Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy Supplement
Application Number(s)	NDA 207695/ S-010
Priority or Standard	Priority
Submit Date(s)	23 September 2019
Received Date(s)	23 September 2019
PDUFA Goal Date	23 March 2020
Division/Office	Division of Dermatology and Dental Products (DDDP)
Review Completion Date	16 March 2020
Established Name	Crisaborole
Trade Name	EUCRISA™ (crisaborole) ointment, 2%
Pharmacologic Class	Phosphodiesterase 4 inhibitor
Code Name	PF-06930164/ AN2728
Applicant	Pfizer Inc.
Formulation(s)	Ointment
Dosing Regimen	Twice daily
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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	For topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older

Consultant Reviews

Labeling Reviews and Consultations

- Division of Medication Error Prevention and Analysis (DMEPA): Rhiannon Leutner, PharmD, MPH, MBA; Review of Prescribing Information (PI) (Review dated 12/20/2019)
- Division of Medical Policy Programs (DMPP): Shawna Hutchins, MPH, BSN, RN Review of Patient Package Insert (PPI) and Instructions for Use (Review dated 1/31/2020)
- Office of Prescription Drug Promotion (OPDP): Laurie Buonaccorsi PharmD; Review of PI and PPI (Review dated 2/4/2020
- Division of Pharmacovigilance I. Jonn Bailey, PharmD; Melissa Reyes, MD, MPH. Section 6.2 Postmarketing Experience (Review dated 1/21/2020)
- Division of Cardiovascular and Renal Products. Shetarra Walker MD, MSCR. (Review dated 1/31/2020)

Division of Pediatric and Maternal Health (DPMH)

- Pediatric Division Consult Response: Erica Radden, M.D. (Review dated 03/2/2020; comments provided for Sections 6, 8, 12 of labeling)

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Glossary

AD	atopic dermatitis
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
AHA	alpha hydroxy acid
AR	adverse reaction
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DILI	drug-induced liver injury
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DPV 1	Division of Pharmacovigilance I
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
ISGA	Investigator's Static Global Assessment
IND	investigational new drug
iPSP	initial pediatric study plan
IVCD	intraventricular conduction delay
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NOAEL	no-observed-adverse effect level
OPDP	Office of Prescription Drug Promotion
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDE-4	phosphodiesterase 4
PE	Pediatric Exclusivity
PeRC	Pediatric Review Committee
PG	propylene glycol
PI	prescribing information
PK	pharmacokinetics

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PMR	postmarketing requirement
POEM	Patient-Oriented Eczema Measure
PPI	patient package insert
PPSR	Proposed Pediatric Study Plan
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
QTc	corrected QT interval
QTIRT	QT Interdisciplinary Review Team
SAE	serious adverse event
SDTM	Study Data Tabulation Modal
sNDA	supplemental new drug application
SOC	system organ class
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TQT	thorough QT
ULN	upper limit of normal
WR	written request

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1. Executive Summary

EUCRISA™ (crisaborole) ointment, 2% is a phosphodiesterase 4 (PDE-4) inhibitor which is indicated for topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. The Applicant, Pfizer Inc. (acquired Anacor in 2016), submitted a supplemental new drug application (sNDA) to support revisions to product labeling which provided for the use of EUCRISA for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 3 months of age and older. The Applicant conducted Trial C3291002 to address the post marketing requirement (PMR) 3142-1 under the Pediatric Research Equity Act (PREA) to evaluate the pharmacokinetics and effects of EUCRISA on safety in the pediatric population age 3 months to less than 2 years. This protocol served as the basis for the issuance of a pediatric written request (WR) for crisaborole (3/16/2017). In addition, the Applicant provided language for section 6.2 Postmarketing Experience and revisions to sections 12.3 Pharmacokinetics, 8.1 Animal Data and 13 Nonclinical Toxicology of the prescribing information (PI) which were previously submitted (S-007, S-009).

Trial C3291002 was an open-label, pharmacokinetic (PK) and safety trial enrolling 137 pediatric subjects age 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%.

In Trial C3291002, there were no deaths, 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.

