rhinitis, and Type 1 hypersensitivity reactions (Weston and Howe 2019). The estimated prevalence of AD among children in the United States is 11 to 15% (Shaw et al. 2011; McKenzie and Silverberg 2019). The prevalence of AD in adults from one cross-sectional study including nearly 1300 adults was 7.3 percent (Chiesa Fuxench et al. 2019). However, epidemiologic data in adults is sparse. The incidence of atopic dermatitis appears to be increasing especially in urban areas and developed countries (Deckers et al. 2012).

The diagnosis of AD relies on clinical information such as the signs and symptoms of the disease, the morphology and distribution of the lesions, the age of onset and personal and family history. Pruritus is almost universally present. In some cases, a biopsy may be necessary to exclude other diagnoses. The clinical manifestations vary with age and duration of the disease. In the youngest pediatric age group (less than 2 years of age), typical lesions are red, scaly, and crusted papules which are distributed on extensor surfaces, face, and scalp. In older pediatric age groups, scaly papules and plaques are distributed on flexor surfaces as well as the neck and back. The intense pruritus and resultant scratching produce secondary changes of lichenification and excoriation which are typical features of chronic AD. In the adult age group, the atopic dermatitis is generally more localized with lichenified plaques distributed on flexor surfaces. However, involvement of the face, neck and hands is not uncommon. Vesicles and exudate may be present in acute AD (Weston and Howe 2019).

The onset of AD commonly occurs between 3 and 6 months of age, although definitive diagnosis may be delayed. Approximately 60% of patients develop AD within the first year of life and 90% by age 5 years. Most patients observe improvement in their disease severity with age. However, 10 to 30% of patients experience signs and symptoms that persist into adulthood. A small proportion of patients develop AD as adults (Weidinger and Novak 2016). Kim et al. (2016) conducted a systematic review and meta-analysis of 45 studies which included 110,651 subjects spanning 434,992 patient-years. In the pooled analysis, the authors found that 80% of patients with AD which was diagnosed in the pediatric population did not persist by 8 years and less than 5% persisted by 20 years after diagnosis (mean [SD]: 6.1 ± 0.02 years). The authors identified risk factors for persistent AD which included disease severity, older age of onset, and female gender. Children with more severe disease at the time of diagnosis had increased risk for persistent disease in 3 of these studies. In addition, the longer that AD was present, the more likely the disease was to persist. Furthermore, the results from this analysis suggested that children who developed AD in the first 2 years of life had significantly lower risk

of persistent disease than those who developed AD later in childhood or adolescence. The authors note that that natural history of the disease is an important consideration for therapeutic management (Kim, 2016).

The majority of patients are diagnosed with AD of mild severity. Among 91,642 children aged 0 to 17 years who participated in the 2007 National Survey of Children's Health (NSCH), the overall prevalence of AD was 13% with 67% reporting their disease severity as mild, 26% as moderate and 7% as severe (Silverberg and Simpson 2014). Epidemiologic data suggests that genetic, environmental, and socioeconomic factors impact disease severity (McKenzie and Silverberg 2019; Weston and Howe 2019).

The pathogenesis of AD is a complex interplay of genetic, immunologic, and environmental factors. These factors include skin barrier abnormalities, defects in innate immunity, Th2-skewed adaptive immune response, and altered microbial flora on the skin. Authors disagree about the initial event which triggers the inflammatory cascade, skin barrier dysfunction versus immune dysregulation (Weston and Howe 2019).

AD is associated with significant morbidity and reduction in the quality of life for patients and their families. Comorbidities may include asthma, allergic rhinoconjunctivitis, food allergies, mood disorders such as anxiety and depression, metabolic disorders, and obesity. Subjects with severe persistent AD carry a higher risk of comorbidities. The combination of these comorbidities and lifestyle choices such as smoking increases the risk for cardiovascular disease, stroke, and hypertension. In addition, greater disease severity tends to be correlated with more severe pruritus. Disruption of sleep is observed in children with AD and is related to nocturnal itching and scratching. Children with AD exhibit disorders of behavior and mood with greater frequency than the general pediatric population. The impact of AD and its comorbidities on quality of life is reported to be comparable to other chronic medical conditions such as diabetes (Hanifin and Reed 2007). Because none of the currently available treatment options provides a sustained remission or cure, the chronicity of the disease places substantial social and financial burden on families and society (McKenzie and Silverberg 2019).

2.2. Analysis of Current Treatment Options

The initial approach to AD management is nonpharmacologic care which includes attention to bathing practices and the regular use of emollients. Emollients may address transepidermal water loss, xerosis, fissuring and erythema. For patients with mild disease, these standard practices may be sufficient to control the disease; for patients with more severe disease, these standard practices may reduce the amount of pharmacologic therapy needed to control the disease (Eichenfeld, 2014.)

Food and Drug Administration (FDA) approved or licensed products for the treatment of AD may be categorized as topical (e.g. corticosteroids, calcineurin inhibitors, phosphodiesterase -4

[PDE-4] inhibitors and Janus Kinase inhibitors [JAKi]) or systemic (dupilumab, tralokinumab, parenteral corticosteroids and JAKi.) Because crisaborole is indicated for mild to moderate AD, this discussion of current treatment options will focus on FDA approved topical therapies.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups (Eichenfeld, 2014.) Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are indicated for a wide range of age groups. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are indicated for treatment of AD in adults and children (2 years and older). Each product targets a slightly different patient population: tacrolimus is indicated for patients with moderate to-severe AD and pimecrolimus is indicated for patients with mild-to-moderate AD. However, both products are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. In addition, labeling for calcineurin inhibitors includes boxed warnings advising that the safety of their long-term use has not been established. Although causality has not been determined, the boxed warnings indicate that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. Another treatment option for patients with mild to moderate AD is crisaborole ointment, 2%, a PDE-4 inhibitor. Crisaborole ointment is approved for treatment of AD in pediatric patients 3 months of age and older.

Recent additions to the limited armamentarium of nonsteroidal topical treatment for AD is ruxolitinib cream, 1.5%. Ruxolitinib cream inhibits Janus kinase (JAK) 1 and JAK2, which mediate the signaling of several cytokines and growth factors that are important for hematopoiesis and immune function. Although the systemic exposure from ruxolitinib 1.5% cream may overlap with that from orally administered ruxolitinib, TEAEs related to systemic effects were infrequent, uncomplicated, and generally resolved without treatment withdrawal. Among the most common TEAEs are application site reactions including acne, pruritus, and erythema.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The FDA approved EUCRISA™ (crisaborole) ointment, 2%, (December 14, 2016) for the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. On March 23, 2020, the FDA approved sNDA S-007, S-009 and S-010 and determined that the Applicant had fulfilled the pediatric study requirement under PREA for pediatric patients with mild to moderate atopic dermatitis ages 3 months to < 2 years of age (S-010 approved March 23, 2020). Refer to the Clinical Review dated March 16. 2020).

3.2. Summary of Presubmission/Submission Regulatory Activity

On April 11, 2018, the FDA held a Type B Guidance meeting with the Applicant to discuss the conduct of a single trial (C3291035) to evaluate the safety and efficacy of crisaborole ointment, (using a different dose regimen than approved) for long-term maintenance treatment of AD. The FDA stated that to establish efficacy of maintenance treatment for their product using a new dosing regimen (for 52 weeks), we generally require replication of trial findings from two adequate and well-controlled clinical trials. If a Sponsor intends to rely on a single trial, this trial should be appropriately designed, of sufficient size and/or rigor to produce results that are "statistically persuasive, clinically meaningful, and robust".

Key discussion topics included the study design and efficacy evaluation. The proposed primary efficacy endpoint was time to occurrence of the first "flare" during the 52- week double-blind period. The Applicant proposed to define treatment success and "flare" based on the Investigator Static Global Assessment (ISGA) scale and EASI50. The FDA recommended that the protocol define treatment success and "flare" using ISGA alone. The FDA recommended that the protocol include the same definition of treatment success as used in the phase 3 trials (e.g., the proportion of subjects achieving a score of 0 [clear] or 1 [almost clear] on ISGA with at least a 2-grade improvement from baseline at a prespecified timepoint.) The proposed key secondary endpoints related to flare appeared to be supportive of the proposed primary efficacy endpoint. (b) (4)

Following review of the full protocol (C3291035), the FDA provided additional comments (Advice Letter dated December 23, 2019) regarding the study design, endpoints, and assessments and reiterated the comments regarding the recommended primary and secondary endpoints. The study design included an open label run-in period with a maximum duration of 8 weeks of twice daily (BID) treatment with crisaborole, a 52-week double -blind, vehicle-controlled period with once daily treatment and a follow-up period. The FDA noted that duration of the run-in period was longer than the interval for the primary efficacy assessment

to support the initial approval (i.e. up to 8 weeks compared with 4 weeks to support the initial approval). It was not clear if the duration of twice daily treatment during the run-in period would impact the maintenance duration. The FDA discouraged the use of "time to first flare" as the primary efficacy endpoint because monthly assessments were too infrequent to provide precise estimates. In addition, the Applicant needed to provide "data to justify and propose a clinically meaningful threshold level for the time to flare endpoint as a mere change on this endpoint may not translate to clinically meaningful treatment effect." The FDA reiterated that the recommended primary efficacy endpoint was the proportion of subjects achieving a score of 0 [clear] or 1 [almost clear] on ISGA with at least a 2-grade improvement from baseline at a prespecified timepoint(s).

The FDA stated that the other two secondary endpoints ("number of flare-free days", the "number of flares") might not be clinically meaningful if subjects who experience flares were considered "maintenance failures." The reviewers also conveyed the limitations of the patient reported outcome instruments (Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index [CDLQI]) including the anchor scales (Patient Global Impression of Severity (PGIS)/ Observer Reported Global Impression of Severity (OGIS)). The FDA conveyed detailed comments regarding the patient reported outcomes in a separate Advice Letter (dated February 19, 2020.)

The proposed safety monitoring which included assessment of adverse events (AEs), physical examinations with vital signs, and clinical laboratory evaluation (hematology, chemistry and pregnancy testing), and screening with the Columbia Suicide Severity Rating Scale (CSSRS) was deemed acceptable. However, the FDA recommended that exclusion of subjects with mood disorders might not be appropriate because an association between crisaborole ointment and the emergence of depression/suicidal ideation and behavior (SIB) had not been established in the initial NDA submission.

The Applicant proposed to conduct an Accelerometry Sub-study to explore impacts of EUCRISA on nocturnal scratch and sleep. The FDA provided extensive comments regarding the general proposal because limited information regarding the device and endpoints was included in the submission. The endpoints related to nocturnal scratch and sleep using accelerometry (actigraphy) were assessed as exploratory and not controlled for multiplicity.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of investigational sites. The statistical team identified one clinical site with a large treatment effect which impacted the efficacy results on the recommended primary efficacy

endpoint. However, this site was recently inspected. Therefore, clinical inspections were not deemed necessary to support the integrity of the efficacy data.

4.2. Product Quality

NDA 207695 SUPPL-12 does not provide any changes to the quality information for the drug substance or for the drug product (the approved product is proposed for use, manufactured at the approved facility). The Applicant did provide a request for categorical exclusion from the requirements to prepare an environmental assessment per 21 CFR 25.31 (b), stating that action on this sNDA might increase use of the drug substance, but the estimated concentration of the drug substance at the point of entry into the aquatic environment (EIC) will be below 1 part per billion.

There are no other quality-related changes within this supplemental NDA application and no changes to the quality information in the labeling. Since the approved drug product is subject to this efficacy supplement, there are also no changes to the labels.

In a review dated March 2, 2023, the OPQ reviewer, David Lewis, chief, Branch 2, DPMAI, OLDP, OPQ, concluded "This supplement is recommended for approval."

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted no new nonclinical data to support the efficacy of once daily dosing for maintenance treatment (b) (4) Refer to the review by Kumar D. Mainigi, PhD dated August 15, 2016, for a detailed discussion of the nonclinical data to support approval of the original NDA.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted no new clinical pharmacology data to support the efficacy of once daily dosing for maintenance treatment (b) (4) Refer to the review by Chinmay Shukla, Ph.D. dated August 30, 2016, for a detailed discussion of the clinical pharmacology data to support approval of the original NDA.

The review team discussed the need for additional pharmacokinetic (PK) data related to the proposed long-term use of crisaborole. Of particular concern is the potential increase in exposure in the youngest pediatric patients whose body surface area to volume ratio may provide increased systemic exposure. From a review of the previous data, Dr. Shukla stated that systemic exposure to crisaborole is expected to be at steady state by Day 7. The Pk assessment in subjects 3 months of age and older was conducted at steady state under maximal use conditions. From the trial results, dosing longer than 8 days is not expected to produce any further increase in systemic exposure. (Refer to the clinical pharmacology review by Luke Oh, PhD dated March 4, 2020). Dr. Shukla concluded that the proposed dosing regimen is not expected to produce systemic exposures higher than previously observed in the completed PK trials that were conducted under maximal use conditions. Therefore, additional PK assessments are not needed.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted a single phase 3 trial (C3291035) to support the use of EUCRISA applied once daily for maintenance treatment. The Applicant submitted data from seven additional trials (C3291001, C3291029, C3291028, C3291032, C3291037, C3291002, C3291027) in integrated datasets to provide a “robust” safety assessment. However, these trials evaluated the effects of EUCRISA using different study designs, dosing regimens and durations of therapy in different study populations. As such, the integrated data is difficult to interpret. Therefore, safety information from the trials that were not conducted to evaluate the efficacy and safety of maintenance treatment and flare reduction with crisaborole ointment, 2%, applied once daily will be reviewed separately and discussed briefly.

Sample Table. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity Conducted under the IND or Non-IND	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
C3291035 IND	NCT 04040192	A phase 3, R, DB, VC trial to evaluate efficacy and safety of maintenance treatment and flare reduction with crisaborole ointment, QD over 52 weeks in pediatric and adult subjects aged 3 months and older with mild to moderate AD who responded to twice daily treatment -Up to 8 week open-label (OL) period was followed by up to 52 weeks of double blind (DB) treatment. -Flare= ISGA≥2 -Resolution of flare= ISGA of clear or almost clear -OL Responder defined as clear [0] or almost clear [1] with a ≥2 grade change	OL Period Crisaborole 2% BID DB Period Crisaborole 2% QD Vehicle QD	**Primary efficacy**: Flare-free maintenance until onset of first flare during the 52-week DB period. **Secondary**: -Number of flare-free days; -Number of flares; -Maintenance of pruritus response (maintenance of improvement of ≥50% from baseline at first randomization) until onset of first flare. **Safety Endpoint**: Incidence of	Mean duration OL: BID 46 days (Range: 4 to 121 days) DB: QD -vehicle 209 days (Range: 6 to 396 days) -crisaborole 237 days (Range: 2 to 420 days) DB Flare: BID: -crisaborole 109 days (Range: 21 to 338 days)	OL Period 497 subjects DB 270 subjects 135: vehicle: (78 completed) 135: crisaborole (79 completed)	-M and F age 3 months and older with mild to moderate AD	Australia (1 site), Canada (5 sites), China (10 sites), Israel (1 site), Turkey (2 sites), US (23 sites)

		from baseline on ISGA and EASI50		TEAEs				
		Additional Studies to Support Safety						
C3291002 IND		Multicenter, open label, safety study	Crisaborole 2% BID Application period: 28 days Follow -up period: 28 days	Incidence of TEAEs, SAEs, changes in height, weight, VS, ECG, laboratory values	Application period: 28 days Follow -up period: 28 days	Enrolled: 137 Completed: 128 PK sub-group: 21	-M and F age 3 months to <24 months -**Non-PK**: ≥5% BSA, ISGA: mild or moderate -**PK**: ≥35% BSA, ISGA: mild or moderate ISGA: moderate	32 sites: Australia (6 sites); Canada (4 sites); US (22 sites)
C3291029 Non-IND		A phase 1 R, DB, VC trial of crisaborole ointment, 2% conducted in 2 cohorts to evaluate: -Cohort 1: the potential for skin irritation with the study product under occlusion in adult Japanese healthy volunteers (HV) -Cohort 2: safety, tolerability and PK in Japanese adults with mild-to -moderate AD .	Cohort 1: Crisaborole Ointment, 2% and Vehicle (not pooled) Cohort 2: 2 arms Crisaborole BID Vehicle BID	PK parameters Safety: TEAEs, laboratory, VS, ECG	Application period: Cohort 1: 2 days Cohort 2: 8 days confined to CRU	Cohort 1 Treated: 20 HV Cohort 2 Treated 10	Cohort 1: HV Cohort 2: adult Japanese subjects with mild to moderate AD. and ≥25% BSA	Japan (1 site)
C3291032 Non-IND		A phase 3, multicenter, R, DB, VC trial of the efficacy and safety of crisaborole ointment, 2%	Vehicle BID Crisaborole BID for 28 days	Efficacy: % change in EASI total score at Day 29	Application period: 28 days	R: 391 subjects	M and F ages 2 years and older with mild to	China (22 sites), Japan (16 sites),

		in Chinese and Japanese pediatric and adult subjects with ages 2 years and older) with mild-to moderate AD.		Safety: TEAEs, SAEs, clinically significant changes in VS or lab values			moderate AD involving at least 5% treatable BSA	Republic of Korea (1 site)
C3291028 Non-IND Within subject comparison		A phase 2b, multi-center, R, DB, VC, intra-subject trial, to evaluate efficacy and safety of two regimens of crisaborole ointment, 2% in Japanese pediatric and adult subjects (2 years and older) with mild-to moderate AD.	2 groups per cohort Cohort 1: ≥12 yrs -Crisaborole QD -Vehicle QD -Crisaborole BID -Vehicle BID Cohort 2: < 12yrs -Crisaborole QD -Vehicle QD -Crisaborole BID -Vehicle BID	Primary Efficacy: Change from baseline in **TSS** in target lesions treated with crisaborole or vehicle on Day 15 Safety: Incidence of TEAEs and SAEs in each regimen for each cohort	Application period 14 days	R: 81 subjects	M and F ages 2 years and older with mild to moderate AD involving at least 1%-30% treatable BSA with 2 lesions 3X3 cm	Japan (3 sites)
C3291001 Non-IND Within subject comparison		A phase 2a, R, DB, VC trial, to characterize the mechanism of action of crisaborole ointment, 2%, by evaluation of efficacy and changes in skin biomarkers using "i**ntra-subject**" comparisons of target lesions	Crisaborole 2% + Vehicle BID, for 14 days followed by OL Crisaborole 2% BID	**Primary Efficacy:** Change from baseline in Total Sign Score (TSS) in target lesions at Day 15. **Biomarker**: Change from baseline in key skin biomarkers of AD at Day 15 **Safety:** incidence of SAEs, vital signs, AEs, PE,	DB applications for 14 days followed by OL applications for 28 days	R: 40 subjects Treated: 40 subjects Completed: 38 subjects	Adult M and F with mild-to moderate AD, BSA 0.5%-10% + 2 lesions of AD Sex: 13 M/27 F Mean age: 32.2 years (Range: 18 to 57 years) Race: 34 White, 3 Black, 3 Asian	Canada (1 site)

				and lab tests				
C3291037 Terminated pre-maturely* IND		A phase 3b/4, multicenter, R, assessor blinded, vehicle and active (TCS and TCI) controlled trial to assess efficacy, safety including PG levels, and local tolerability of crisaborole ointment, 2% in pediatric and adult subjects (ages 2 years and older) with mild-to- moderate AD.	4 arms: -Vehicle BID -Crisaborole 2% BID -Hydrocortisone butyrate 0.1 BID -Pimecrolimus 1% BID	**Primary efficacy**: % change from Baseline in the EASI total score at Day 29. **Safety:** TEAEs, SAEs, local tolerability, changes in VS and laboratory parameters	Mean duration 27-29 days	Planned-600 R-237 (power not adequate for primary comparison of crisaborole with vehicle)	Pediatric and adult subjects ages 2 years and older with mild-to moderate AD and ≥5% Treatable %BSA (w/o scalp)	26 sites in 7 countries (Germany Italy, Poland, Sweden, Switzer-land UK, US)
C3291027 Terminated pre-maturely * Non-IND		A phase 3, multicenter, OL study of the long-term safety of crisaborole ointment, 2% in Japanese pediatric and adult subjects with mild to moderate AD (intended to be an OL extension trial of C3291032 and C3291031)	Crisaborole 2% BID	Safety incidence of treatment emergent AEs and SAEs	Mean duration: 27 days (Range: 0 to 56 days)	Entered-40 Completed-0	Mild to moderate AD age ≥ 2 years completed C3291032 or C3291031 Sex: 21 M/ 19 F Mean age: 15.0 years (Range: 4 to 45 years) Race: 40 Asian	Japan (15 sites)

BID= twice daily; BSA= body surface area; DB= Double-blind; ISGA=Investigator's Static Global Assessment; QD= once daily; R= randomized; TEAEs= treatment-emergent AEs, SAEs= serious AEs; EASI=Eczema Area and Severity Index; Lesion Total Sign Score =TSS; VC=vehicle-controlled; VS= vital signs; CRU =Clinical Research Unit; PG= propylene glycol; R=randomized; TCS=topical corticosteroid; TCI=topical calcineurin inhibitor; w/o=without; PE= physical examination; M=male; F=female*Per Sponsor, these trials were terminated prematurely due to a "business decision and portfolio reprioritization".