The applicant addressed PMR 3142-1 by conducting Trial C3291002 and met the terms of the WR exactly (Prong 1). PMR 3142-1 is fulfilled. The Applicant provided sufficient data to confirm that the risk benefit conclusions in this pediatric population are similar to the older pediatric age groups and the adult population. This reviewer recommends an approval action for this application, NDA 207695 Supplement-010, to revise the current indication to the topical treatment of atopic dermatitis in patients 3 months of age and older. As the labeling review is still in progress, this recommendation is contingent upon the successful completion of labeling negotiations with the Applicant.

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1.1. Benefit-Risk Assessment

Review of the data from subjects 3 months to 2 years of age does not change the benefit-risk profile of EUCRISA. The review team based the analysis of the benefits and risks of EUCRISA on two adequate, well-controlled phase 3 clinical trials (AN2728-AD-301 and AN2728-AD-302) enrolling a total of 1522 subjects 2 to 79 years of age [1]with 5% to 95% BSA affected with AD. In both trials, EUCRISA ointment, 2% was statistically superior to vehicle ointment on the primary endpoint, success in ISGA at Day 29. Success in ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. In Trial AN2728-AD-301, 32.8% of subjects who were treated with EUCRISA achieved success at Day 29 compared with 25.4% who were treated with vehicle. In Trial AN2728-AD-302, 31.4% of subjects who were treated with EUCRISA achieved success at Day 29 compared with 18.0% who were treated with vehicle.

The safety profile for EUCRISA was adequately characterized during the original development program (NDA 207695 approved 12/14/2016). There were no deaths and no serious adverse events that were attributed to the study product. The only adverse reaction observed in greater than 1% of subjects compared with vehicle was application site pain. However, a total of 6 subjects reported application urticaria in the phase 3 trials (AN2728-AD-301 and AN2728-AD-302), 3 subjects who received EUCRISA and 3 subjects who received vehicle. There was no imbalance in the treatment arms but the finding of urticaria was deemed clinically meaningful and possibly related to an excipient or other component in the vehicle.

The review team evaluated significant, potential, safety concerns which were observed with orally administered PDE-4 inhibitors. A comprehensive analysis of weight loss and suicidal ideation and behavior during the review cycle of the original application did not support a causal link with EUCRISA.

In this supplement, the Applicant submitted results from Trial C3291002 to provide safety and bioavailability data for EUCRISA for the treatment of AD in subjects age 3 months to < 2 years. The trial enrolled a total of 137 subjects with mild to moderate AD defined as an ISGA Score of mild (2) or moderate (3) at Baseline/Day 1 and at least 5% of the "treatable" body surface area (BSA) affected, excluding the scalp. Subjects participating in pharmacokinetic (PK) assessments (PK cohort) had moderate AD according to the ISGA (3) and at least 35% of the "treatable" BSA affected (excluding the scalp) and adequate venous access to permit repeated PK sampling. Of these subjects, at least 3 subjects were less than 9 months of age.

The data indicated no new safety signals. There were no deaths; one subject experienced a serious adverse event (febrile seizure which was assessed as not related) and no subjects withdrew from the trial due to adverse events. The treatment-emergent adverse events (TEAEs) observed in this pediatric population age 3 months to <2 years and assessed to be related to

[1] Intent to treat (ITT) or randomized population

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the study product (e.g., application site pain/discomfort, application site erythema/erythema and pruritus) were similar to the TEAEs observed in subjects age 2 years and older.

The submitted PK, PD and safety data in the pediatric population indicate a favorable risk benefit conclusion and support approval of this sNDA which provides for the use of EUCRISA in the population 3 months and older with mild to moderate AD.

2. Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease that occurs predominantly in the pediatric population. The presence of AD is frequently associated with elevated serum immunoglobulin (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 atopic dermatitis 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 atopic dermatitis commonly occurs between 3 and 6 months of age. Although the onset of AD may occur within the first few months of life, the definitive diagnosis may not occur until later. 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% experience signs and symptoms that persist into adulthood. A small proportion of patients develop the disease as adults (Weidinger and Novak 2016).

The majority of patients are diagnosed with AD of mild severity. Among 91,642 children age 0

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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. Greater disease severity tends to be correlated with more severe pruritus. Disruption of sleep is observed in up to 80% of children with atopic dermatitis and is related to nocturnal itching and scratching. Mood and behavior disorders occur with greater frequency in children with atopic dermatitis 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

See the Clinical Review of the original submission (dated 11/3/2016) for a discussion of the management of mild to moderate atopic dermatitis.

2.3. Patient Experience Data

In addition to clinician reported outcome measures of treatment effect, the protocol included one observer reported outcome assessment, Patient-Oriented Eczema Measure (POEM). Parent(s)/legal guardian completed this instrument at Baseline, Day 8, 15 and 29. POEM contains 7 questions related to signs and symptoms of AD (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking and dryness/ roughness). The responder rated the frequency that the infant experienced the sign or symptom over the past week, from 0 (no days) to 4 (every day). Total scores are associated with the following disease severities:

- 0 to 2 = Clear or almost clear;
- 3 to 7 = Mild eczema;
- 8 to 16 = Moderate eczema;
- 17 to 24 = Severe eczema;
- 25 to 28 = Very severe eczema.

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☐	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)	
		X	Observer reported outcome (ObsRO)	7.3.4
		X	Clinician reported outcome (ClinRO)	7.2.2
		☐	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		
	X	Patient-focused drug development or other stakeholder meeting summary reports		2.3
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

In this age group, observers provided data regarding the symptoms experienced by subjects. As such, this adverse event data is imprecise. Erica Radden, MD, Division of Pediatric and Maternal Health (DPMH) states:

> "This subpopulation of subjects is largely nonverbal, and there are no validated measures to accurately assess pain in this age group. Additionally, the protocol suggests that either caregivers or investigators should note observed adverse events on the clinical report form; however, the method for assessment of pain or pruritis is not described in the protocol or study reports. Reliance on observer or clinician reported outcomes without a clearly described method for making these assessments makes interpreting the results difficult." (Review dated 3/2/2020)

At the Patient Focused Drug Development Meeting which included FDA participants

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(September 23, 2019), patients and their families discussed current challenges with the variability in effectiveness, tolerability, access to treatments, and uncertainty regarding long-term effects of available treatments. Therefore, the development and approval of additional safe and effective therapies for children and adults with AD continues to be an important goal.

3. Regulatory Background

The FDA approved EUCRISA (crisaborole) ointment, 2% (NDA 207695) on December 14, 2016 for the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. The approval letter included a partial waiver of the pediatric study requirement for ages 0 to <3 months because the diagnosis of atopic dermatitis may not be confirmed in this age group and studies are highly impracticable. In addition, the Agency deferred the submission of the pediatric study for ages 3 months to <2 years for this application because the product was ready for approval for use in patients 2 years and older, and the pediatric study in the remaining pediatric age groups had not been completed.

This required clinical study was the following:

3142-1
Conduct an open-label safety trial in at least 100 evaluable pediatric subjects with mild to moderate atopic dermatitis ages 3 months to <2 years and at least 5% treatable percent body surface area (%BSA). Evaluate the pharmacokinetics of crisaborole under maximal use conditions in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).

Final Protocol Submission: 03/2017
Trial Completion: 08/2019
Final Report Submission: 01/2020

Written Request
Pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act, the Applicant submitted a Proposed Pediatric Study Plan (PPSR) on 1/29/2015. The Applicant requested that the required evaluation of their product in the pediatric population under PREA serve as the basis for the issuance of a pediatric written request for crisaborole in the pediatric population age 3 month to <2 years under the Best Pharmaceuticals for Children Act.

The proposed trial in the pediatric population with atopic dermatitis (AD) was consistent with the Agreed iPSP (Advice Letter dated 10/6/2014). (b) (4)

(b) (4)
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On May 14, 2015, the Applicant resubmitted a PPSR (IND 77,537, SN0122) that included (b) (4) a trial in subjects aged 3 months to 24 months with AD (b) (4) On June 19, 2015, the Division issued an Inadequate Study Request letter informing the sponsor that "Your Proposed Pediatric Study Request is inadequate to provide a Written Request (b) (4) until the safety and efficacy of your drug product in the treatment of AD have been established in a patient population 2 years and older. (b) (4)

On November 18, 2016, the Applicant submitted another PPSR and Protocol C3291002 to address the required evaluation of their product in the pediatric population under PREA. The Applicant requested that this protocol serve as the basis for the issuance of a pediatric written request for crisaborole. Prior to initiation of the clinical studies, the sponsor agreed to complete two non-clinical studies: a pilot dose range-finding study and a pivotal juvenile rat toxicology study with results to be reported to the FDA. The FDA issued a WR on March 16, 2017.