7.2. Review Strategy

Data Sources
The data sources used for the evaluation of the efficacy and safety of crisaborole ointment included the submitted clinical study reports, datasets, clinical summaries, and proposed labeling. The supplement was submitted in electronic common technical document format and was entirely electronic. The Applicant submitted both Study Data Tabulation Model datasets and Analysis Data Model datasets. The analysis datasets used in this review are archived at:

\\CDSESUB1\evsprod\NDA207695\0801\m5\datasets\c3291035\analysis\adam\datasets

Data and Analysis Quality
OCS Clinical Services and the statistical and clinical teams evaluated the data fitness. The data submitted by the Applicant to support the safety and efficacy of crisaborole ointment for the proposed indication was adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

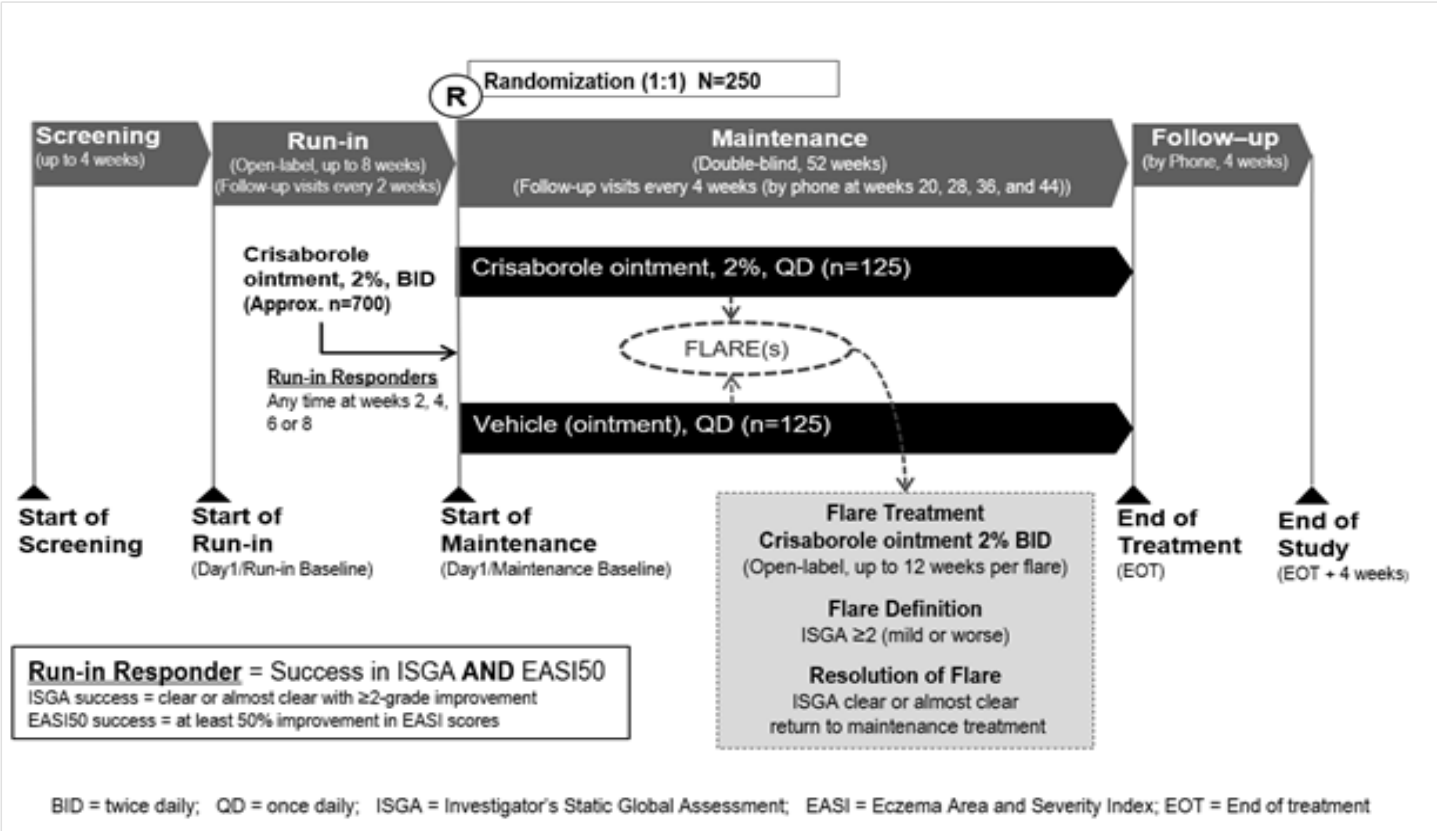
8.1.1. Trial C3291035

Trial Design

The Applicant conducted a randomized, double-blind, vehicle-controlled, phase 3 trial (C3291035) to evaluate the efficacy and safety of maintenance treatment and flare reduction with crisaborole ointment, 2%, once daily (QD) in subjects (ages 3 months and older) with mild-to-moderate atopic dermatitis (AD), who responded to twice daily crisaborole ointment, 2%, treatment.

The trial consisted of a screening period (up to 4 weeks), an open label (OL) run-in period (up to 8 weeks), a double-blind (DB) maintenance period (52-week) and a follow up period (4 weeks) after treatment completion. Figure 1 below presents the trial design schematic.

Figure 1: Trial Design Schematic



Source: Protocol, page 12

Open-label (OL) run-in period:
All eligible subjects first entered an open-label treatment period, where they applied crisaborole 2% twice daily (BID) for up to 8 weeks. For enrollment, the protocol specified the following key inclusion criteria:

- Male or female must be 3 months of age or older at the time of signing the informed consent/assent.
- Confirmed clinical diagnosis of AD according to the criteria of Hanifin and Rajka.
- AD involvement of ≥5% treatable % body surface area (BSA) (excluding the scalp) at entry into the run-in period.
- Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) at entry into the open-label run-in period.

Subjects were eligible to enter the DB maintenance period if identified as a responder at any trial visit (i.e., 2, 4, 6 or 8 Week) of the run-in period. A responder is defined as an ISGA score

of clear [0] or almost clear [1], with a ≥2 grade improvement from baseline AND a 50% change from baseline on the eczema area and severity index (EASI). Non-responders at the end of the 8-week run-in period were discontinued from the trial.

Double-blind maintenance period:
Eligible subjects were randomized (1:1 ratio) to enter the double-blind (DB) maintenance period and received crisaborole 2% once daily (QD) or vehicle QD for 52 weeks.

Subjects were scheduled to be assessed by the investigator at trial visits every 4 weeks. The trial protocol specified that at any time of the maintenance period, if a flare was suspected by a subject or caregiver of a subject, the subject/caregiver should contact their trial site as soon as possible to arrange an unscheduled clinic visit. If a subject met the criteria for having a flare (ISGA score ≥2), the subject was switched to enter a flare treatment period during which the subject received an open label crisaborole ointment, 2%, BID for up to 12 weeks.

During flare treatment period, a subject was scheduled to be assessed by the investigator on site after 4 weeks. If the flare was resolved (ISGA clear or almost clear), the subject resumed treatment with their original assigned blinded QD therapy and return to the maintenance period visit schedule.

A flare treatment period may comprise of up to 3 consecutive 4-week treatment courses with crisaborole BID. If a flare was not resolved after 3 consecutive treatment courses, the subject was withdrawn from the trial. For flare treatments that cannot be completed by Week 52 or flares that begin at Week 52, then a maximum of one treatment course (4 weeks) was allowed. Any subject developing a flare after Week 52 did not receive flare treatment, and the subject was discontinued from the trial.

Follow-up period:
An end of trial /study (EOS) safety follow-up by phone was required for subjects who discontinued from the trial at any trial period (run-in, maintenance, or flare treatment), 4 weeks after the last trial treatment.

Trial Endpoints

The protocol-specified primary efficacy endpoint was the flare-free maintenance until onset of first flare during the 52-week double- blind period. Flare was defined as an ISGA score ≥2.

The protocol specified the following key secondary efficacy endpoints during the 52- week double-blind period:

- Number of flare-free days
- Number of flares
- Pruritus response maintenance until onset of first flare

Investigator's Static Global Assessment (ISGA)
The ISGA is a 5-point scale (0-4), reflecting a global assessment of AD severity based on erythema, induration/papulation, and oozing/crusting (Table 1).

Table 1: Investigator's Static Global Assessment

Score	Grade	Definition
0	Clear	Minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting
1	Almost Clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

Source: Protocol, page 43

Statistical Analysis Plan

Analysis Populations:
The protocol and statistical analysis plan (SAP) specified the following analysis sets:

- Evaluable - Open Label (Evaluable-OL) Set: All subjects who received at least 1 dose of trial intervention in the open- label run-in period.
- Safety- Open Label (SAF-OL) Set: All subjects who received at least 1 dose of trial intervention in the open- label run-in period, same definition as Evaluable-OL set.
- Safety - Double-Blind (SAF-DB): All subjects randomly assigned to trial intervention and who take at least 1 dose of trial intervention in the double-blind maintenance period.
- Evaluable - Double-Blind (Evaluable-DB) Set: All randomized subjects with success in ISGA and EASI50 criteria as responders at randomization and who received at least 1 dose of trial intervention in the double-blind maintenance period. Evaluable-DB was specified as the primary analysis population

The definition of the Evaluable-DB in the protocol did not include the ISGA and EASI50 criteria. The protocol defined the Evaluable-DB as all randomized subjects who received at least 1 dose of trial intervention in the double-blind maintenance period. The statistical analysis plan (SAP) version 3 (dated 23 September 2021) modified the definition of the Evaluable-DB population such that only subjects with ISGA success and EASI50 at randomization be included in the Evaluable-DB population. The trial was completed on January 19, 2022.

Analysis Methods:
For the analysis of the primary efficacy endpoint (i.e., time to first flare), a log-rank test, stratified by age group, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization was used to test the difference between crisaborole 2 % versus vehicle. The proportion of subjects maintaining flare-free at each month

until the first flare onset in the maintenance period and the median time of flare-free up until the first flare onset were both estimated by the product limit method. If an intercurrent event (e.g., death, dropout, loss to follow up, or end of trial/study) occurred before the first flare, the duration of flare-free maintenance was considered as the time from randomization to the first intercurrent event and was censored. When a flare occurred first, or a prohibited treatment was used before a flare, the duration of flare-free maintenance was considered as the time from randomization to the first flare or a prohibited treatment use, whichever occurred first, and was not censored.

A sensitivity analysis was performed where flare definition included an AD worsening event reported by a subject prior to a confirmatory ISGA ≥2. In this analysis, the time of onset of such event was used as the onset of the flare. In contrast, under the primary definition, if a subject reported an AD worsening event but the investigator assessment was not a flare at the subsequent visit, this event was not considered a flare. Another sensitivity analysis conducted was interval censoring survival analysis. Time of flare was between the time of subjects reported AD worsening and the time of investigator confirmed ISGA ≥2. Because the exact flare time was not known, the midpoint of the above interval was used as the flare time.

Number of flare-free days was analyzed using an analysis of covariance model, with treatment, age, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization as factors. Addressing intercurrent events for the duration of flare-free maintenance at each flare-free period was the same as that for the primary endpoint during the first flare- free period.

Number of flares was analyzed using Wilcoxon rank sum test stratified by age group, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization. Subjects were ranked according to the number of flares adjusted for length of time in the maintenance period (i.e., if subjects have same number of flares: the subject with longer time in maintenance period received a higher rank; if subjects have the same time in maintenance period as well, the subject with longer time in QD period received a higher rank; subjects who prematurely discontinue the trial for efficacy reasons were ranked below others). Prohibited treatment use was considered as a flare.

Multiplicity Testing Procedure (MTP):

A step-down closed testing procedure and Bonferroni's method was used for Type I error control for testing the primary endpoint and the secondary endpoints. Order of testing was as follows:

1. Flare-free maintenance up until the onset of the first flare during the maintenance period
2. Number of flare-free days over 52 weeks
3. Number of flares over 52 weeks
4. Pruritus response maintenance up until the onset of the first flare (ISGA ≥2), defined as the maintenance of improvement ≥50% (if 50% or more of the improvement in pruritus

from the baseline to the randomization is maintained). Analysis will be performed for 5 responder subgroups:

a) ≥12 years of age with OL baseline Peak Pruritus NRS ≥3 and ≥3 points reduction OL baseline to randomization in Peak Pruritus NRS.
b) ≥12 years of age with OL baseline Peak Pruritus NRS ≥4 and ≥4 points reduction OL baseline to randomization in Peak Pruritus NRS.
c) 6-<12 years of age with OL baseline patient reported itch severity (PRIS) Scale ≥2 and ≥2 points reduction OL baseline to randomization in PRIS Scale.
d) 3 months-<6 years of age with OL baseline observer reported itch severity (ORIS) Scale ≥3 and ≥3 points reduction OL baseline to randomization in ORIS Scale.
e) 3 months-<6 years of age with OL baseline ORIS Scale ≥4 and ≥4 points reduction OL baseline to randomization in ORIS Scale.

The statistical significance was claimed for a given endpoint only if the prior endpoint was significant. For the endpoints of 1-3, the significance level was 0.05. For pruritus response maintenance, Bonferroni's method was used to adjust the significance level. The significance level of 0.01 for each subgroup was used, there was no testing order. Only the subgroup with p-value ≤0.01 claimed significance.

Protocol Amendments

The Applicant submitted one protocol amendment (May 19, 2020). The amendment included the following elements:

- Inclusion of the age group of 3 months to <24 months.
- The Enrolled and Safety – Double-Blind populations were added.
- "Duration of the BID treatment in open-label period" was added as a stratification factor for the primary and secondary analyses.

8.1.2. Study Results including sensitivity and supplementary analyses

Compliance with Good Clinical Practices

According to the submission, the Applicant conducted all clinical trials in the development program in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki, and in compliance with FDA regulations for informed consent and protection of patient rights as described in 21 CFRs 50, 56, and 312. Institutional Review Boards/Independent Ethics Committees approved the protocols. The Sponsor or appointed Contract Research Organizations conducted regular monitoring by including periodic site visits to investigators

with review of all reported SAEs and other relevant efficacy data resulting in assurance of quality without the knowledge of any critical or major monitoring observations. The standards of the ICH Guideline for Structure and Content of Clinical Study Reports (CSR: ICH-E3) guided the content and format of the CSR.

Financial Disclosure

The Applicant submitted the required certification and disclosure information for participating investigators (Forms 3454 and 3455). Refer to Section 16.2 Financial Disclosure of this review for additional information.

Patient Disposition

A total of 497 subjects were enrolled in the trial and received crisaborole BID during the OL run-in period. The trial was conducted at 42 sites in 6 countries, including the US, Australia, Canada, China, Israel, and Turkey. Out of the 497 subjects enrolled to the OL run-in period, 227 (45.7 %) subjects were not randomized into the DB period. The most common reason for subjects not to be randomized was failure to meet randomization criteria. Table 2 presents disposition for subjects in the OL run-in period.

Table 2: Subjects Disposition (SAF-OL*)

	Crisaborole 2% **N=497**
Randomized to DB	270 (54.3)
Not Randomized to DB (including follow-up period)	227 (45.7)
Adverse event	18 (3.6)
Lost to follow-up	14 (2.8)
Physician's decision	3 (0.6)
Protocol deviation	3 (0.6)
Withdrawal by subject	8 (1.6)
Withdrawal by parent/guardian	18 (3.6)
Failure to meet randomization criteria	152 (30.6)
Other	11 (2.2)

Source: Reviewer's Analysis
***** Safety - Open Label (Eval-OL), all Subjects who received at least 1 dose of trial intervention in the open- label run-in period.

A total of 270 (54.3%) were randomized to the DB period in a 1:1 ratio and received crisaborole ointment, 2%, once daily (QD), or vehicle ointment. Out of the 270 randomized subjects, 55 (40.7%) and 56 (41.5%) subjects discontinued from the crisaborole QD and vehicle QD groups, respectively. The most common reason for discontinuations was lack of efficacy. Table 3 presents disposition for subjects in the maintenance period.

Table 3: Subjects Disposition (SAF-DB*)

	Crisaborole 2% N=135	**Vehicle N=135**
Completed n (%)		
Yes	80 (59.3)	79 (58.5)
No	55 (40.7)	56 (41.5)
Reasons of Discontinuation, n (%)		
Adverse event	1 (0.7)	3 (2.2)
Lack of efficacy	18 (13.3)	23 (17.0)
Lost to follow-up	11 (8.1)	6 (4.4)
Physician's decision	2 (1.5)	0
Pregnancy	0	2 (1.5)
Protocol deviation	3 (2.2)	1 (0.7)
Withdrawal by subject	12 (8.9)	7 (5.2)
Withdrawal by parent/guardian	6 (4.4)	8 (5.9)
Other	2 (1.5)	6 (4.4)

Source: Reviewer's Analysis

***** Safety - Double-Blind (SAF-DB), all subjects randomly assigned to trial intervention and who take at least 1 dose of trial intervention in the double-blind maintenance period.

Protocol Violations/Deviations

The Applicant randomized 270 subjects, however 16 of those subjects did not meet the responder definition for randomization (6 subjects from the vehicle arm and 10 subjects from the crisaborole arm). A responder was defined as a subject with an ISGA score of clear [0] or almost clear [1], with a ≥2 grade improvement from baseline AND a 50% change from baseline on the eczema area and severity index (EASI). This reviewer explored the 16 subjects in terms of ISGA randomization criteria:

- 13 subjects failed ISGA randomization criteria (3 of those failed EASI-50 randomization criteria and 10 did not fail EASI-50 randomization criteria). Out the 13 subjects, 9 subjects had an ISGA DB baseline score of 1, however they failed to achieve the ≥2 grade improvement from OL run-in period baseline. A majority of those 9 subjects (6 subjects) were from the same site (site 1080, in the USA).
- 3 subjects did not fail ISGA randomization criteria, however they failed the EASI-50 randomization criteria.

Table 4: Failures to meet randomization criterion (SAF-DB*)

Met the ISGA criteria (clear [0] or almost clear [1] with ≥2 grades reduction from baseline)		Met the EASI 50 criteria		Total
		No	Yes	
No	Baseline ISGA (DB) = almost clear [1] (but not ≥2 grades reduction from baseline)	0	9	9
	Baseline ISGA (DB) = mild [2]	0	1	1
	Baseline ISGA (DB) = moderate [3]	3	0	3
Yes	Baseline ISGA (DB) = almost clear [1] (and ≥2 grades reduction from baseline)	3	0	3
Total		6	10	16

Source: Reviewer's Analysis

* Safety - Double-Blind (SAF-DB), all Subjects randomly assigned to trial intervention and who take at least 1 dose of trial intervention in the double-blind maintenance period.

Table of Demographic Characteristics and Other Baseline Characteristics

A total of 254 (94.1) out of the 270 randomized subjects were responders. Table 5 presents the demographics and baseline disease characteristics for responders randomized into the maintenance period. The demographics and baseline disease characteristics were generally balanced across the two treatment groups for the randomized maintenance period.

Table 5: Demographics and Baseline Disease Characteristics (Eval-DB *)

	Crisaborole 2% (N=125)	Vehicle (N=129)	Total (N=254)
Age, years			
Mean (SD)	22.10 (19.85)	20.98 (20.06)	21.53 (19.93)
Median	14.45	13.20	14.00
Range	1.15-79.13	0.45-76.11	0.45-79.13
Sex, n (%)			
Male	56 (44.8)	59 (45.7)	115 (45.3)
Female	69 (55.2)	70 (54.3)	139 (54.7)
Race, n (%)			
White	49 (39.2)	50 (38.8)	99 (39.0)
Black or African American	38 (30.4)	45 (34.8)	83 (32.7)
Other	38 (30.4)	34 (26.4)	58 (28.3)
Ethnicity, n (%)			
Hispanic or Latino	18 (14.4)	0 (7.0)	27 (10.6)
Not Hispanic or Latino	107 (85.6)	120 (93.0)	111 (89.4)
Country, n (%)			
America	90 (72.0)	88 (68.2)	178 (70.1)
Australia	12 (9.6)	14 (10.9)	26 (10.2)
Canada	4 (3.2)	(6.2)	12 (4.7)
China	15 (12.0)	15 (11.6)	30 (11.8)
Israel	2 (1.6)	3 (2.3)	5 (2.0)
Turkey	2 (1.6)	1 (0.8)	3 (1.2)

	Crisaborole 2% (N=125)	Vehicle (N=129)	Total (N=254)
Investigator's Static Global Assessment (ISGA), n (%)			
0= Clear	48 (38.4)	56 (43.4)	104 (40.9)
1 = Almost clear	77 (61.6)	73 (56.6)	150 (59.1)
Eczema Area and Severity Index (EASI) Score			
Mean (SD)	1.5 (1.6)	1.5 (2.1)	1.6 (1.9)
Median	1.2	0.9	1.0
Range	0.0 – 7.0	0.0 – 13.4	0.0-13.4

Source: Reviewer's Analysis
***** Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
During the double-blind period, the protocol defined compliant subjects as those who received 80-120% of the expected number of doses. In both treatment groups, the compliance was 99% among subjects without missing data.

Concomitant Medications
At baseline, 70% of subjects received concomitant medications. The most common concomitant medications included: antihistamines, emollients, albuterol, and corticosteroids.

Rescue Medication
The study design did not include rescue medication. Subjects who developed an ISGA ≥ 2 during the double- blind period with once daily dosing of the study product received twice daily dosing with crisaborole.

Efficacy Results – Primary Endpoint

Table 6 presents the results for the primary efficacy endpoint (i.e., flare-free maintenance until onset of first flare during the 52-week double- blind period). The results indicates that crisaborole 2% group was statistically superior compared to the vehicle group (p-value =0.0034). The median time of flare-free maintenance was 111 days in crisaborole 2% group compared to 30 days in the vehicle group. A lower proportion of subjects with first flare was observed in the crisaborole 2% group (64.8 %) compared to the vehicle group (74.4 %).

Table 6: Analysis of Flare-Free Maintenance until Onset of First Flare (Eval-DB*)

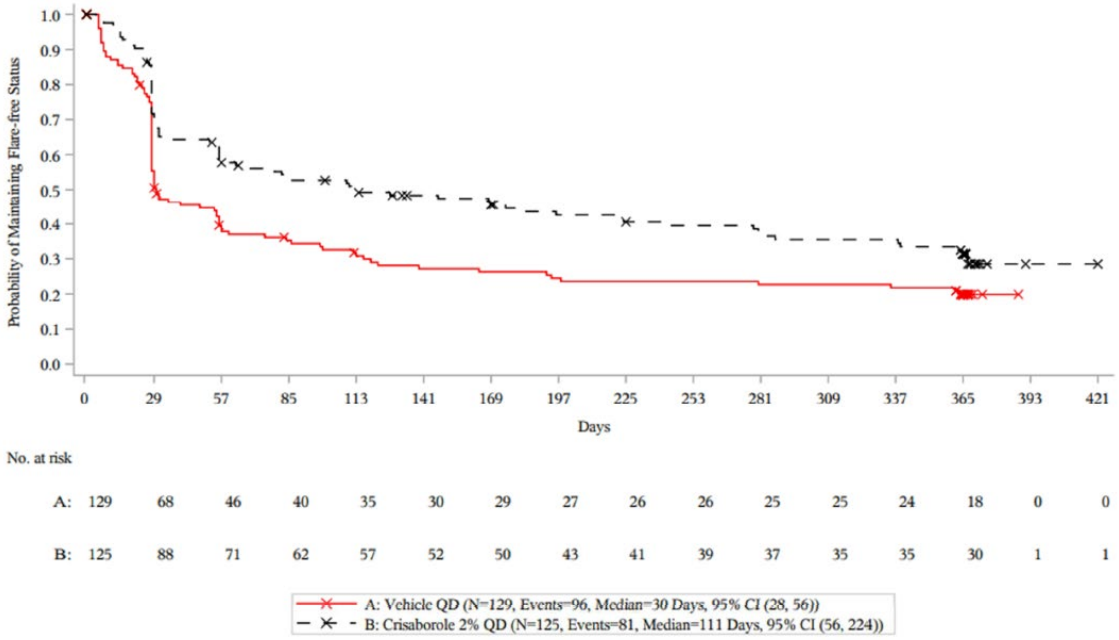
	Crisaborole 2% N=125	Vehicle N=129
Subjects with First Flare, n (%)	81 (64.8)	96 (74.4)
Subjects Censored, n (%)	44 (35.2)	33 (25.6)
Median (95% CI) **	111 (56,224)	30 (28,56)

	Crisaborole 2% N=125	Vehicle N=129
Stratified Log-rank Test p-value***	0.0034	---

Source: Reviewer's Analysis (same results as Applicant's analysis)
* Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.
** Estimated by the Kaplan-Meier (product limit) method
*** Estimated by the log-rank test, stratified by age group, duration of the BID treatment in OL period, and ISGA score at randomization.

Figure 2 presents the results of probability of maintaining flare-free status from baseline (Day 0) through Week 52 (Day 365). Crisaborole 2% consistently showed a higher probability of maintaining flare-free status compared to vehicle, with of probability of maintaining flare-free status for crisaborole 2% arm relatively flat compared to the vehicle arm.

Figure 2: Kaplan-Meier Plot with Maintenance of Pruritus Response until Onset of First Flare - Eval-DB (Eval-DB*)



Source: Reviewer's Analysis (same results as Applicant's analysis)
* Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

The Agency advised the Applicant during the development program at a guidance meeting (held on 4/11/2018) and in an Advice Letter (dated 12/23/2019) that the recommended primary endpoint is the proportion of subjects who maintain their response (i.e., ISGA of 0 or 1) at a prespecified timepoint during the maintenance period. Because the Applicant never specified a specific timepoint to assess maintenance of response, this reviewer explored the proportion of subjects who maintained their response over the maintenance period at all different timepoints. Table 7 presents the proportion of subjects maintaining response (ISGA score of clear [0] or almost clear [1]) from Week 4 through Week 52. The proportion of subjects

maintaining response in the crisaborole 2% QD group was higher than that in the vehicle QD group at each timepoint. Because this endpoint was not prespecified and included in the multiplicity control scheme the p-values are not interpretable, however, the proportion of subjects maintaining response was <0.05 only for Week 4 through Week 32.

Table 7: Proportion of subjects maintaining response by timepoint (Eval-DB*)

	Crisaborole 2% N=125 n (%)	Vehicle N=129 n (%)	Response Rate Difference ** % (95% CI)	p-value**
Week 4	80 (64.0)	57 (44.2)	19.2 (6.9, 30.8)	0.002
Week 8	69 (55.2)	44 (34.1)	20.0 (7.8, 31.5)	0.001
Week 12	62 (49.6)	39 (30.2)	18.9 (6.8, 30.3)	0.002
Week 16	58 (46.4)	33 (25.6)	20.1 (8.2, 31.2)	0.001
Week 24	48 (38.4)	29 (22.5)	15.6 (4.2, 26.5)	0.007
Week 32	41 (32.8)	26 (20.2)	12.4 (1.5, 23.1)	0.022
Week 40	36 (28.8)	25 (19.4)	9.1 (-1.6, 19.5)	0.082
Week 48	33 (26.4)	24 (18.6)	7.1 (-3.3, 17.4)	0.159
Week 52	30 (24.0)	22 (17.1)	6.4 (-3.7, 16.4)	0.192

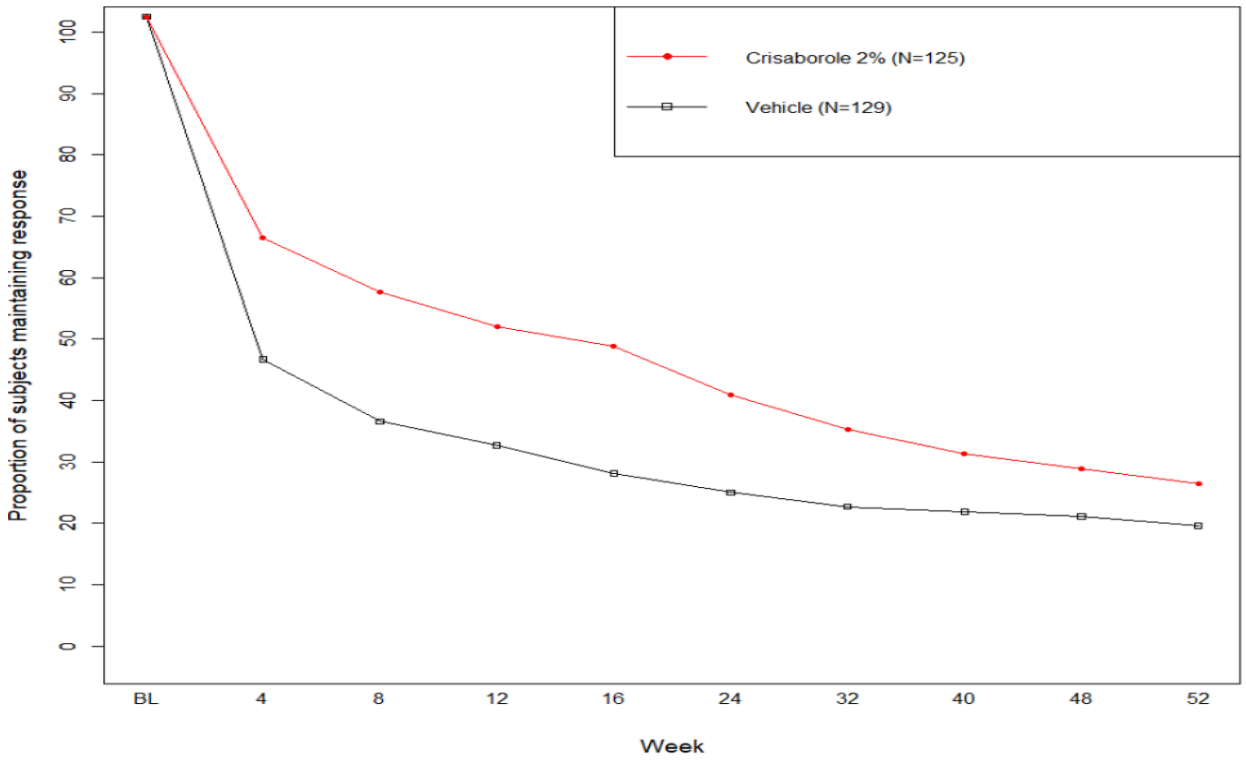
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

*Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

** Response rate difference, CI and p-value are calculated using Cochran Mantel Haenszel (CMH) weight method stratified by age group (3 months-<12 years, >=12 years), duration of the BID treatment in OL period (<=4, >4 weeks), and ISGA score (clear [0], almost clear [1]) at randomization

Figure 3 presents the results of proportion of subjects maintaining response from baseline through Week 52 (N=254 subjects who met the prespecified enrollment criteria in the SAP). Crisaborole 2% showed a higher proportion of subjects maintaining response compared to vehicle.

Figure 3: Proportion of subjects maintaining response from Baseline through Week 52 (Eval-DB*)



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)
*Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

Sensitivity Analysis– Primary Endpoint

As mentioned, 16 subjects were randomized without meeting the responder definition of success in ISGA and EASI50 criteria, those 16 subjects were excluded from the evaluable-double blind (Eval-DB) analysis population, however this reviewer explored the proportion of subjects maintaining ISGA response in safety-double blind (SAF-DB) analysis population (N=270 subjects as randomized). Table 8 presents results from the SAF-DB analysis population for the proportion of subjects maintaining response (ISGA score of clear [0] or almost clear [1]) from Week 4 through Week 52 in the crisaborole 2% QD group was higher than that in the vehicle QD group, however the p-values for the proportion of subjects maintaining response was <0.05 only for Week 4 through Week 40.

Table 8: Proportion of subjects maintaining response by timepoint (SAF-DB *)

	Crisaborole 2% N=135 n (%)	Vehicle N=135 n (%)	Response Rate Difference ** % (95% CI)	p-value**
Week 4	86 (63.7)	58 (43.0)	20.9 (8.9, 32.4)	0.001
Week 8	72 (53.3)	45 (33.3)	19.8 (7.8, 31.0)	0.001
Week 12	65 (48.2)	40 (29.6)	18.6 (6.8, 29.7)	0.002
Week 16	61 (45.2)	33 (24.4)	20.6 (9.1, 31.4)	0.0004
Week 24	51 (37.8)	29 (21.5)	16.4 (5.3, 26.9)	0.003
Week 32	44 (32.6)	26 (19.3)	13.3 (2.7, 23.6)	0.012
Week 40	39 (28.9)	25 (18.5)	10.2 (-0.2, 20.3)	0.044
Week 48	35 (25.9)	24 (17.8)	7.7 (-2.4, 17.6)	0.117
Week 52	32 (23.7)	22 (16.3)	7.1 (-2.7, 16.7)	0.137

Source: Statistical Reviewer's Analysis

*Safety - Double-Blind (SAF-DB), all Subjects randomly assigned to trial intervention and who take at least 1 dose of trial intervention in the double-blind maintenance period.

** Response rate difference, confidence interval (CI) and p-value are calculated using Cochran Mantel Haenszel (CMH) weight method stratified by age group (3 months-<12 years, >=12 years), duration of the BID treatment in OL period (<=4, >4 weeks), and ISGA score (clear [0], almost clear [1]) at randomization

This reviewer also explored the Applicant's primary efficacy endpoint (i.e., flare-free maintenance until onset of first flare during the 52-week double- blind period) for the SAF-DB population. Table 9 presents the results of the analysis, indicating that crisaborole 2% group was statistically superior compared to the vehicle group (p-value =0.0025). The median time of flare-free maintenance was 110 days in crisaborole 2% group compared to 29 days in the vehicle group. A lower proportion of subjects with first flare was observed in the crisaborole 2% group (64.4 %) compared to the vehicle group (74.8 %).

Table 9: Analysis of Flare-Free Maintenance until Onset of First Flare (SAF-DB*)

	Crisaborole 2% N=135	Vehicle N=135
Subjects with First Flare, n (%)	87 (64.4)	101 (74.8)
Subjects Censored, n (%)	48 (35.6)	34 (25.2)
Median (95% CI) **	110 (56,224)	29 (28,55)
Stratified Log-rank Test p-value***	0.0025	---

Source: Reviewer's Analysis

***** Safety - Double-Blind (SAF-DB), all Subjects randomly assigned to trial intervention and who take at least 1 dose of trial intervention in the double-blind maintenance period.

****** Estimated by the Kaplan-Meier (product limit) method

******* Estimated by the log-rank test, stratified by age group, duration of the BID treatment in OL period, and ISGA score at randomization.

CI=confidence interval

Findings in Special/Subgroup Populations– Primary Endpoint

Table 10 presents the results of the protocol-specified primary efficacy endpoint (i.e., flare-free maintenance until onset of first flare during the 52-week double- blind period) by race, age, number of OL weeks before randomization and ISGA score at randomization. Subjects in the crisaborole group experienced a longer duration of flare-free maintenance until onset of first flare compared with the vehicle group for all subgroups. The small sample size in some of the subgroups limits the interpretation.

Table 10: Analysis of Flare-Free Maintenance until Onset of First Flare (Eval-DB*)

Subgroups (n [crisaborole 2%], n[vehicle])		**Crisaborole 2% Median (95% CI) ****	**Vehicle Median (95% CI) ****
Overall (125,129)			
Race	White (49,50)	56 (30, 111)	28 (27, 31)
	Black or African American (38,45)	365 (33, -)	57 (29, 280)
	Other (38,34)	181 (69, -)	29 (28,122)
Age	3 month - >12 years (47,60)	56 (30, 224)	28 (28, 56)
	>=12 Years (78,69)	175 (79, 364)	31 (28, 84)
Number of Run-in Weeks	<= 4 Weeks (36,41)	84 (30, 287)	28 (28, 35)
	> 4 Weeks (89,88)	169 (56, 280)	48 (28, 75)
ISGA Score at Randomization	Clear (ISGA =0) (48,56)	111 (56, .)	56 (28, 194)
	Almost clear (ISGA=1) (77,73)	111 (30, 224)	29 (28, 35)

Source: Reviewer's Analysis(same as Applicant's analysis)

***** Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

****** Estimated by the Kaplan-Meier (product limit) method

CI=confidence interval

Data Quality and Integrity

This reviewer identified no major issues with data quality and integrity during the review of the data from Trial C3291035. However, because of the lack of specificity in the protocol regarding the criteria for randomization, some subjects were randomized to the double- blind period who

did not meet the criteria for treatment success as defined in the statistical analysis plan. See Section 8.3.

In addition, no clinical sites required inspection. See Section 4.1.