The Applicant did not request any meetings to discuss the WR or PMR 3142-1. However, the Applicant submitted a proposal to amend the WR (IND 77537: Letter dated 5/2/2017) with the following changes:

- Eliminate the assessment of propylene glycol systemic levels at each PK sampling timepoint and include assessment of propylene glycol systemic levels, lactate levels, calculation of osmolar gap and anion gap at pre-dose on Day 8 only.
- Remove the requirement to obtain propylene glycol systemic levels in all subjects with abnormal renal or hepatic function at Baseline.
- Obtain the initial assessments at screening rather than baseline

The FDA agreed with the proposed revisions (Written Request Amendment 1 Letter dated 07/05/2017). The Applicant submitted an amended protocol (07/10/2017) which conformed with the terms of the revised WR. The team reviewed the protocol (Clinical Review dated 10/12/2017), agreed with the general design, study population and assessments and provided minor comments.

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 domestic sites.

4.2. Product Quality

The Applicant determined that the formulation of EUCRISA which was approved for use in the population age 2 years and older was acceptable for use in the target pediatric population. Therefore, the Applicant submitted no new product quality data. For the analysis of the chemistry, manufacturing, and controls (CMC) information which supported the original approval and assured the identity, strength, purity and quality of the drug product refer to the Product Quality Assessment Review (Application Technical Lead, Yichun Sun, PhD. review archived 08/17/2016).

Joel S. Hathaway, Ph.D., Office of Pharmaceutical Quality, reviewed this submission (Review dated 02/10/2020) and stated:

> "No changes were proposed to the CMC-related sections of the labeling (Sections 3, 11 or 16) or to the administrative information regarding the manufacturing and packaging of the drug product.
>
> The Applicant provided a Claim for Categorical Exclusion from the requirement for an Environmental Assessment (EA), per 21 CFR 25, Part 25.15 (a) and (d).
>
> Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (b), applicable for action on a supplement to an NDA resulting in an increase in use, but where the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion.
>
> As the Applicant has certified that the expanded patient population will not increase the exposure of the drug substance to the environment above the 1ppb threshold, the request for Categorical Exclusion from the requirement for a revised EA is acceptable.
>
> Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (b), applicable for action on a supplement to an NDA resulting in an increase in use, but where the

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estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion.

As the Applicant has certified that the expanded patient population will not increase the exposure of the drug substance to the environment above the 1ppb threshold, the request for Categorical Exclusion from the requirement for a revised EA is acceptable."

Dr. Hathaway concluded, "This supplement is recommended for approval."

5. Pharmacology Toxicology

The Applicant submitted no new pharmacology/toxicology data in this pediatric efficacy supplement. The Pharmacology/Toxicology team conducted a comprehensive review of the nonclinical data which was submitted to support the original approval of EUCRISA Ointment. For the analysis and discussion of the nonclinical data, refer to the reviews by Kumar D. Mainigi, MSc., M.P.H., PhD, DABT dated 8/15/2016 and Barbara Hill, PhD dated 11/17/2016.

Per written request, "Based on review of the available nonclinical toxicology data, the following studies must be conducted prior to the start of the clinical study described in this written request.

Study 1:

Pilot dose oral (gavage) range-finding study in juvenile rats (1 week of age at the start of dosing).

This study will assess a range of oral gavage doses and evaluate the toxicokinetics to compare potential toxicity and exposures with crisaborole in studies of older rats. The results from this dose range-finding study will be used to determine the appropriate dose range to use in the systemic juvenile rat toxicology study (Study 2).

Study 2:

Systemic toxicology study in juvenile rats (1 week of age at the start of dosing).