Efficacy Results – Secondary and other relevant endpoints

Table 11 presents result for the analysis of the number of flare-free days. Subjects in the crisaborole 2% group experienced 34.59 ± 16.27 more flare free days during the 52-week DB period in comparison with subjects in the vehicle group (p-value 0.0346)

Table 11: Analysis of Number of Flare-Free Days (Eval-DB*)

	Crisaborole 2% N=125	**Vehicle N=129**
LS mean (SE)	234.01 (12.32)	199.42 (11.82)
Treatment difference (SE) **	34.59 (16.27)	---
95% CI **	(2.53, 66.64)	---
p-value**	0.0346	---

Source: Reviewer's Analysis (same results as Applicant's analysis)

* Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.

** Analysis of covariance (ANCOVA) model that includes fixed effects of treatment group, age group, duration of the BID treatment in OL period, and ISGA score at randomization.

LS=Least squares, SE=standard error, CI=confidence interval, Treatment difference = Crisaborole - Vehicle

Table 12 presents result for the analysis of the total number of flares. The median difference (Crisaborole - Vehicle) in total number of flares was -0.50 flares during the 52-week DB period (p-value= 0.0042).

Table 12: Analysis of Total Number of Flares (Eval-DB*)

	Crisaborole 2% N=125	**Vehicle N=129**
Mean	0.95	1.36
Median	1.00	1.00
Median difference **	-0.5	---
Median difference (95% CI) **	(-1.00, 0.00)	---
p-value***	0.0042	---

Source: Reviewer's Analysis (same results as Applicant's analysis)

* Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period.
** Estimated by the Hodges-Lehmann method. Treatment difference = Crisaborole – Vehicle
*** Estimated by Wilcoxon rank sum test stratified by age group, duration of the BID treatment in OL period, and ISGA score at randomization.

Table 13 presents the frequency of total number of flares. In the trial, 99 (79.2%) subjects in the crisaborole 2% group had 0 or 1 flare compared with 84 (65.1%) subjects in the vehicle experienced 0 or 1 flare.

Table 13: Frequency of Total Number of Flares (Eval-DB*)

Total Number of Flares	Crisaborole 2% N=125	Vehicle N=129
0	44 (35.20)	33 (25.58)
1	55 (44.00)	51 (39.53)
2	19 (15.20)	23 (17.83)
3	2 (1.60)	14 (10.85)
4	5 (4.00)	5 (3.88)
5	0 (0.0)	2 (1.55)
6	0 (0.0)	1 (0.78)

Source: Reviewer's Analysis (same results as Applicant's analysis)
*Evaluable-DB (Eval-DB), all randomized subjects with success in ISGA and EASI50 criteria as responders and received at least 1 dose of trial intervention in the DB period

Durability of Response/ Persistence of Effect

The Applicant did not conduct an assessment of durability of response or persistence of effect of the approved dosing regimen.

Efficacy Results – Secondary COA (PRO) endpoint

The third key secondary endpoint was "pruritus response maintenance until onset of first flare". (b) (4)

(b) (4)

(b) (4)

[redacted]

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary source of data to support the safety of EUCRISA® (crisaborole) ointment, 2% for maintenance treatment and "flare reduction" in adult and pediatric patients with mild to moderate atopic dermatitis was Trial C3291035. The Applicant conducted a single randomized, double-blind, vehicle-controlled, phase 3 trial (C3291035) that enrolled 497 subjects 3 months of age and older with mild to moderate atopic dermatitis. The design of Trial C3291035 included two primary treatment periods: an open-label (OL) period during which subjects received twice daily applications of crisaborole for up to 8 weeks. Responders at any time during the OL period were randomized 1:1 to receive once daily applications of crisaborole or vehicle for 52 weeks during the double- blind (DB) period. Subjects who developed a flare of AD according to ISGA (ISGA ≥2) during the DB period received twice daily (BID) applications of crisaborole.

Enrolled subjects met the following criteria at Baseline:

- Confirmed clinical diagnosis of AD according to the criteria of Hanifin and Rajka
- AD treatment naïve, prior non-responder to emollient use, or previously received topical corticosteroids (TCSs) or topical calcineurin inhibitor (TCIs).
- AD involvement of ≥5% Treatable %BSA (excluding the scalp) at entry into the OL period.
- ISGA score of Mild (2) or Moderate (3) at entry into the OL period.

Because the FDA informed the Applicant that findings from a single trial needed to be robust to support a maintenance claim, the submission included safety data from seven other trials to establish a "favorable safety profile" for this intended use. However, these trials (C3291001, C3291029, C3291028, C3291032, C3291037, C3291002, C3291027) evaluated the effects of EUCRISA using different study designs, dosing regimens, randomization ratios and durations of therapy in different study populations. As such, the integrated data is difficult to interpret and does not directly support the safe use of crisaborole ointment once daily for maintenance

treatment. Therefore, data from these seven trials will be evaluated and briefly discussed separately with the objective of safety signal detection.

Also, the Applicant provided additional safety data in the 120-Day safety update report (SUR) (SDN 1692 dated October 7, 2022).

The review team analyzed following types of data: exposure, demographics and baseline characteristics, treatment-emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation from the trial, and other abnormal findings observed on physical examination and vital signs.

The primary populations used in the analysis of safety for Trial C3291035 were:

- Safety-open label (OL): SAF-OL which included all subjects who received at least one dose of study medication during the open label period.
- Safety-double blind (DB): SAF-DB which included all randomized subjects who received at least one dose of study medication during the double- blind period. Analyses of findings that occurred during a flare (ISGA ≥2 triggering BID treatment with crisaborole) were separate from analyses of assessments during maintenance with once daily treatment with crisaborole or vehicle. According to the statistical analysis plan, subjects enrolled in the DB period were treatment responders on ISGA and EASI50.

8.2.2. Review of the Safety Database

Overall Exposure

The design of Trial C3291035 included two primary treatment periods: an open-label (OL) "run-in" period for up to 8 weeks and a double-blind (DB) maintenance period for up to 52 weeks. At baseline in the DB maintenance period, investigators determined the "treatable BSA" for each subject "based on the %BSA of the most commonly affected skin areas that are identified and recorded on the AD lesion checklist." Daily applications of the study product continued even if the most commonly affected areas appeared "normal". All new lesions were treated.

The approximate dose of the study product was 3 mg/cm^2. Investigators calculated the dose for each subject based on the %BSA affected by AD adjusted by height and weight using an unspecified "tool" provided by the Applicant. Stable regimens of bland (non-medicated) emollient(s) were permitted during the trial if not applied to treatment areas within 60 minutes before or after dosing with the study product. Investigators monitored compliance with the prespecified dosing regimen using a "dosing diary."

Treatment duration, number of applications, number of dosing days and amount of product used varied widely.

Table 14: Exposure and Compliance-Open-label period

Crisaborole 2% BID (N=497)	
Duration of Treatment (days)	
n	493
Mean (SD)	46 (17)
Median (Range)	55 (4, 121)
Total Number of Applications	
n	492
Mean (SD)	90 (34)
Median (Range)	110 (0, 232)
Total Number of Days of Dosing	
n	493
Mean (SD)	46 (17)
Median (Range)	55 (4, 121)
Amount of Intervention Used, g	
n	432
Mean (SD)	405 (537)
Median (Range)	237 (3, 5034)
Compliance, n (%)	
Yes	483 (98)
No	9 (2)

Source: Modified from Table 14.4.1.1 Crisaborole from the CSR C3291035
Compliant: received 80-120% of the expected number of doses

Table 15: Exposure and Compliance-Double- blind period

	Vehicle QD (N=135)	Crisaborole 2% QD (N=135)
Duration of Treatment (days)		
n	129	132
Mean (SD)	209 (135)	237 (129)
Median (Range)	246 (6, 396)	283 (2, 420)
Total Number of Applications		
n	129	131
Mean (SD)	207 (135)	236 (130)
Median (Range)	245 (6, 396)	283 (2, 420)
Total Number of Days of Dosing		
n	129	132
Mean (SD)	209 (135)	237 (129)
Median (Range)	246 (6, 396)	283 (2, 420)
Amount of Intervention Used, g		

	Vehicle QD (N=135)	Crisaborole 2% QD (N=135)
n	100	100
Mean (SD)	771 (993)	886 (1284)
Median (Range)	404 (5, 5027)	486 (5, 7507)
Compliance, n (%)		
Yes	127 (98)	130 (99)
No	2 (2)	1 (1)

Source: Modified from Table 14.4.1.2 Crisaborole from the CSR C3291035

Table 16: Exposure and Compliance-Double-blind period during Flares

	Vehicle QD (N=135)	Crisaborole 2% QD (N=135)
Duration of Treatment (days)		
n	88	78
Mean (SD)	109 (74)	84 (60)
Median (Range)	85 (21, 338)	82 (12, 346)
Total Number of Applications		
n	88	78
Mean (SD)	215 (147)	164 (119)
Median (Range)	168 (42, 676)	155 (24, 692)
Total Number of Days of Dosing		
n	88	78
Mean (SD)	109 (74)	84 (60)
Median (Range)	85 (21, 338)	82 (12, 346)
Amount of Intervention Used, g		
n	71	67
Mean (SD)	543 (873)	395 (447)
Median (Range)	356 (6, 7047)	217 (2, 2066)
Compliance, n (%)		
Yes	87 (99)	77 (99)
No	1 (1)	1 (1)

Source: Modified from Table 14.4.1.3 Crisaborole from the CSR C3291035

During the DB period, subjects randomized to once daily maintenance therapy with crisaborole used more active product overall (administration QD crisaborole during maintenance plus administration BID for flare=mean 886+395 grams) than subjects randomized to once daily maintenance therapy with vehicle (administration of BID crisaborole for flare=mean 543 grams). See tables above. As such, subjects randomized to active treatment QD compared to vehicle QD had greater overall exposure to crisaborole. Greater exposure in the long- term may increase the risk for rare but potentially serious adverse events such as hypersensitivity

reactions.

By comparison, the Applicant explored another maintenance dosing strategy in an open-label, 52-week, long- term safety trial, AN2728-AD-303, that enrolled 517 subjects who completed one of the phase 3 trials (AN2728-AD-301 or AN2728-AD-302). Crisaborole was used as maintenance therapy BID only as needed when the ISGA became ≥2. This design reflected real world conditions of use. The mean and median total usage of crisaborole with intermittent twice daily applications in Trial AN2728-AD-303 (760 g and 435 g, respectively) was less than in Trial C3291035 with chronic once daily use of crisaborole with twice daily use for flares of AD (mean: 886 + 395 g and median: 486 +217 g). Data from cross study comparisons should be interpreted with caution. However, the data also supports the observation that maintenance dosing QD increases the overall use of crisaborole in the long- term. (See Clinical Review dated November 3, 2016).

Relevant characteristics of the safety population

During the double-blind period, the demographics of the safety population were similar to the demographics of the ITT population. Overall, the majority of the subjects were female (54%) and not Hispanic or Latino (85%). The median duration since diagnosis was 10 years (range 0 years to 50 years). All subjects had a history of prior treatment for AD. Most subjects were White (40%), Black /African American (33%) or Asian (20%). The mean age was 22 years. The age groups with the fewest subjects were: 3-<24 months [8 subjects (3%)] and 12 -<18 years [55 subjects (20%)]. The majority of subjects were in the age groups 2-<12 years [103 (38%) subjects] and ≥18 years [104 (39%) subjects]. Overall, the demographic characteristics were balanced across treatment groups and study periods.

Refer to Table 5 for a summary of the baseline characteristics of the study population.

Adequacy of the safety database:

Crisaborole ointment is an approved product. The safety of BID dosing was established for pediatric and adult patients 3 months of age and older. The total exposure to crisaborole ointment which was administered QD for up to 52 weeks in Trial C3291035 provides adequate data for the evaluation of safety. The demographics of the trial population are sufficiently representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the safety profile of crisaborole ointment for the maintenance treatment of mild to moderate AD in adult and pediatric patients 3 months of age and older. The Applicant submitted additional safety data from seven trials that is supportive of the overall safety of crisaborole ointment in various populations and for various durations of treatment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

We evaluated data quality and fitness in conjunction with the Office of Computational Science (OCS) Clinical Services team. Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of crisaborole ointment. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

Phase 3 protocol C3291035 defined an adverse event (AE) as

- "An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention."

This definition includes clinically significant abnormal laboratory test results, an exacerbation of a chronic or intermittent pre-existing condition, a new condition detected or diagnosed after study intervention, a suspected drug-drug interaction or overdose or the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy.

A serious adverse event (SAE) is defined as "any untoward medical occurrence that, at any dose":

a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent disability/incapacity
e. Is a congenital anomaly/birth defect
f. Other situations: as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

According to the protocol, investigators reported all SAEs and exposures to the study product during pregnancy and lactation to the Sponsor within 24 hours. Investigational staff recorded all non-serious AEs and SAEs on the Case Report Forms. For all AEs and SAEs, the investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information, determined the intensity and relationship to the study intervention, and scheduled supplemental assessments and follow-up as medically indicated or requested by Pfizer.

Assessment of Intensity Categories

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort

and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An AE defined as "related" had a "reasonable possibility" of a relationship to the study intervention. Facts, evidence, and/or arguments supported a causal relationship and alternative etiologies were considered in the determination.

Routine Clinical Tests

Investigators monitored the safety of crisaborole ointment in Trial C3291035 by documenting AEs, concomitant medications, complete or targeted physical examinations (skin, heart, lungs, abdomen, and symptom directed body system) with vital signs (temperature and pulse) and pregnancy testing at every visit. An active assessment of local safety was not conducted as recommended.

The safety evaluation at Screening included laboratory parameters (hematology and serum chemistry) and administration of the Columbia Suicide Severity Rating Scale (C-SSRS). In view of the well characterized safety profile of this topical product, routine laboratory testing was not included in the protocol. The emergence or worsening of depression, suicidal thoughts or other mood changes are class effects observed with orally administered phosphodiesterase 4 inhibitors (Warnings and Precautions for DALIRESP and OTEZLA). Therefore, investigators administered the Columbia Suicide Severity Rating Scale (C-SSRS) to subjects 7 years of age and older to exclude children and adults at increased risk for potential adverse events related to suicidal ideation and behavior. For children younger than 7 years old, investigators determined eligibility in consultation with parents/caregivers for participants < 7 years at Screening. Investigators performed the Hospital Anxiety and Depression Scale (HADS) at Baseline, end of the run-in period, Weeks 8, 16, 32 and 52.

8.2.4. Safety Results

Deaths

There were no reports of death in Trial C3291035.

Serious Adverse Events

Open-label (OL) Period

During the open label period of Trial C3291035, 3 subjects (3/497; 0.6%) developed 5 serious adverse events (SAEs). One subject developed an exacerbation of AD and cutaneous infection

both at the application site and surrounding skin which resulted in hospitalization. These SAEs was considered related. Two subjects developed SAEs of acute exacerbation of asthma and bronchospasm, respectively, which were considered unrelated to the study product.

Preferred Term	Crisaborole 2% BID N=497 Subject Count (%)
Application site infection	1 (<1)
Skin infection	1 (<1)
Asthma	1 (<1)
Bronchospasm	1 (<1)
Dermatitis Atopic	1 (<1)

Source: Reviewer's table <1%=0.2%

Brief narratives are below.

- 16- year- old Asian male (Subject (b) (6) from China with a history of allergic rhinitis and cutaneous infections developed SAEs of **worsening of atopic dermatitis** on Day 32, **skin infection of application and non-application sites** on Day 40 of twice daily dosing of crisaborole. At Baseline, the subject had 72% body surface area (BSA) involvement, ISGA grade of moderate and an EASI score of 24.1. His status worsened despite treatment with oral antibiotics (no pretreatment culture was documented). The subjects was hospitalized and received ciclosporin, an antiviral agent, traditional Chinese medicine, laser treatments, and topical and oral corticosteroids. The SAEs of worsening of dermatitis atopic, application site and non-application site skin infection were considered moderate in severity, **related** to the investigational product (IP) and resolved on Day 46. The subject did not enroll in the randomized, controlled portion of the trial and permanently withdrew.
- 40-year-old Black/African American male (Subject (b) (6) with a history of hypertension and recent bronchitis and cocaine use developed severe **bronchospasm,** shortness of breath and chest pain on Day 52 of twice daily dosing of crisaborole. The echocardiogram and electrocardiogram were normal. The subject received azithromycin, methylprednisolone, and budesonide/formoterol fumarate and salbutamol with resolution of his SAE. The SAE was considered **not related** to the IP. The subject discontinued the IP and withdrew from the trial due to a protocol violation, use of high dose corticosteroid.
- 2-year-old White male (Subject (b) (6) with asthma and food allergies developed a severe **exacerbation of asthma** requiring hospitalization on Day 3 of twice daily dosing of crisaborole. He received oxygen, albuterol nebulization, intravenous (IV) magnesium sulfate, fluids and oral prednisone. The SAE resolved on Day 5 and the subject continued in the trial. The SAE of exacerbation of asthma was considered **not related**. The subject withdrew from the trial for lack of efficacy on Day 147 after he was randomized to vehicle during the maintenance period.

Double-Blind (DB) Period

All SAEs that developed in the DB period of Trial C3291035, were considered **not related** to the investigational product (IP).

Flare-free (ISGA ≤ 1: clear or almost clear) interval

A total of 2 subjects (2/135; 1.5%) who received crisaborole ointment once daily (QD) developed 3 SAEs (Cardiac failure congestive, Cardiomyopathy and Osteomyelitis) while 3 subjects (3/135; 2.2%) who received vehicle QD developed 3 SAEs (pregnancy).

Preferred Term	Crisaborole 2% QD N=135 Subject Count (%)	Vehicle QD N=135 Subject Count (%)
Cardiac failure congestive	1 (1)	0 (0.0)
Cardiomyopathy	1 (1)	0 (0.0)
Osteomyelitis	1 (1)	0 (0.0)
Maternal exposure during pregnancy	0 (0.0)	2 (2)
Paternal exposure during pregnancy	0 (0.0)	1 (1)

Source: Reviewer's table

- 61-year-old African American female (Subject (b) (6) with a history of hypertension was hospitalized with **cardiac failure congestive and cardiomyopathy** on Day 54 of the trial and Day 11 of QD treatment with crisaborole. An electrocardiogram showed left atrial enlargement and left ventricular hypertrophy, an echocardiogram showed an ejection fraction of 48% and a chest computerized tomography revealed mild intrathoracic lymphadenopathy. The subject permanently discontinued the IP and the SAEs resolved with sequalae.
- 77-year-old American Indian/Alaskan native female (Subject (b) (6) with a history of diabetes mellitus and "spinal osteoarthritis" developed an SAE of **osteomyelitis** of the coccyx on Day 237 of the trial and Day 194 of QD treatment with **crisaborole**. The subject discontinued the IP and was lost to follow-up.
- 34-year-old Black or African American male (Subject (b) (6) who received **vehicle** QD for maintenance treatment reported a **partner pregnancy** on Day 415. His partner smoked and consumed illicit drugs weekly. The obstetrical history was significant for 3 children from 3 pregnancies. She gave birth to a full term, normal male infant. The subject completed the trial.
- 27-year-old White female (Subject (b) (6) who received **vehicle** QD for maintenance treatment reported a **pregnancy** on Day 59. The subject withdrew from the trial and was lost to follow-up.
- 30-year-old Black/African American female (Subject (b) (6) with a history of irregular menses who received vehicle QD for maintenance treatment reported a

pregnancy on Day 126. Her obstetrical history was significant for 2 previous pregnancies with 2 healthy children. The subject did not smoke, drink alcohol, or use illicit drugs during this pregnancy and gave birth to a full-term healthy normal male infant.

Flare (ISGA ≥2) interval

A total of 2 (1.2%) subjects experienced SAEs (**pneumonia and foreign body ingestion**) during a flare of AD while the subjects received BID crisaborole ointment.

- 57-year-old Black/African American male (Subject (b) (6) with a history of diabetes mellitus and hypertension developed pneumonia of moderate severity on Day 88 and was admitted to the intensive care unit (ICU). The subject received intravenous antibiotics and corticosteroids and the SAE resolved on Day 109. The subject discontinued the study product. Investigators withdrew the subject from the trial for protocol violation, use of high dose corticosteroids.
- 3-year-old White female (Subject (b) (6) who was randomized to vehicle and experienced intermittent flares during the double-blind period ingested magnets on Day 135. The foreign bodies were removed during esophagogastroduodenoscopy. The subject remained in the trial after the SAE but later withdrew on Day 310 due to lack of efficacy.

Dropouts and/or Discontinuations Due to Adverse Effects

OL Period

Subjects withdrew from the trial due to TEAEs during each treatment period. Some subjects had study drug discontinuation, dose reduction or temporary discontinuation of the study drug during each treatment period. The greatest proportion of subjects withdrew due to TEAEs during the open-label period (26 subjects, 5%). During the open label period, total of 4 subjects (<1%) discontinued the study drug due to TEAEs but continued in the trial and 3 subjects (<1%) had dose reductions or temporary discontinuations due to TEAEs. Most TEAEs resulting in discontinuation were cutaneous reactions (eczema/ dermatitis atopic, application site pain, application site infection, skin irritation, application site irritation, application site reaction, application site erythema, dermatitis contact and acne.) Other adverse events resulting in discontinuation included: bronchitis, osteoarthritis, bursitis, and hepatic function abnormal.

Table 17: Summary of TEAEs Leading to Discontinuation from the Trial-OL

Preferred Term	Crisaborole 2% BID (N=497) n (%)
Dermatitis atopic	9 (1.8)
Eczema	4 (0.8)
Application site pain	3 (0.6)
Dermatitis contact	3 (0.6)
Application site infection	2 (0.4)
Application site irritation	2 (0.4)
Maternal exposure during pregnancy	2 (0.4)
Acne	1 (0.2)
Application site erythema	1 (0.2)
Application site reaction	1 (0.2)
Bronchitis	1 (0.2)
Bursitis	1 (0.2)
Cardiac failure congestive	1 (0.2)
Cardiomyopathy	1 (0.2)
Hepatic function abnormal	1 (0.2)
Osteoarthritis	1 (0.2)
Skin infection	1 (0.2)
Skin irritation	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Crisaborole 2% BID" and SAFFL = "Y" (Crisaborole 2% BID); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

DB period

During the DB period with once daily dosing, the proportion of subjects who withdrew from the trial due to TEAEs was well balanced between treatment groups. None of the TEAEs was considered related to treatment. One subject (1%) in the crisaborole group and 3 subjects (2%) in the vehicle group discontinued due to TEAEs (eczema/dermatitis atopic). Among subjects receiving crisaborole BID for flares of AD, one subject (1%) originally randomized to crisaborole and 2 subjects (2%) originally randomized to vehicle withdrew from the trial due to TEAEs. No subjects withdrew from the DB period due to adverse reactions (ARs). In addition, two of the subjects in the vehicle group discontinued the trial due to pregnancy.

Table 18: Summary of TEAEs Leading to Discontinuation from the Trial-DB Period

Preferred Term	Crisaborole QD (N=135) n (%)	Vehicle QD (N=135) n (%)
Cardiac failure congestive	1 (0.7)	0 (0.0)
Cardiomyopathy	1 (0.7)	0 (0.0)
Dermatitis atopic	1 (0.7)	2 (1.5)
Eczema	0 (0.0)	1 (0.7)
Maternal exposure during pregnancy	0 (0.0)	2 (1.5)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFL = "Y" (Crisaborole QD); TRT02A = "Vehicle QD" and SAFFL = "Y" (Vehicle QD); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Significant Adverse Events

The protocol for Trial C3291035 did not pre-specify adverse events of special interest (AESI). However, in response to Agency recommendations, the Applicant designated narratives for TEAEs related to hypersensitivity, contact dermatitis and diarrhea/vomiting as AESI. The Applicant selected the adverse events of diarrhea and vomiting because they represented potential class effects that were associated with PDE4 inhibitors.

Other class effects such as anxiety/depression/suicidal ideation and weight loss were addressed in the protocol with relevant assessment tools. Subjects completed the Columbia Suicide Severity Rating Scale (C-SSRS) at baseline for exclusionary purposes, and investigators administered the Hospital Anxiety and Depression Scale (HADS) periodically during the trial. The HADS mean depression and anxiety scores were within the normal range at baseline and showed no meaningful changes from baseline through Week 52. During the DB period, a few subjects in each treatment group had elevated scores for depression and anxiety; however, the mean changes from baseline were numerically similar between crisaborole QD and vehicle QD groups. There were no reports of SAEs or TEAEs of anxiety, depression or suicidal ideation and behavior. For the evaluation of weight loss, investigators recorded weight at screening, baseline, Day 1 of the maintenance period, Week 24 and Week 52. There were no reports of TEAEs related to change in weight.

The narratives for some of the reactions provided limited descriptions of the cutaneous findings or alternate etiologies and included the following disclaimer, “This narrative reflects information available to the Sponsor in the clinical database at the time of the cutoff date of 15 Feb 2022.”

Hypersensitivity reactions

A total of 4 subjects experienced hypersensitivity reactions (Preferred terms [PTs]: hypersensitivity, urticaria [2 subjects], and angioedema.) Of these, three subjects received crisaborole and one received vehicle. In all cases, the study product continued to be administered and the reactions resolved. However, the Applicant provides no support for an alternative etiology. Brief narratives are included below.

- 4-year-old multiracial male (Subject (b) (6)) with a history of food allergy and seasonal allergy developed intermittent urticaria on Day 194 of treatment with crisaborole once daily. The subject received diphenhydramine and prednisolone and the TEAE of urticaria resolved on Day 200. No action was taken with crisaborole. The event of urticaria was considered **not related** to the study product but related to food allergy. The subject withdrew from the trial on Day 312 due to lack of efficacy (3 consecutive flares.)

- 40-year-old Black/African American female (Subject (b) (6)) with a history of allergies to dust, food, animal dander and fungus developed a hypersensitivity reaction on Day 13 of open- label crisaborole applied twice daily. The narrative includes no description of the reaction which resolved on the same day with no action with crisaborole administration. The event was considered **not related** and the subject withdrew from the trial on Day 58 because she failed to meet the randomization criteria for the double-blind period.

- 11-year-old male (unknown race) (Subject (b) (6)) with a history of allergies to animal dander, asthma and seasonal allergies had two episodes of "facial" angioedema of moderate severity on Day 416 and Day 429 of treatment with crisaborole. Distribution, signs, and symptoms of the reaction were not described. Both events resolved on the same day with prednisone and no action was taken with crisaborole. The subject completed the trial. The event of angioedema was considered **not related** but "due to allergic reactions". Signs and symptoms of the reaction were not provided.

- 16-year-old Asian female (Subject (b) (6)) with no relevant history developed urticaria of mild severity on Day 8, Day 25, and Day 29 of the use of vehicle. Treatment with loratadine resulted in resolution of the urticaria in one or two days with the first two events. No treatment was received for the third event of urticaria. The events of urticaria were considered **not related** to crisaborole but the subject withdrew on Day 96 due to "worsening symptoms."

In response to a request for additional information regarding the occurrence of serious hypersensitivity reactions in association with crisaborole, the Applicant conducted a search of their post-marketing safety database using three Standardized MedDRA Queries (SMQs): Anaphylactic reactions, Angioedema, and Hypersensitivity (SDN 1696 dated November 30, 2022). This strategy identified 96 serious cases including 3 deaths. One patient with a history of severe asthma exacerbations experienced a fatal "asthma attack" that was considered not related to crisaborole. Two male patients ages 84 years and 68 years died of unknown causes

during treatment with crisaborole. In the first case, the 84-year-old subject applied crisaborole for the treatment of pruritus and developed an application site "redness and burning" requiring no treatment. The MedWatch form includes no information regarding the manner or cause of his subsequent death, past medical history, concomitant medications, or autopsy results.

In addition, the search identified 4 cases of anaphylactic reaction in patients using crisaborole. All patients permanently discontinued the product. In two cases, a role for crisaborole could not be excluded. A 6-year-old male with a history of food allergies, AD, and allergic rhinitis developed severe erythema "like a bad burn" and severe pruritus after receiving crisaborole for 2 days. The patient received liquid Zyrtec, oral antibiotics, and Cerave cream. After discontinuation of crisaborole, the signs and symptoms subsided. A 54-year-old male developed contact dermatitis, syncope, and anaphylaxis including throat tightening after approximately 45 days of treatment with crisaborole. In the emergency room (ER), the patient responded to IV antihistamines and IV corticosteroids and was discharged from the ER after 5 hours. The patient discontinued crisaborole.

In two cases, the event of anaphylactic reaction was "possibly related" to crisaborole based on temporal association. A 72-year-old female with multiple medical conditions and a history of drug allergies developed erythema at the application site on her neck, shortness of breath, wheezing, swelling of the tongue, neck and jaw and jaw tenderness after one day of treatment with crisaborole. Concomitant medications included: bupropion, metformin, codeine, apixaban and sulfamethoxazole, trimethoprim, and rifampicin for an ulcer. The patient responded to an "injection" and discontinued crisaborole. The initiation of other concomitant medications relative to the SAEs was not well documented. In addition, a male of unknown age developed tongue swelling and "respiratory issues" after using crisaborole twice daily for three days for the treatment of atopic dermatitis on his feet. He presented to the ER with a "life threatening" anaphylactic reaction. Other information regarding concomitant medications or past medical history was not provided.

In addition, there was a serious case of angioedema in a 3-year-old male who developed "angioedema of the face" within 5 minutes of the application of crisaborole. When the swelling failed to respond to oral Benadryl, the family brought the patient to the ER where he was treated with antihistamines and corticosteroids. According to the Applicant, the treating physician considered the event to be unrelated to crisaborole. Information regarding the outcome and further administration of crisaborole was unknown.

Regardless of the temporal association with exposure to crisaborole, the cases of anaphylaxis from the post-marketing safety database were confounded and do not include all of the relevant information for a definitive conclusion regarding the etiology of the reactions. In addition, uncontrolled, post-marketing data has inherent limitations in interpretability. Therefore, no changes to labeling regarding hypersensitivity reactions are recommended at this time.

Current labeling includes the following language:

4 CONTRAINDICATIONS

EUCRISA is contraindicated in patients with known hypersensitivity to crisaborole or any component of the formulation. [see Warnings and Precautions (5. 1)]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with EUCRISA. Hypersensitivity should be suspected in the event of severe pruritus, swelling and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Less common (<1%) adverse reactions in subjects treated with EUCRISA included contact urticaria [see Warnings and Precautions (5.1)].

Contact dermatitis

Nine subjects developed contact dermatitis. Of these, four received crisaborole and five received vehicle. Allergic contact dermatitis is a labeled adverse reaction (section 6.) These narratives provide limited information regarding the presentation or distribution of the lesions that might allow consideration of alternative etiologies. However, some of these cases support a relationship between the use of crisaborole and the onset of contact dermatitis. Representative narratives are included below.

- 23-year-old Asian female (Subject (b) (6) with no reported medical history developed contact dermatitis on Day 9 of open- label **crisaborole** applied twice daily. Distribution, signs and symptoms of the reaction were not described. Concomitant medications included antihistamines and emollients. The AE was considered **related** to the study product which was permanently discontinued. The AE of contact dermatitis resolved in 10 days without reported treatment. The subject withdrew from the trial on Day 43.
- 7-year-old Asian male (Subject (b) (6) with a history of food allergies and allergic rhinitis developed severe contact dermatitis on Day 4 of open- label **crisaborole** applied twice daily. Distribution, signs and symptoms of the reaction were not described. However, the site received “wound treatment” with wet to dry dressings. The AE was considered **related** to the study product which was permanently discontinued. The subject withdrew from the trial.
- 17-year-old Asian male (Subject (b) (6) with allergic rhinitis and eosinophilia

developed severe contact dermatitis on Day 5 of open- label **crisaborole** applied twice daily. Distribution, signs and symptoms of the reaction were not described. The subject received tacrolimus and the AE resolved on Day 8. The subject discontinued the study product on Day 8 and withdrew from the trial on Day 37. The AE was considered **related** to the study product.

- 3-year-old White male (Subject (b) (6) with seasonal allergies, and congenital ankyloglossia developed contact dermatitis of moderate severity on the right side of face, chin, right arm, left arm and nape of neck on Day 253. The subject received prednisone and diphenhydramine and the AE resolved on Day 300. The subject completed the trial on Day 404. The AE was considered **not related** to crisaborole but associated with a contact irritant.
- 6-year-old multiracial female (Subject (b) (6) with seasonal allergies developed mild contact dermatitis on Day 122 while receiving **vehicle** and on Day 262 while receiving crisaborole for a flare. The second AE did not occur at the application site. Both AEs were considered **not related** but associated with a "change in soap" and "irritation" respectively. The subject completed the trial on Day 437.The subject also reported moderate application site stinging, burning and pain on crisaborole.
- 37-year-old Black/African American female (Subject (b) (6) with no relevant medical history developed contact dermatitis on the scalp on Day 137 of treatment with **vehicle.** The AE was considered to be **related to a new hair piece** and not the study product. The subject was lost to follow-up and withdrawn from the trial on Day 278.
- 39-year-old Black/African American female (Subject 1080 10801019) with no relevant medical history developed mild contact dermatitis on Day 121 of treatment with **vehicle**. Distribution, signs and symptoms of the reaction were not described. No action was taken with regard to the study product. The AE was considered **not related** and the subject withdrew on Day 234 due to lack of efficacy (no response to flare treatment.)

Diarrhea or vomiting

Eight subjects developed diarrhea (4 subjects) or vomiting (4 subjects). Of these, three received crisaborole and five received vehicle. The AEs of diarrhea and vomiting were considered not related to the study product. Investigators did not withdraw the study product due to these events. Representative narratives are included below.

- 3-year-old White male (Subject (b) (6) with no relevant medical history developed diarrhea of moderate severity on Day 18 of twice daily crisaborole. No action was taken with the study medication in response to the event. The AE of diarrhea resolved in on Day 21 with treatment. The subject withdrew from the trial on Day 60 due to the failure to meet the randomization criteria.
- 16-year-old Asian male (Subject (b) (6) with no relevant medical history developed diarrhea of mild severity on Day 78 of once daily crisaborole. No action was taken with the study medication in response to the event. The AE of diarrhea resolved in on Day 80. The AE of diarrhea resolved in on Day 21 with treatment and the subject

completed the trial.

- 4-year-old multiracial male (Subject (b) (6) with a history of food allergy and seasonal allergy developed vomiting and headache of mild severity on Day 74. No action was taken with the study medication in response to these AE which resolved on Day 75). subject withdrew from the trial on Day 284 due to lack of efficacy (3 consecutive flares.)

In view of the information provided in the submission, I agree with the Applicant that the AEs of diarrhea and vomiting are not likely to be related to the use of crisaborole.

Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions (AR)

TEAEs

Among subjects who received twice daily applications of crisaborole during the OL period or in response to a flare of AD, the frequency of TEAEs was approximately 22%. The system organ classes (SOCs) with the greatest proportion of reported TEAEs and ARs across both treatment periods were Infections and infestations and Skin and subcutaneous tissue disorders. In addition, subjects commonly reported TEAEs in the General disorders and administration site conditions SOC related to the application site.

In the open label period (OL), a total of 109 subjects (22%) developed 166 AEs with twice daily application of crisaborole. The TEAEs that occurred with the greatest frequency when related terms were grouped or pooled were application site pain (6%*), upper respiratory tract infection (6%*) and dermatitis atopic (5%*). The following table provides the frequency of the most common TEAEs when related terms were grouped*.

Table 19: Grouped Preferred Term Frequency-OL Period

Summary of TEAEs - Grouped Terms

Grouped Term	Crisaborole BID (N=497) n (%)
Upper respiratory tract infection*	32 (6.4)
Application site pain*	31 (6.2)
Dermatitis atopic*	26 (5.2)
Hypersensitivity *	4 (0.8)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Crisaborole 2% BID" and SAFFL = "Y" (Crisaborole BID); TRTEMFL = "Y" (Adverse Events).
Application site pain* includes Application site discomfort, Application site pain, Application site paresthesia.
Dermatitis atopic* includes Dermatitis atopic, Eczema.
Hypersensitivity * includes Angioedema, Hypersensitivity, Urticaria.

Upper respiratory tract infection* includes: Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

The TEAEs that occurred in ≥1% during the OL period are summarized below by system organ class (SOC) and preferred term (PT) (PTs not grouped). This safety profile is similar to that observed in the original application (Refer to the Clinical Review dated November 3, 2016).

Table 20: TEAEs Reported in ≥1% - OL Period by SOC and PT

Summary of TEAEs

System Organ Class - Preferred Term	Crisaborole 2% BID (N=497) n (%)
Infections and infestations	**89 (17.9)**
Upper respiratory tract infection	16 (3.2)
Application site infection	13 (2.6)
Nasopharyngitis	10 (2.0)
Covid-19	7 (1.4)
Influenza	7 (1.4)
Bronchitis	5 (1.0)
Viral infection	5 (1.0)
Skin and subcutaneous tissue disorders	**53 (10.7)**
Dermatitis atopic	19 (3.8)
Dermatitis contact	9 (1.8)
Eczema	7 (1.4)
General disorders and administration site conditions	**48 (9.7)**
Application site pain	29 (5.8)
Application site erythema	6 (1.2)
Application site pruritus	6 (1.2)

Respiratory, thoracic and mediastinal disorders	**23 (4.6)**
Injury, poisoning and procedural complications	**22 (4.4)**
Gastrointestinal disorders	**21 (4.2)**
Musculoskeletal and connective tissue disorders	**10 (2.0)**
Immune system disorders	**8 (1.6)**
Nervous system disorders	**6 (1.2)**
Psychiatric disorders	**6 (1.2)**
Metabolism and nutrition disorders	**5 (1.0)**

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Crisaborole 2% BID" and SAFFL = "Y" (Crisaborole 2% BID); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Crisaborole 2% BID ≥ 1%.

During the double- blind period (DB), a total of 36 subjects (27%) who received crisaborole once daily developed 83 TEAEs and 49 subjects (36%) who received vehicle once daily developed 76 TEAEs. The TEAEs that occurred with the greatest frequency after pooling included upper respiratory tract infection (9%*) dermatitis atopic (3%*) and application site pain (2%*), as summarized below.