The route of administration in this study will be determined based on the results from the pilot dose range-finding study in juvenile rats and must be agreed upon with the Agency. This toxicology study will assess clinical observations, food consumption, body weight, motor activity, acoustic startle habituation, macroscopic and limited microscopic pathology evaluations, and toxicokinetics. The protocol must be agreed upon with the Agency before initiation of the study."

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The Applicant submitted the nonclinical data to support the assessments in the population age 3 months to 2 years on August 11, 2017. The Pharmacology/ Toxicology Daivender Mainigi, PhD. Evaluated the data and provided the following comments:

> "the highest oral test dose of 100mg/kg/day did not produce any local or systemic toxicity in juvenile male and female Sprague Dawley rats. Therefore, this dose was established as NOAEL (no-observed-adverse effect level)." (Pharmacology/ Toxicology Review under IND 77537 dated 12/30/2019)

Dr. Mainigi indicated that the safety margin was substantial and systemic exposure was sufficiently low ("picograms if detectable") as to be "below any threshold level of toxicity" (email communication dated 1/7/2020).

During the review of NDA 207695 S-007, the Pharmacology/Toxicology team provided comments regarding the proposed changes to the safety margins in Sections 8 *Use in Specific Populations* and 13 *Nonclinical Toxicology* of the USPI for EUCRISA. See labeling reviews by Barbara Hill, PhD, Pharmacology/Toxicology Supervisor dated 08/18/2017 (S-007) and 02/20/2020 (S-010) for labeling comments and a discussion of the methodology of the calculation of the safety margins.

6. Clinical Pharmacology

The Applicant submitted pharmacokinetic (PK) data from a subset of subjects enrolled in Trial C3291002 and the following two population modeling analysis reports:

- Non-linear regression analysis of crisaborole systemic exposures
- Regression analysis of crisaborole and propylene glycol (PG) systemic exposure

The Clinical Pharmacology team focused their review on the analysis of the pharmacokinetics (PK) of twice daily topical administration of EUCRISA™ (crisaborole) ointment, 2% in 21 subjects age 3 months to < 2 years with mild to moderate AD. In addition, the Pharmacometric reviewer, Da Zhang, PhD, confirmed the conclusions of the population modeling analysis reports. For a detailed analysis of the PK data, population modeling and recommended revisions to the proposed language in Section 12 of labeling, see the review by Luke Oh, PhD, and Da Zhang, PhD dated March 4, 2020. A summary of the clinical pharmacology and biopharmaceutics findings from their review are presented below. For a discussion of the data which supported approval of EUCRISA for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older, see the Clinical Pharmacology Review by Chinmay Shukla, PhD. dated August 30, 2016.

After review of the results of Trial C3291002, Luke Oh, PhD and Da Zhang, PhD, Office of Clinical Pharmacology/Division of Clinical Pharmacology III, concluded, "From a Clinical

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Pharmacology perspective, this supplement is acceptable provided the labeling comments are adequately addressed by the Applicant; furthermore, PMR 3142-1 is considered fulfilled."

6.1. Pharmacokinetics

The PK cohort enrolled 21 subjects age 3 months to less than 2 years with moderate AD who received EUCRISA under maximal use conditions. Among these subjects, there were 3 subjects who were considered non-compliant with protocol procedures. In addition, the Applicant identified 5 subjects from one study site (1009) as "outliers" due to possible cross-contamination of their samples (sampling sites were not cleansed per protocol and sampling occurred adjacent to treatment sites). A total of 18 subjects completed the PK assessments as specified in the WR. However, after exclusion of the 5 "outliers", the number of evaluable subjects in the PK cohort to be described in labeling was 13. Among the 13 subjects in this cohort, the youngest was 4 months of age.

The protocol specified sparse sampling because of the age of study population. Sampling for plasma concentrations of crisaborole and its metabolites (AN7602 and AN8323) occurred on Day 8 prior to the dose and 3 and 12 hours after the dose. For all subjects, blood sampling for the assessment of propylene glycol (PG) concentration occurred at Screening and Day 28 prior to the dose. Subjects in the PK cohort provided an additional pre-dose sample on Day 8. Dr. Oh indicated that assays which were used to measure the concentration of the active moiety and metabolites and PG concentrations were acceptable.