Table 21: Grouped Preferred Term Frequency-DB Period

Summary of TEAEs - Grouped Terms

Grouped Term	Crisaborole QD (N=135) n (%)	vehicle (N=135) n (%)
Upper respiratory tract infection*	12 (8.9)	11 (8.1)
Dermatitis atopic*	4 (3.0)	8 (5.9)
Application site pain*	2 (1.5)	5 (3.7)
Hypersensitivity *	2 (1.5)	1 (0.7)

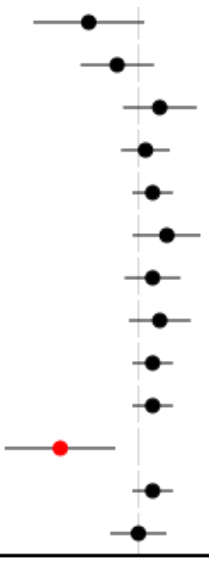
Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFL = "Y" (Crisaborole QD); TRT02A = "Vehicle QD" and SAFFL = "Y" (vehicle); TRTEMFL = "Y" (Adverse Events).
Application site pain* includes: Application site pain.
Dermatitis atopic* includes: Dermatitis atopic, Eczema.
Hypersensitivity * includes: Angioedema, Urticaria.
Upper respiratory tract infection* includes: Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

The TEAEs that occurred in ≥1% during the DB period are summarized below by system organ class (SOC) and preferred term (PTs not grouped/pooled). The frequency of the common PTs is lower with QD dosing than BID dosing. The safety profile of once daily dosing with crisaborole is similar to vehicle as indicated by the risk difference.

Table 22: TEAEs Reported in ≥1% - DB Period by SOC and PT

System Organ Class - Preferred Term	Crisaborole (N=135) n (%)	vehicle (N=135) n (%)	Risk Difference RD (95% CI)	Forest Plot
Infections and infestations	**29 (21.5)**	**39 (28.9)**	**-7.41 (-17.73, 2.91)**	
Upper respiratory tract infection	7 (5.2)	3 (2.2)	2.96 (-1.53, 7.45)	
Covid-19	6 (4.4)	1 (0.7)	3.70 (-0.06, 7.47)	
Influenza	4 (3.0)	2 (1.5)	1.48 (-2.03, 4.99)	
Application site infection	3 (2.2)	6 (4.4)	-2.22 (-6.50, 2.05)	
Nasopharyngitis	3 (2.2)	5 (3.7)	-1.48 (-5.52, 2.56)	
Otitis media	3 (2.2)	1 (0.7)	1.48 (-1.40, 4.36)	
Hand-foot-and-mouth disease	2 (1.5)	1 (0.7)	0.74 (-1.76, 3.24)	
Oral herpes	2 (1.5)	0 (0.0)	1.48 (-0.56, 3.52)	
Pharyngitis streptococcal	2 (1.5)	1 (0.7)	0.74 (-1.76, 3.24)	
Rhinitis	2 (1.5)	2 (1.5)	0.00 (-2.88, 2.88)	
Skin and subcutaneous tissue disorders	**15 (11.1)**	**15 (11.1)**	**0.00 (-7.50, 7.50)**	
Dermatitis atopic	2 (1.5)	6 (4.4)	-2.96 (-6.99, 1.07)	
Eczema	2 (1.5)	2 (1.5)	0.00 (-2.88, 2.88)	
Injury, poisoning and procedural complications	**9 (6.7)**	**11 (8.1)**	**-1.48 (-7.73, 4.76)**	
Skin abrasion	3 (2.2)	1 (0.7)	1.48 (-1.40, 4.36)	
Skin laceration	2 (1.5)	1 (0.7)	0.74 (-1.76, 3.24)	
Respiratory, thoracic and mediastinal disorders	**9 (6.7)**	**12 (8.9)**	**-2.22 (-8.61, 4.16)**	
Oropharyngeal pain	3 (2.2)	1 (0.7)	1.48 (-1.40, 4.36)	
Nasal congestion	2 (1.5)	2 (1.5)	0.00 (-2.88, 2.88)	

General disorders and administration site conditions	**5 (3.7)**	**12 (8.9)**	**-5.19 (-10.95, 0.58)**
Application site pain	2 (1.5)	5 (3.7)	-2.22 (-6.00, 1.56)
Musculoskeletal and connective tissue disorders	**5 (3.7)**	**2 (1.5)**	**2.22 (-1.56, 6.00)**
Pain in extremity	2 (1.5)	1 (0.7)	0.74 (-1.76, 3.24)
Rotator cuff syndrome	2 (1.5)	0 (0.0)	1.48 (-0.56, 3.52)
Nervous system disorders	**5 (3.7)**	**1 (0.7)**	**2.96 (-0.54, 6.46)**
Headache	3 (2.2)	1 (0.7)	1.48 (-1.40, 4.36)
Psychiatric disorders	**4 (3.0)**	**1 (0.7)**	**2.22 (-0.98, 5.43)**
Insomnia	2 (1.5)	0 (0.0)	1.48 (-0.56, 3.52)
Sleep disorder	2 (1.5)	0 (0.0)	1.48 (-0.56, 3.52)
Gastrointestinal disorders	**3 (2.2)**	**14 (10.4)**	**-8.15 (-13.86, -2.44)**
Eye disorders	**2 (1.5)**	**0 (0.0)**	**1.48 (-0.56, 3.52)**
Metabolism and nutrition disorders	**2 (1.5)**	**2 (1.5)**	**0.00 (-2.88, 2.88)**



Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFL = "Y" (Crisaborole QD); TRT02A = "Vehicle QD" and SAFFL = "Y" (vehicle); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Crisaborole QD ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Flare

During the DB period, 78 subjects who were originally randomized to crisaborole and 89 subjects who were originally randomized to vehicle developed a flare of AD (ISGA≥2). These subjects discontinued their QD randomized treatment and received crisaborole BID. Among the subjects who developed a flare, a total of 15 subjects (19%) who were originally randomized to crisaborole once daily developed 19 TEAEs and 22 subjects (25%) who were originally randomized to vehicle once daily developed 46 TEAEs. These TEAEs are summarized below by system organ class (SOC) and preferred term (PT). TEAEs that were reported by single subjects are not included in the table. Overall, across both groups the most common TEAEs were upper respiratory tract infection, application site infection and nasophyngitis.

Table 23: TEAEs Reported by ≥ 1 Subject in the Crisaborole Group during a Flare of AD

Summary of TEAEs

Preferred Term	Crisaborole 2% QD (N=78) n (%)	Vehicle QD (N=89) n (%)	Risk Difference RD (95% CI)	Forest Plot
Upper respiratory tract infection	7 (9.0)	3 (3.4)	5.60 (-1.76, 12.97)	
Covid-19	4 (5.1)	1 (1.1)	4.00 (-1.36, 9.37)	
Influenza	3 (3.8)	2 (2.2)	1.60 (-3.66, 6.86)	
Nasopharyngitis	3 (3.8)	3 (3.4)	0.48 (-5.21, 6.16)	
Application site infection	2 (2.6)	5 (5.6)	-3.05 (-8.99, 2.88)	
Dermatitis atopic	2 (2.6)	4 (4.5)	-1.93 (-7.48, 3.62)	
Hand-foot-and-mouth disease	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Headache	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Insomnia	2 (2.6)	0 (0.0)	2.56 (-0.94, 6.07)	
Oral herpes	2 (2.6)	0 (0.0)	2.56 (-0.94, 6.07)	
Oropharyngeal pain	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Otitis media	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Rhinitis	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Skin laceration	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFAFL = "Y" and SAFFL = "Y" (Crisaborole 2% QD); TRT02A = "Vehicle QD" and SAFFAFL = "Y" and SAFFL = "Y" (Vehicle QD); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Crisaborole 2% QD ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Adverse Reactions (ARs)

The adverse reactions that occurred in Trial C3291035 were similar to those that occurred in the phase 3 trials. Application site pain was the most common AR in both treatment periods. Subjects who failed to improve with treatment reported dermatitis atopic/ eczema. The tables for the DB period include the risk difference to support the analysis for potential safety signals.

Table 24: Adverse Reactions Reported in ≥1% - OL Period by SOC and PT

System Organ Class - Preferred Term	Crisaborole (N=497) n (%)
General disorders and administration site conditions	**41 (8.2)**
Application site pain	29 (5.8)
Application site erythema	6 (1.2)
Skin and subcutaneous tissue disorders	**16 (3.2)**
Dermatitis atopic	8 (1.6)
Infections and infestations	**6 (1.2)**

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Crisaborole 2% BID" and SAFFL = "Y" (Crisaborole 2% BID); TRTEMFL = "Y" and AEREL = "RELATED" (Adverse Events). Crisaborole BID

Table 25: Adverse Reactions Reported in ≥1% - DB Period by SOC and PT

System Organ Class - Preferred Term	Crisaborole (N=135) n (%)	Vehcile (N=135) n (%)	Risk Difference RD (95% CI)	Forest Plot
General disorders and administration site conditions	**2 (1.5)**	**8 (5.9)**	**-4.44 (-8.92, 0.03)**	
Application site pain	2 (1.5)	5 (3.7)	-2.22 (-6.00, 1.56)	
Infections and infestations	**2 (1.5)**	**0 (0.0)**	**1.48 (-0.56, 3.52)**	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFL = "Y" (Crisaborole 2% QD); TRT02A = "Vehicle QD" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" and AEREL = "RELATED" (Adverse Events).
Percent Threshold: Crisaborole 2% QD ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).AR=Adverse reactions, DB=Double-blind, treatments QD

The ARs that occurred during the DB period after subjects developed a flare are summarized in the following table by PT. The table includes only the PTs that occurred in more than one subject in the crisaborole arm with the risk difference to identify safety signals.

Table 26: Adverse Reactions Reported by More than One Subject during Flare of AD

Summary of TEAEs

Preferred Term	Crisaborole 2% QD (N=78) n (%)	Vehicle QD (N=89) n (%)	Risk Difference RD (95% CI)	Forest Plot
Upper respiratory tract infection	7 (9.0)	3 (3.4)	5.60 (-1.76, 12.97)	
Covid-19	4 (5.1)	1 (1.1)	4.00 (-1.36, 9.37)	
Influenza	3 (3.8)	2 (2.2)	1.60 (-3.66, 6.86)	
Nasopharyngitis	3 (3.8)	3 (3.4)	0.48 (-5.21, 6.16)	
Application site infection	2 (2.6)	5 (5.6)	-3.05 (-8.99, 2.88)	
Dermatitis atopic	2 (2.6)	4 (4.5)	-1.93 (-7.48, 3.62)	
Hand-foot-and-mouth disease	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Headache	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Insomnia	2 (2.6)	0 (0.0)	2.56 (-0.94, 6.07)	
Oral herpes	2 (2.6)	0 (0.0)	2.56 (-0.94, 6.07)	
Oropharyngeal pain	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Otitis media	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Rhinitis	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	
Skin laceration	2 (2.6)	1 (1.1)	1.44 (-2.69, 5.58)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Crisaborole 2% QD" and SAFFAFL = "Y" and SAFFL = "Y" (Crisaborole 2% QD); TRT02A = "Vehicle QD" and SAFFAFL = "Y" and SAFFL = "Y" (Vehicle QD); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Crisaborole 2% QD ≥ 1%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Adverse Reactions (ARs) by Severity

Most ARs that occurred during the trial in both treatment periods (OL and DB) were mild to moderate in severity. During the OL period, 1% of subjects developed severe ARs including two subjects with severe contact dermatitis and two subjects with severe application site pain. During the DB period, one subject in the vehicle group (1%) developed a severe AR of application site dermatitis. During the DB period, one subject in the vehicle arm (application site dermatitis) and no subjects in the crisaborole arm developed a severe AR.

Laboratory Findings

The protocol specified that serum chemistry and hematology were obtained at screening for exclusionary purposes. Study staff conducted laboratory testing during the trial only if clinically indicated.

One subject had a laboratory abnormality that was categorized as a TEAE. A 35-year-old Asian

male (Subject (b) (6) with abnormal liver enzymes at screening developed worsening liver enzymes (ALT and AST increased) on Day 28. Alkaline phosphatase and bilirubin levels remained normal. The subject reported no concomitant medications. The subject discontinued open-label crisaborole on Day 40 and was lost to follow-up on Day 42. The TEAE was considered moderate in severity and not related to treatment with crisaborole because the hepatic enzymes were elevated at screening. However, past medical history, prior systemic therapies used for atopic dermatitis, risk factors for hepatic injury and additional laboratory assessments and procedures used to evaluate the abnormal hepatic enzymes were not provided. In response to a request for additional information, the Applicant confirmed that the "narrative includes all the information known and gathered for this event."(SDN 1696 dated November 30, 2022) Despite the absence of pertinent information regarding this case, the pre-existing hepatic dysfunction and amount of estimated systemic exposure argues against a role for crisaborole in the occurrence of this adverse event.

The results of the monthly pregnancy testing are discussed above and in Section 8.2.9 Additional Safety Explorations.

Vital Signs

Study staff evaluated subjects for changes in vital signs at every visit during the trial. Height and weight were documented at Screening and Baseline during the Open-label period and Week 0, 24 and 52 during the Maintenance period. Shift tables for pulse and temperature (SDN 1696 dated November 30, 2022) showed no clinically meaningful changes in the vital signs.

Electrocardiograms (ECGs)/ QT

The safety evaluation for Trial C3291035 did not include routine cardiac safety monitoring. Nonclinical data demonstrated no effect of crisaborole on hERG receptors at a dose of 1 micromolar and no effects in dogs at doses up to 300 mg/kg (Refer to the Clinical Pharmacology review by Kumar D. Mainigi, PhD dated 8/15/2016). To support approval of the original application for EUCRISA, the Applicant conducted a thorough QT (TQT) Study (AN2728-TQT - 108) and obtained electrocardiograms in multiple trials. Upon review of the TQT study results and ECGs from phase 3, the QT-IRT team concluded that crisaborole had no significant QTc prolongation effect up to supratherapeutic doses and caused no substantial increase in cardiac adverse events compared to vehicle. [Review by Qianyu Dang 5/20/2014 and Jiang Liu dated 4/20/2016].

In addition, Shetarra Walker MD, Division of Cardiovascular and Renal Products, reviewed the cardiovascular safety data from Trial C3291002 to evaluate potential cardiotoxicity in neonates and infants related to propylene glycol (PG) exposure, an excipient in the product. Dr. Walker concluded

> "In Study C3291002, we did not identify a cardiac signal associated with PG-induced toxicity. Therefore, we do not recommend adding safety information to labeling

pertaining to potential cardiotoxicity associated with PG exposures." (Review dated January 31, 2020).

Dr. Walker recommended that the following language be included in labeling:

12.2 Pharmacodynamics

Cardiac Electrophysiology
At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent.

Immunogenicity

Because the product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity during product development or related to the use of crisaborole as maintenance treatment.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no submission specific safety issues.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant included no patient-reported outcome measures (PROs) for safety in this sNDA submission.

8.2.7. Safety Analyses by Demographic Subgroups

Adverse reactions (ARs) were analyzed by age, sex and race. The number of subjects in each demographic subgroup during the open-label period were adequate to support review. In the double-blind period, subgroup sizes and the frequency of reported ARs were not sufficient to detect clinically meaningful differences in the frequency of ARs between individual subgroups. While there were minor differences by subgroup, the distribution of ARs by age, sex and race was similar. These findings support the initial determination in the original NDA submission that there were no clear trends in the risk of adverse reactions by demographic subgroup. (Refer to the Clinical Review dated November 3, 2016).

A greater proportion of subjects in all subgroups developed any AR during the 8- week open-label period with twice daily administration of crisaborole compared with the double- blind maintenance period with once daily application of the study product (crisaborole or vehicle). For all age groups, races and both sexes, application site pain was the most common AR. AR by preferred terms with a frequency >=1 % are tabulated below for the open-label period by age, sex and race. AR by preferred terms with a frequency >=1 % are tabulated below for the

double-blind period by age to illustrate the difficulty with interpretation of the data for events of such low frequency.

Adverse reactions (ARs) by age

Open-Label Period (OL)

Table 27: Adverse Reactions by Preferred Terms with a Frequency >=1 % (OL: Age 3 Months -<6 Years)

Open-Label Period (OL) crisaborole 2% BID n (%)	
Age Group: 3 Months -<6 Years	
Number of Evaluable Subjects	116
# Subjects with any AR	14 (12)
Application site pain	13 (11)
Eczema	2 (2)
Application site erythema	2 (2)

Source: Reviewer's Table; AR=adverse reaction. Data from SDN 1702 dated Jan 20, 2023
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity;
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 28: Adverse Reactions by Preferred Terms with a Frequency >=1 % (OL: Age 6 Years -<12 Years)

Open-Label Period (OL) crisaborole 2% BID n (%)	
Age Group: 6 Years -<12 Years	
Number of Evaluable Subjects	106
# Subjects with Any AR	6 (6)
Application site pain	4 (4)
Eczema	1 (1)
Application site infection	1 (1)

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:

Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 29: Adverse Reactions by Preferred Terms with a Frequency >=1 % (OL: Age 12 Years - <18 Years)

Open-Label Period (OL) crisaborole 2% BID n (%)	
Age Group: 12 Years -<18 Years	
Number of Evaluable Subjects	105
# Subjects with Any AR	10 (10)
Application site pain	8 (8)
Application site reaction	1 (1)
Eczema	1 (1)
Skin infection	1 (1)
Application site erythema	1 (1)

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 30: Adverse Reactions by Preferred Terms with a Frequency >=1 % (OL: Age ≥18 Years)

Open-Label Period (OL) crisaborole 2% BID n (%)	
Age Group: ≥18 Years	
Number of Evaluable Subjects	170
# Subjects with any AR	11 (7)
Application site pain	4 (2)
Eczema	3 (2)
Application site irritation	2 (1)

Open-Label Period (OL) crisaborole 2% BID n (%)	
Age Group: ≥18 Years	
Application site reaction	2 (1)
Application site erythema	2 (1)

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Double-Blind Period (DB)

Table 31: Adverse Reactions by Preferred Terms with a Frequency >=1 % (DB: Age 3 Months - <6 Years)

Double-Blind Period (DB) n (%)				
	Maintenance (Study product QD)		**Flare (crisaborole BID)**	
Randomized arm following run-in period	**Vehicle QD**	**Crisaborole 2% QD**	**Vehicle QD**	**Crisaborole 2% QD**
Age Group: 3 Months -<6 Years				
# of Evaluable Subjects	37	29	30	24
# Subjects with any AR	0	0	1 (3)	1 (4)
Application site pain	0	0	1 (3)	1 (4)
Eczema	0	0	0	0
Application site erythema	0	0	0	0

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 32: Adverse Reactions by Preferred Terms with a Frequency >=1 % (DB: Age 6 Years - <12 Years)

Double-Blind Period (DB) n (%)				
	Maintenance (Study product QD)		Flare (Crisaborole BID)	
Assigned arm following run-in period	Vehicle QD	Crisaborole 2% QD	Vehicle QD	Crisaborole 2% QD
Age Group: 6 Years -<12 Years				
# of Evaluable Subjects	24	21	15	11
# Subjects with any AE	1 (4)	0	0	0
Application site pain	1 (4)	0	0	0

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 33: Adverse Reactions by Preferred Terms with a Frequency >=1 % (DB: Age 12 Years - <18 Years)

Double-Blind Period (DB) n (%)				
	Maintenance (Study product QD)		Flare (Crisaborole BID)	
Assigned arm following run-in period	Vehicle QD	Crisaborole 2% QD	Vehicle QD	Crisaborole 2% QD
Age Group: 12 Years -<18 Years				
# of Evaluable Subjects	24	21	15	11
# Subjects with any AR	2 (9)	0	0	0
Application site pain	1 (4)	0	0	0
Application site irritation	1 (4)	0	0	0

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Table 34: Adverse Reactions by Preferred Terms with a Frequency >=1 % (DB: Age ≥ 18 Years)

Double-Blind Period (DB) n (%)				
	Maintenance (Study product QD)		Flare (Crisaborole BID)	
Assigned arm following run-in period	Vehicle QD	Crisaborole 2% QD	Vehicle QD	Crisaborole 2% QD
Age Group: ≥18 Years				
# of Evaluable Subjects	24	21	15	11
# Subjects with any AR	0	0	1 (4)	0
Eczema	0	0	1 (4)	0

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Adverse Reactions by Sex (OL)

ARs reported by females and males during the open-label period are presented below.

Table 35: Adverse Reactions by Preferred Terms with a Frequency >=1 % by Sex (OL)

Open-Label Period (OL) Crisaborole 2% BID n (%)		
	Females	***Males***
Number of Evaluable Subjects	283	214
# Subjects with any AR	25 (9)	16 (8)
Application site pain	17 (6)	12 (6)
Eczema	5 (2)	2 (1)
Application site irritation	2 (1)	0
Application site reaction	2 (1)	1 (1)
Application site erythema	2 (1)	3 (2)
Skin infection	1 (<1)	1 (1)

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;

Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

Adverse Reactions by Race (OL)

Racial subgroups evaluated for ARs reported during the open-label period are presented below. The racial subgroups with sufficient data available for comparison included: White, Black/African American and Asian.

Table 36: Adverse Reactions by Preferred Terms with a Frequency >=1 % by Race (OL)

Open-Label Period (OL) Crisaborole 2% BID n (%)			
	White	***Black/African American***	***Asian***
Number of Evaluable Subjects	204	161	101
# Subjects with any AR	22 (11)	6 (4)	11 (11)
Application Site Pain	19 (9)	2 (1)	6 (6)
Application site erythema	4 (2)	0	1 (1)
Eczema	2 (1)	0	5 (5)
Application Site Irritation	1 (1)	1 (1)	0
Application Site Reaction	0	2 (1)	1 (1)
Skin Infection	0	1 (1)	1 (1)

Source: Reviewer's Table; AR=adverse reaction
The terms presented in the tables in this section represent pooled terms defined as follows:
Eczema: including eczema and dermatitis atopic
Hypersensitivity: including urticaria, angioedema, facial angioedema, and hypersensitivity.
Skin Infection: including impetigo, eczema infected, application site infection, skin infection, and bacterial infection
Upper Respiratory Tract Infection (URI): including pharyngitis, URI viral, nasopharyngitis, sinusitis, and URI;
Application Site Irritation: including application site dermatitis and application site irritation
Application site Reaction: including application site rash and application site reaction
Application Site Pain: including application site discomfort, application site burning, and application site pain.

8.2.8. Supportive Clinical Trials

The Applicant submitted data from seven additional trials (C3291001, C3291029, C3291028, C3291032, C3291037, C3291002, C3291027) in integrated datasets to provide an overall "robust" safety assessment. Some of these trials were conducted under the IND. For example, Trial C3291002 was conducted to address PMR 3142-1 and to respond to the Written Request (WR) (Clinical review dated March 16, 2020). However, most of these trials were not conducted under the IND and were intended to address other objectives. The study designs reflect the individual study objectives: open- label with a treatment duration of up to 8 weeks or double-blind with the study duration of up to 4 weeks. The utility of the integrated safety databases is limited by the variability in the trial designs, duration of treatment, randomization ratios and

study populations. Therefore, these trials and key safety findings will be discussed individually in brief summaries below.

Trial C3291001

This was a Phase 2a, randomized, **double-blind**, vehicle-controlled, intra-subject trial that was conducted in Canada. The objective was to explore the mechanism of action by evaluation of changes in key skin biomarkers and efficacy of crisaborole ointment 2% in **40 adult subjects** with mild to moderate AD. After screening, the double-blind, vehicle-controlled, period continued until a biopsy was obtained on Day 15. Then all subjects received open label treatment until Day 43. The primary efficacy endpoint was the change from baseline in Total Sign Score (TSS) in target lesions at Day 15. The key skin biomarkers assessed at Day 15 were: S100A12, CCL17, CCL18, CCL22, Keratin 16, elafin/PI3 and Interleukin (IL)-13.

Eligible subjects had mild to moderate AD defined as an ISGA score of 2 or 3, a BSA of 0.5% to 10% involved with AD and at least 2 patches of AD (>3 X 3 cm) with identical ISGA of ≥3. Subjects with infected AD by clinical examination, requiring high potency topical or oral corticosteroid therapy and a history of angioedema or hypersensitivity to topical products were excluded.

Safety Results
The majority of subjects were female (68%), White (85%) with a mean age of 32 years. The mean BSA was 29%. Approximately 98% of subjects had a lesion score of 3.

There were no deaths or serious adverse events (SAEs). A total of 29 subjects (73%) developed 81 TEAEs. The most common TEAEs were nasopharyngitis (11 subjects) and headache (9 subjects). Eleven TEAEs were considered treatment related (AR). The most frequent AR was application site pain (7 subjects, 18%). There were no clinically meaningful changes in laboratory parameters or on physical examination.

Trial C3291002
Trial C3291002 was an **open-label**, pharmacokinetic (PK) and safety trial enrolling **137 pediatric subjects** ages 3 months to <2 years with mild to moderate atopic dermatitis. Enrolled subjects had an Investigator's Static Global Assessment (ISGA) Score of mild (2) or moderate (3) at Baseline/Day 1 and a body surface area (BSA) affected with AD of at least 5%. Subjects who participated in PK assessments under maximal use conditions (referred to as the PK cohort) had an ISGA of moderate (3) and a BSA of at least 35%.

Safety Results

In Trial C3291002, there were no deaths, and no unexpected adverse events or safety signals. One subject experienced a serious adverse event (febrile seizure), and no subjects withdrew from the trial due to adverse events. Investigators temporarily modified the dose or withdrew the study drug for some subjects who experienced treatment emergent adverse events (TEAEs) but these subjects remained in the trial.

Overall, 88 subjects (88/137, 64%) experienced a total of 192 TEAEs. The most common system organ classes were Infections and Infestations (43/137, 31%), Skin and Subcutaneous Tissue Disorders (37/137, 27%), General Disorders and Administration Site Conditions (26/137, 19%) and Gastrointestinal Disorders (15/137, 11%). The most common preferred terms (PT) were pyrexia (13/137, 10%), upper respiratory tract infection (10/137, 7%) and diarrhea (10/137, 7%).

A total of 21 (15%) subjects experienced 27 adverse reactions (ARs) at the application site. The most common preferred terms were application site pain, application site discomfort, erythema, application site erythema and pruritus. Investigators categorized the majority of local ARs as mild in severity. However, the evaluation of symptoms of pain, discomfort and pruritus in this population is imprecise and the distinctions in severity may not be meaningful.

Applicant identified and analyzed AEs of special interest which were related to PDE-4 class effects, propylene glycol (PG) toxicity, or hypersensitivity reactions. There were 3 TEAEs which were considered to be potentially associated with PG toxicity: irritability, intraventricular conduction delay (IVCD) and seizure. However, there was insufficient data in any case to support a relationship between these AEs and exposure to PG. Two subjects experienced hypersensitivity reactions (anaphylaxis and urticaria); neither TEAE was assessed as related to crisaborole. One subject experienced weight loss, a potential TEAE related to PDE-4 inhibition; however, the assessment of weight loss was based on a home measurement conveyed to the study staff in a telephone interview in a subject with elevated albumin levels. There was no data to suggest that the subject was evaluated for other causes of weight loss and elevated albumin (e.g., dehydration).

Trial C3291037

Trial C3291002 was a phase 3b/4 multicenter, randomized, **assessor blinded**, vehicle and active (topical corticosteroid [TCS] and topical calcineurin inhibitor [TCI]) controlled trial to evaluate the efficacy, safety, and local tolerability of crisaborole ointment, 2% in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD involving at least 5% treatable body surface area (%BSA). Following the screening period of up to 35 days, eligible subjects were randomized (1:1:2) at Baseline/Day 1 visit to crisaborole 2%, vehicle, or active comparator, hydrocortisone butyrate 0.1%, or pimecrolimus 1% cream. A total of **235 subjects** received twice daily treatment with the study product for 28 days. The Applicant discontinued the trial prematurely as a "business decision". The reduced sample sizes prohibited a meaningful comparison of crisaborole with the active drugs.

Safety Results

A majority of subjects (n=151 subjects) were enrolled from the United States and completed the trial (88%). Most subjects were female (59%), White (67%) and in the pediatric age group 2 to 17 years (61%).

Greater numbers of subjects demonstrated improvement on the primary efficacy endpoint (percent change in total EASI score) in crisaborole, TCS, and TCI groups than in the vehicle group.

There were no deaths or other SAEs and most TEAEs were mild. Overall, 11 subjects (5%) discontinued treatment due to adverse events. Most of the AR were at the application site and were assessed as mild to moderate. Among the adverse reactions, application site pain and atopic dermatitis were the most frequent. There were no new safety issues related to clinical laboratory or vital signs findings.

The following trials were conducted in **Asian subjects**:

Trial C3291028

Trial C3291028 was a Phase 2b, multicenter, randomized, **double-blind**, vehicle-controlled, **intra-subject** trial to evaluate efficacy and safety of 2 regimens of crisaborole ointment 2% in **81 Japanese pediatric and adult subjects.** Subjects received once (QD) or twice (BID) daily treatment with vehicle and crisaborole to target lesions of moderate severity (ISGA of 3) for **14 days**. The trial included 2 Cohorts: 41 subjects in Cohort 1 were ≥12 years of age and 40 subjects in Cohort 2 were 2 years to 12 years of age.

Eligible subjects had an ISGA Score of mild (2) or moderate (3) at Baseline/Day 1, a BSA affected with AD of 1% to 30% and at least 2 target areas of AD (>3 X 3 cm) with identical ISGA of 3. Subjects were excluded who had a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of crisaborole ointment 2%, prior treatment with topical or systemic phosphodiesterase-4 inhibitor, other acute or chronic medical or psychiatric condition or prior treatment for cancer (except NMSC).

Safety Results

In Cohort 1 (≥12 years of age) most subjects were male with a mean age of 33-34 years and a BSA of 18-19%. In Cohort 2, most subjects who received QD treatment were female and the majority who received BID treatment were male, the mean age was 8 years and the treatable BSA was 5 to 9%.

There were no deaths, SAEs or severe TEAEs reported in either cohort in the trial.

In Cohort 1, 29 to 30% of subjects (6 subjects) reported a TEAE; in Cohort 2, 10% of subjects (2 subjects) reported a TEAE. For both cohorts, the majority of TEAEs were in the General Disorders and Administration Site Conditions system organ class (application site coldness, application site irritation, application site pain, application site pruritus and application site folliculitis). For the QD dosing regimen, 6 subjects reported 9 TEAE of which 8 were considered treatment related. The most frequently reported TEAEs by preferred term (PT) were application site irritation and application site pruritus (3 subjects each). For the BID dosing regimen, 6 subjects reported 12 TEAEs of which 8 were considered treatment related. The most frequently

reported TEAEs by preferred term (PT) were application site irritation (4 subjects) and oropharyngeal pain (3 subjects).

In Cohort 2, for the QD dosing regimen, there were 2 TEAEs (arthralgia and hand-foot-and-mouth disease). Neither TEAE was considered related to treatment.

The events of application site irritation and application site pruritus were considered related while the events of oropharyngeal pain were considered not related.

Trial C3291029

Trial C3291029 was a phase 1, single-center, randomized, vehicle-controlled, parallel-cohort study of crisaborole ointment 2% to evaluate the irritation potential to the skin of **20 healthy** adult Japanese subjects in Cohort 1, and safety, tolerability and PK in **12 adult Japanese** subjects with mild to moderate AD in Cohort 2. Subjects enrolled in Cohort 1 had the investigational products applied to a pre-specified site on Day 1 for 48 hours with assessments approximately 30 minutes and 24 hours after patch removal. In Cohort 2, investigational staff applied the study products twice daily for 8 days. Safety evaluations included skin irritation assessment (Cohort 1), AEs, safety laboratory tests, vital signs (heart rate, blood pressure), and 12-lead ECGs. Vital signs and 12-lead ECGs were observed at Screening in Cohort 1 and at Screening, on Day 1 and Day 8 in Cohort 2.

Eligible subjects were age 20 to 55 years old. In Cohort 1, subjects were healthy and in Cohort 2 subjects had at least 25% treatable %BSA affected by AD and mild to moderate AD defined as a score of 2 or 3 on ISGA. Subjects with clinically significant medical conditions or findings at screening were excluded from participation.

Safety Results

There were no deaths, SAEs or severe TEAEs. For both cohorts, all subjects were male, and the majority of subjects were aged 20 to 44 years. In Cohort 2, the majority of subjects (83%) had a moderate AD, ISGA score of 3, and the mean treatable %BSA was 64% overall (range: 35% to 87%).

No subjects in Cohort 1 reported TEAEs; 11 subjects in Cohort 2 (9 assigned to crisaborole and 2 assigned to vehicle) reported TEAEs. In Cohort 2, 13 subjects who received crisaborole reported a total of 13 TEAEs, all of mild intensity. The most frequently reported TEAEs by preferred term were application site irritation (7 subjects) and application site pain (4 subjects). One subject reported application site coldness. All TEAEs were considered related to crisaborole except for eyelid edema. In the vehicle group, 6 AEs were reported in 2 subjects. Two AEs (nasopharyngitis and dermatitis atopic) were of moderate intensity and 4 AEs (application site coldness, application site irritation, application site pain, and application site pruritus) were of mild intensity. All TEAEs in the vehicle group were considered treatment-related except for nasopharyngitis.

In Cohort 1, most subjects developed an irritation score of 0 or 0.5 (rating scale: 0, 0.5, 1, 2, 3, 4).

Trial C3291032

Trial C3291032 was a phase 3, multicenter, randomized, **double blind**, vehicle-controlled trial to evaluate the efficacy and safety of crisaborole ointment, 2% in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD. Eligible subjects had at least 5% treatable BSA. The primary efficacy endpoint was percent change from baseline in Eczema Area and Severity Index (EASI) total score at Day 29. Safety endpoints included TEAEs, SAEs and clinically significant changes in vital signs and clinical laboratory parameters.

Safety Results

A total of **391 subjects** were randomized 2:1 ratio to crisaborole 2% or vehicle applied twice daily for 28 days. Overall, 61% of the subjects were from China and 39% were from Japan with a mean age of 19 years and 16 years in the crisaborole and vehicle arms, respectively.

There were no deaths and one subject in the vehicle group (<1%) and one subject in the crisaborole group (<1%) developed unrelated SAEs (myocardial necrosis marker increased and carpel tunnel syndrome, respectively). The most frequently reported TEAEs in the vehicle and crisaborole 2% BID groups were application site pain (4% and 13%, respectively), dermatitis atopic (12% and 8%, respectively), folliculitis (5% and 3%, respectively), nasopharyngitis (3% and 4%, respectively), upper respiratory tract infection (3% and 4%, respectively) and application site discoloration (<1% and 4%, respectively).

The most frequently reported adverse reactions in the vehicle and crisaborole 2% BID groups were application site pain (4% and 13%, respectively and application site discoloration (1% and 3%, respectively).
The most frequently reported laboratory abnormality in the vehicle and crisaborole groups was Increased eosinophils (33% and 31%, respectively.) The Applicant reported no clinically significant changes or pattern in vital sign data.

Trial C3291027

Trial C3291027 was a phase 3, multicenter, **open-label**, long-term safety extension trial that enrolled Japanese pediatric (down to one month of age) and adult subjects with mild to moderate atopic dermatitis (AD) who completed trials C3291032 and C3291031. Subjects with an active systemic or local infection including eczema herpeticum of significant severity were excluded from the trial. Enrolled subjects with treatment success at the conclusion of trials C3291032 and C3291031 did not receive treatment. Subjects were evaluated monthly to document the need for a cycle of treatment. The Applicant (b) (4) terminated the trial prematurely as a "business decision". Safety assessments included AEs and SAEs.

A total of **40 subjects** enrolled in Trial C3291027 and 37 subjects applied crisaborole twice daily for a mean of 29 days (range of 0 to 56 days.) Of these 40 subjects, 30 subjects were <18 years of age and 10 subjects were ≥18 years of age. One subject discontinued treatment due to an adverse event.

Safety Results

In the age group less than 18 years, the most frequently reported TEAEs by PT were nasopharyngitis (3 subjects) and dermatitis atopic (2 subjects), all other TEAEs were reported in 1 subject each. In the age group ≥18 years, the TEAEs by PT were gastroenteritis, wound, and joint effusion (1 subject each). One subject in the age group less than 18 years developed an adverse reaction (application site pain) which was considered of mild severity.

Exploratory accelerometry sub-study

The Applicant conducted an accelerometry sub-study to explore the use of digital wearable technology to quantify the impact of crisaborole on nocturnal scratching and sleep in the home environment over time. Subjects who participated in the accelerometry portion of the trial wore watch-like accelerometry devices (GENEActiv Original accelerometry devices) on each wrist to continuously monitor nocturnal scratching and sleep quantity for one week prior to the Day 1 visit and Day 1 through Day 15 during the OL period of the trial. Accelerometry devices measured the number of events and duration of nocturnal scratching, and the sleep quantity (total sleep time [TST], total sleep opportunity [TSO], sleep efficiency [TST/TSO], number of arousals, wake after sleep onset [WASO], and sleep onset latency [SOL]).

The sample size was limited (**28 evaluable subjects** for the sleep measures and 20 evaluable for nocturnal scratch) and subjects were analyzed by age group (aged 2-11 years or ≥ 12 years). For the youngest subgroup (aged 2-11 years), there was a slight trend toward greater sleep efficiency and decreased nocturnal scratch duration and events following drug initiation. This trend was less definitive in the older age group (aged ≥ 12 years) due to greater variability in the data. The Applicant plans (b) (4) However, the small sample size limited the utility of this data.

The protocol contained limited information regarding the devices, scales and algorithms that the Applicant intended to use to conduct and analyze this data. The Agency provided general comments and requested additional information to support the potential use of this data for labeling. However, the Applicant chose to consider this evaluation as exploratory at this time.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or

tumor development. During the development of crisaborole ointment, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. However, no subjects enrolled in C3291035 reported malignant neoplasms.

Human Reproduction and Pregnancy

During the development of crisaborole ointment, all female subjects of childbearing potential were required to use acceptable methods of contraception that were consistent with local regulations. Trial staff performed pregnancy testing at Screening/Baseline and monthly throughout the trials. According to the protocol, pregnant and lactating females were excluded from the trials. If subjects reported pregnancy, the investigators discontinued the investigational product and followed the pregnancy to delivery or final outcome if feasible. The Applicant did not conduct a specific clinical trial to evaluate the effects of exposure to crisaborole during pregnancy or lactation.

Current labeling for EUCRISA includes the following information regarding the risk of exposure to crisaborole during pregnancy and lactation.

8.1 Pregnancy

(b) (4)

8.2 Lactation

During the double-blind period of Trial C3291035, there were two pregnancies and a partner pregnancy among subjects in the vehicle group and none in the crisaborole group. Per protocol both pregnant subjects discontinued the IP and withdrew from the trial. One subject had a healthy infant and one subject was lost to follow-up. The partner pregnancy resulted in a healthy infant. Refer to Section 8.2.4 for brief narratives of these events.

The Maternal Health team from the Division of Pediatrics and Maternal Health (DPMH) reviewed the pregnancy data, provided recommendations for labeling and discussed their findings with the review team on January 17, 2023. In a review dated January 27, 2023, Katherine Kratz, M.D. stated the following:

Pregnancy

"There were 18 postmarketing reports of crisaborole use during pregnancy; however, the data are insufficient to identify a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Labeling language in subsection 8.1 will be updated to reflect this information. Postmarketing pregnancy safety studies are not recommended as there is no evidence of a new safety concern."

Lactation

"No new information is available on the presence of crisaborole in human milk, or the effects of crisaborole on the breastfed infant or on milk production. DPMH does not recommend any changes to subsection 8.2 of the labeling for crisaborole. Postmarketing lactation studies are not recommended as there is no evidence of a new safety concern."

Females and Males of Reproductive Potential

"There is no new information available on the effect of crisaborole on fertility, and subsection 8.3 is not present in the currently approved labeling for crisaborole. As there are no changes to the information available, DPMH recommends continuing to omit subsection 8.3, Females and Males of Reproductive Potential."

Dr. Kratz recommended the following changes (additions in red; deletions in ~~strike out~~) to labeling in section 8.1.

Risk Summary
Available data from case reports with EUCRISA use (b) (4) in pregnant women are insufficient to inform (b) (4) a drug-associated risk for major birth defects, (b) (4)-miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to 3 and 2 times, respectively, the maximum recommended human dose (MRHD) *(~~[~~see Data~~]~~)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects in the U.S. general population is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Pediatrics and Assessment of Effects on Growth

The new dosing regimen for crisaborole ointment triggered the Pediatric Research Equity Act (PREA). Initially, the Applicant planned to request a partial waiver of assessments in the pediatric population with mild to moderate AD aged 0 to <24-months for the QD dosing regimen. Their rationale was that safety information could be leveraged from Trial C3291002 which was conducted to address the pediatric PMR to support the safety of EUCRISA applied twice daily in the population age 3 months to 2 years. In addition, efficacy could be extrapolated from older pediatric age groups and adults. However, the Division recommended that the trial also seek to enroll subjects aged 3 months to 24 months.

The Agreed Initial Pediatric Study Plan (iPSP under IND 77537; dated April 24, 2020) included a partial waiver of assessments in subjects 0 to <3 months of age for the QD maintenance treatment regimen. The basis for the waiver is that studies are impossible or highly impractical because the diagnosis of AD is uncommon and often unreliably made before age 3 months. In addition, the Applicant agreed to enroll subjects ages 3 months to 2 years in the ongoing Trial C3291035 to obtain safety information with maintenance dosing in this population. The Applicant stated than no additional assessments in the pediatric population were planned and, therefore, no deferral was necessary.

The Pediatric Review Committee (PeRC) agreed with the assessment and plan presented by the Division. (Meeting held March 14, 2023.)

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
There were no new reports of treatment emergent adverse events that related to overdose with crisaborole ointment.

Drug Abuse Potential/ Withdrawal and Rebound
In view of the mechanism of action, there is no reason to anticipate any potential for abuse or dependency. There were no data to indicate the occurrence of physical dependency or abuse liability for crisaborole ointment to date. The review team did not consult with the Controlled Substance Staff.

The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound.

120-Day Safety Update

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a Periodic Safety Update Report (PSUR) to serve as the 120- Day Safety Update Report (SUR) (SDN 1692 dated October 7, 2022). The Reporting Period was December 14, 2021, through June 13, 2022. The review team identified no new safety signals in the SUR. The Applicant stated that additional safety information was available from three trials that were completed during the reporting interval: Trials C3291032 (Chinese and Japanese pediatric and adult subjects aged 2 years and older with mild to moderate AD), C3291038 (decentralized trial in subjects with stasis dermatitis) and C3291035 (the primary trial to support this submission.) There was no new information from non-interventional trials. There was one completed clinical research collaboration and one ongoing investigator-initiated trial which provided no substantive safety information.
Safety topics that have been monitored by the Applicant include cutaneous infections as recommended by Pharmacovigilance Risk Assessment Committee (PRAC) in the European Medicines Agency. Search of the safety database identified 5 non-serious cases, of which 3 were herpes infections and two were non-specific infections.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The analysis of the safety data from Trial C3291035 confirmed the association of crisaborole with allergic contact dermatitis. This signal was previously identified from postmarket data and included in labeling. Review of the available postmarketing data identified no other safety concerns.

Expectations on Safety in the Postmarket Setting

The analysis of the safety data from Trial C3291035 identified no new safety signals in the population age 3 months and older with mild to moderate AD. In addition, review of the findings from other trials which were submitted to support the safety of crisaborole and information included in the SUR identified no new safety issues. Therefore, we anticipate that no new safety concerns will arise in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile for crisaborole, 2% ointment applied twice daily for the treatment of mild to moderate AD was adequately characterized during the original development program. The primary source of safety data to support a once daily dosing regimen for maintenance treatment and flare reduction was Trial C3291035. The Applicant submitted data from seven additional trials (C3291001, C3291029, C3291028, C3291032, C3291037, C3291002, C3291027) to provide support for their safety conclusions. Because of the variability in the trial designs, duration of treatment, randomization ratios and study populations, the utility of an integrated analysis was limited.

The safety outcomes from Trial C3291035 were similar to the findings in the original application to support approval of crisaborole applied twice daily for the topical treatment of mild to moderate AD. The SAEs that occurred in both treatment periods were limited in number and largely unrelated to the study product. However, one subject developed an exacerbation of AD and cutaneous infection at the application site and surrounding skin which resulted in hospitalization. These SAEs which occurred on Days 32 to 40 of the OL period were moderate in severity and considered to be related to the use of crisaborole. For the other SAEs (Bronchospasm, Asthma, Cardiac failure congestive, Cardiomyopathy, Osteomyelitis, Maternal/Paternal exposure during pregnancy), causality is not supported by a mechanistically plausible relationship to the study product. The most common TEAEs associated with discontinuation of subjects from the trial in both treatment periods were cutaneous reactions in the system organ classes of Skin and subcutaneous tissue disorders (4%) and General disorders and administration site conditions (2%) (e.g., eczema/ dermatitis atopic, application site pain, application site infection, skin irritation, application site irritation, application site reaction, application site erythema, dermatitis contact and acne.)

AESI were not pre-specified in the protocol for C3291035. However, the Applicant presented narratives related to hypersensitivity, contact dermatitis and some potential class effects associated with PDE4 inhibitors (diarrhea and nausea) as AESI. The data confirmed the association of crisaborole with events of severe contact dermatitis. The AEs of hypersensitivity (urticaria, angioedema and hypersensitivity) that occurred during Trial C3291035 were considered unrelated and the administration of crisaborole continued. However, findings from

the post marketing safety database identified 2 cases of anaphylaxis that were "possibly related" to crisaborole. However, despite a temporal association, both cases included confounding factors that impacted a causality assessment.

During the OL, a total of 109 subjects (22%) developed 166 TEAEs with twice daily application of crisaborole. When related terms were grouped together, the TEAEs that occurred with the greatest frequency were application site pain (6%), upper respiratory tract infection (6%) and dermatitis atopic (5%). During the DB period, a total of 36 subjects (27%) who received crisaborole once daily developed 83 TEAEs and 49 subjects (36%) who received vehicle once daily developed 76 TEAEs. The TEAEs that occurred with the greatest frequency after pooling related terms included upper respiratory tract infection (9%) dermatitis atopic (3%) and application site pain (2%). Because the safety findings were similar to those observed in the original application, specific ARs are not repeated in Section 6 of labeling.

The review team did not perform an integrated analysis of all of the data from trials submitted to support safety. Review of the data in the clinical study report (CSR) for each trial provided some consistent findings regardless of the duration of the trial or study population. There were no deaths or serious unexpected TEAEs. Application site pain and dermatitis atopic were frequent TEAEs. Individually, the safety databases of some of these trials were too small to support a safety conclusion.

8.3. Statistical Issues

Crisaborole, 2% is approved for twice daily (BID) administration for the topical treatment of mild to moderate atopic dermatitis (AD) in subjects ages 3 months and older. In the current submission, the Applicant is seeking a modification to the Dosage and Administration section of labeling for the use of crisaborole, 2% applied once daily (QD) for maintenance treatment and flare reduction in subjects (ages 3 months and older) with mild-to-moderate atopic dermatitis (AD), who responded to twice daily treatment with crisaborole ointment, 2% for up to 8 weeks.

The Applicant defined the Evaluable-Double-Blind (Eval-DB) population as all randomized subjects with success in ISGA and EASI50 criteria and received at least 1 dose of trial intervention in the DB period. Eval-DB was specified to be the primary analysis population. The Safety-Double-Blind (SAF-DB) population was defined as all subjects randomly assigned to trial intervention and who received at least 1 dose of trial intervention in the DB maintenance period. This reviewer identified 16 subjects who were incorrectly randomized to the DB period and received at least 1 dose of trial intervention in the DB maintenance period. These subjects did not meet the randomization criteria (an ISGA score of clear [0] or almost clear [1], with a ≥2 grade improvement from baseline AND at least a 50% change from baseline on the eczema area and severity index (EASI). Therefore, this reviewer explored the Applicant-specified primary analysis in both populations (Eval-DB and SAF-DB). Results from the two populations were consistent.

The pre-specified primary efficacy endpoint was flare-free maintenance until onset of first flare during the 52-week double- blind period. However, the Agency advised the Applicant that the recommended primary endpoint was the proportion of subjects who maintain their response (i.e., ISGA of 0 or 1) at a prespecified timepoint during the maintenance period. Because the Applicant never specified an endpoint based on the maintenance of response at a specific timepoint, this reviewer explored the proportion of subjects who maintained their response over the maintenance period at all different timepoints for both populations Eval-DB and SAF-DB. Results from the two populations were consistent, indicating a higher proportion of subjects-maintained response in the crisaborole 2% QD group compared to the vehicle QD group at each timepoint.

8.4. Conclusions and Recommendations

There were several issues regarding the study design and endpoints that impacted the labeling recommendations and approval considerations. The original version of the protocol did not clearly specify how to handle subjects who did not fully meet the responder criteria (success on ISGA and EASI50) at the end of the run-in period; therefore, some non-responders were randomized into the maintenance period. However, the results are similar for the Eval-DB population (which excludes the non-responder subjects who were randomized) and SAF-DB population (which includes the non-responder subjects who were randomized). The inclusion or exclusion of these subjects did not impact the efficacy conclusions. For labeling, it may be reasonable to present results using the Eval-DB population as defined in the final version of the SAP which does not include all randomized subjects. The point estimates using the Eval-DB population more closely align with the original intent of the analysis.

During the development program, the Agency communicated to the Sponsor that the proposed primary efficacy endpoint "time to first flare" and secondary endpoints "number of flare free days and number of flares" were difficult to interpret. One reason was that assessment visits were not conducted daily (flare assessment were conducted every 4 weeks). To obtain more precise estimates for these endpoints, subjects needed to be assessed more frequently. Furthermore, the Applicant would need to provide additional data to justify and propose a clinically meaningful threshold level for the time to flare endpoint because a mere change on this endpoint may not translate to a clinically meaningful treatment effect. In view of these considerations, it is more appropriate to present estimates of proportion of subjects who maintain their response (i.e., ISGA of 0 or 1) over time in labeling, rather than presenting a single point estimate for “time to flare".

To establish the safety of crisaborole over 52 weeks of treatment, the Applicant evaluated AEs, concomitant medications and clinically meaningful changes in vital signs, and physical examinations. There were no deaths. One subject was hospitalized with SAEs (exacerbation of AD and cutaneous infection) that were considered related to crisaborole. Common TEAEs included nasopharyngitis/URI, dermatitis atopic/eczema and application site pain; common ARs included application site pain and dermatitis atopic/eczema. There were no new safety signals.

The review team considered multiple factors in the final labeling recommendations for the use of crisaborole, 2% applied once daily (QD) for maintenance treatment and flare reduction in subjects with mild to moderate atopic dermatitis. Over 52 weeks, subjects required a greater mean total amount of crisaborole to maintain a response if they used the product once daily for maintenance and twice daily for flares than if they used crisaborole only for flares. Although the data confirm the safety of crisaborole for long term use, AEs of severe contact dermatitis and hypersensitivity do occur. Therefore, a maintenance strategy which increases exposure to the product must confirm that the differences in outcomes from chronic use are statistically superior AND clinically meaningful to patients.

Therefore, the review team recommends approval of S-012 with the addition of the results from trial C3291035 to Section 14 Clinical Studies, (b) (4) in Section 2 Dosage and Administration of the labeling. However, the data support the addition of language to consider reducing application to once daily after clinical effect is achieved.

9 Advisory Committee Meeting and Other External Consultations

The Division conducted no Advisory Committee Meeting regarding this application because the safety profile of crisaborole in the population who received once daily dosing as maintenance was expected to be similar to the safety profile in the population who received twice daily dosing for active disease. In addition, the key issue, data needed to support a maintenance claim for a topical product, was discussed with the Medical Policy and Program Review Council (MPPRC) during the development program (April 20, 2018.) At the time, there were no topical products that had included labeling for maintenance treatment for any indication in the Division of Dermatology and Dentistry (DDD). The Division discussed the approach to study design and the data requirements to support this novel claim with the MPPRC.

10 Pediatrics

In the current supplement, the Applicant evaluated a maintenance dosing regimen in pediatric subjects aged 3 months to 17 years as well as adult subjects. The Applicant included a description of the trial and results in multiple relevant sections of labeling. The pediatric review team (Karen Fratantoni, MD; Shetarra Walker, MD; Shamir Tuchman, MD; and John Alexander, MD) from DPMH provided comments regarding the content of labeling for Section 8.4 Pediatric Use.

Current labeling for EUCRISA includes the following information regarding the use of the

product in the pediatric population.

Section 8.4 Pediatric Use

(b) (4)

The Division revised the labeling in Section 8.4 to reduce redundancy and enhance clarity. FDA proposed labeling for Section 8.4. (FDA additions in red; deletions in ~~strike-out~~ and additions from the Applicant in blue)

Section 8.4 Pediatric Use

The safety and effectiveness of EUCRISA have been established in pediatric patients ages 3 months and older for topical treatment of mild to moderate atopic dermatitis. Use of EUCRISA administered twice daily in this age group is supported by data from two 28-day adequate, vehicle-controlled safety and efficacy trials (b) (4) 1,313 pediatric subjects ages 2 years to 17 years of whom 874 received EUCRISA (b) (4) a 28-day open-label, safety and pharmacokinetics (PK) trial (137 subjects ages 3 months to less than 2 years who received EUCRISA) and another trial with an open-label period of up to 8 weeks (327 pediatric subjects ages 5 months to less than 18 years who received EUCRISA) *[see Clinical Pharmacology (12.3), and Clinical Studies (14)].*

(b) (4)

The safety and effectiveness of EUCRISA in pediatric patients below the age of 3 months have not been established.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted proposed prescribing information (PI) and a patient package insert (PPI) for EUCRISA. David Foss, PharmD, MPH, BCPS, RAC from the Office of Prescription Drug Promotion (OPDP) reviewed the PI and PPI and stated that "we do not have any comments at this time". (Review dated 2/28/2023). Katherine Kratz, M.D., and Karen Fratantoni M.D. from the Division of Pediatric and Maternal Health (DPMH) reviewed the proposed labeling and provided recommendations regarding the content of section 8 of labeling in accordance with 21 CFR 201.57(c)(9). See the review by Katherine Kratz, M.D., Medical Officer from the Maternal Health Team (dated January 27, 2023) regarding the pregnancy and lactation labeling. Clinical comments related to the content of labeling are integrated into the relevant sections of this review.

The review teams that provided recommendations regarding PI are tabulated below.

Table 37: Labeling Recommendations

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Clinical Team Section 1.1
2 DOSAGE AND ADMINISTRATION	Clinical Team Section 1.3, 8.4
5 WARNINGS AND PRECAUTIONS	Clinical Team Section 8.2.4
6 ADVERSE REACTIONS	Clinical Team Section 8.2.4
8 USE IN SPECIFIC POPULATIONS	Clinical & DPMH Teams Section 8.2.9, 10
14 CLINICAL STUDIES	Statistical Team Section 8.1.2, 8.1.3
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14.

Source: Reviewer's Table

Other Prescription Drug Labeling

The Applicant submitted a proposed patient package insert (PPI). In a collaborative review, Susan Redwood, MPH, BSN, RN from the Division of Medical Policy Programs (DMPP) and David Foss, PharmD, MPH, BCPS, RAC from OPDP reviewed the PPI and concluded that the proposed PPI was "acceptable with our recommended changes". The recommended changes were intended to provide consistency with the PI including the naming convention. Refer to the Patient Labeling Reviews dated March 2, 2023).

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard post-marketing surveillance are not warranted at this time.

13 Postmarketing Requirements and Commitment

None.

14 Division Director (Clinical) Comments

Not applicable.

15. Division Director (OB) Comments

Not Applicable

16 Appendices

16.1. References

Eichenfield LF et. Al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014 Jul;71(1):116-32. doi: 10.1016/j.jaad.2014.03.023. Epub 2014 May 9.

Hanifin, JM and ML Reed, 2007, A population-based survey of eczema prevalence in the United States, Dermatitis, 18(2):82-91.

Kim JP et al. 2016, Persistence of atopic dermatitis (AD): A systematic review and meta-analysis,J AM Acad Dermatol, 75 (4):681-687. http://dx.doi.org/10.1016/j.jaad.2016.05.028

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Silverberg, JI and Simpson EL, 2014, Associations of childhood eczema severity: a US population-based study, Dermatitis, 25(3):107-114.

Weston, WL and W Howe, 2019, Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis, UpToDate, accessed March 9, 2020,

https://www.uptodate.com/contents/atopic-dermatitis-eczema-pathogenesis-clinical-manifestations-and-diagnosis

Other references are included as footnotes.

16.2. Financial Disclosure

In accordance with 21 CFR Part 54 and Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators (Final, February 2013), Pfizer Inc. submitted financial disclosure information on the Covered Studies listed below. The financial disclosure information covers the time period from the start of the trial through one year after the completion of the trial.

The Applicant submitted financial disclosure information on Trial C3291035 only and none of the trials used to provide supportive safety information. The Applicant certified that no investigators participating in the trial were full time employees, and no investigators required due diligence activities. Among the 190 clinical investigators , only one had financial information to disclose, which represents (b) (6) of the total number of all clinical investigators who participated in the trial. (b) (6) received a total of $28,012.00 (b) (6)

Steps initiated to minimize bias

- The trial was conducted according to International Conference on Harmonisation (ICH) Good Clinical Practices.
- The current FDA Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators were checked where applicable.
- The facility performing the safety and efficacy evaluations was determined to be acceptable based on appropriate certification or historical performance and/or qualifications and credentials.
- Frequent monitoring of investigator trial site.
- The validity of the data collected during the study was confirmed by standard monitoring procedures.
- Procedures were scheduled at the same fixed intervals for subjects in all treatment arms.
- During the course of processing, analyzing, and reporting data from clinical trials, Pfizer applied procedures (e.g., querying data through electronic edit checks and clinical reviews) designed to ensure that errors were eliminated.
- Appropriate statistical methods were employed by use of an approved statistical analysis plan.

Covered Clinical Study: C3291035

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 190		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINDA L MCCORD
04/03/2023 12:12:16 PM
For myself and on behalf of Kevin Clark, MD, Acting Team Leader

RABAB M ELNAIEM
04/03/2023 12:27:43 PM

KATHLEEN S FRITSCH
04/03/2023 12:42:16 PM

TATIANA OUSSOVA
04/03/2023 02:04:15 PM