As observed with topical products, the PK results varied widely. See the Clinical Pharmacology review for a tabulation of the PK parameters. The Clinical Pharmacology team proposed that the following statement be included in section 12.3 Pharmacokinetics of labeling:

> The PK of EUCRISA were investigated in 13 subjects 4 months to less than 24 months of age. The mean ± SD Cmax and AUC0-12 for crisaborole were 188±100 ng/mL and 1164±550 ng·h/mL, respectively.

Dr. Oh conducted an exploratory analysis of the impact of intrinsic factors such as age and BSA affected with AD on systemic exposure. The results suggested that exposure increased with age but not BSA. In addition, the daily dose appeared to have limited impact on systemic exposure. However, the small sample size precluded support for any definitive conclusions.

In the safety population, the plasma levels of propylene glycol (PG) ranged from 0 (below the lower limit of quantitation) to 44,000 ng/mL (or 4.4 mg/dL). Other concomitant topical sources of PG (baby wipes, emollients and barrier creams) were not restricted or subject to a wash- out period during the trial. See section 7.3.5 of this review for a discussion of the results of the evaluation of potential PG toxicity with the use of EUCRISA.

During the labeling discussions, the Clinical Pharmacology team reviewed their recommendations regarding the data submitted in S-007 and S-009. These submissions

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contained reports of in vitro studies that were conducted to evaluate the inhibitory effect of crisaborole and its two metabolites (AN7602 and AN8323) on following enzymes and transporters:

- UDP-glucuronosyltransferase: 1A1, 1A4, 1A6, 1A9, 2B7, 2B15
- BCRP, MATE1, MATE2K, MDR1, OAT1, OAT3, OATP1B1, OAT1B3, OCT1, OCT2.

Although reviews were finalized for S-007 and S-009, the Division did not complete labeling negotiations. For a discussion of the findings and labeling recommendations by the Clinical Pharmacology team, see reviews by Jihye Ahn, Pharm.D. dated 2/28/2019 and 5/31/2019. The Clinical Pharmacology team provided recommendations that will be included in section 12.3 of labeling.

6.2. Pharmacometrics

Population PK Modeling Analysis Review
To characterize the PK of EUCRISA in different study populations and to identify important covariates that impact these PK parameters, the Applicant conducted a non-linear regression analysis of crisaborole systemic exposures including data from three phase 1 trials in healthy volunteers, two phase 1b in trials in subjects with AD and 1 Phase 1b trial in subjects with psoriasis (approximately 244 subjects). Review of the results of this model suggested that disease status had a significant impact on systemic exposure while race, gender and disease severity were unlikely to have a clinically meaningful impact on systemic exposure. In addition, for individuals receiving treatment to a similar percent BSA, exposure across age groups is expected to be similar.

To characterize the relationship between PK parameters and dose, to identify covariates that impact the systemic PK parameters of crisaborole and to explore the relationship between dose and propylene glycol concentrations in plasma, the Applicant developed the non-linear regression model. This model was based on data from 8 clinical trials (approximately 271 subjects). Review of the results of this model confirmed that disease state impacts systemic exposure and suggested that crisaborole dose does not correlate statistically with the change of propylene glycol concentration. Dr Zang concluded that “Crisaborole systemic exposures in children (>3 months of age) at maximum possible dose are unlikely to exceed the systemic exposures at the maximum possible dose in adults.” (See the Clinical Pharmacology Review, pharmacometic analysis by Da Zhang, PhD dated 3/4/2020.)

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7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The Applicant conducted a single, open-label clinical Trial C3291002, to address PMR 3142-1 and to respond to the WR. Trial C3291002 was entitled, "A Phase 4 Multicenter, Open-Label Safety Study Of Crisaborole Ointment 2% In Children Aged 3 Months to Less Than 24 Months With Mild To Moderate Atopic Dermatitis." Key elements of the trial are summarized below.

Table 1: Clinical Trial C3291002

Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Study to support safety						
Multicenter, open label, safety study	Twice daily in a thin layer to all affected areas	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	-Male or female 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)

Abbreviations: TEAE = treatment-emergent adverse events; VS = vital signs; ECG = electrocardiograms; PK = pharmacokinetics; BSA = body surface area; ISGA = Investigator's static Global Assessment scale
*Excluding the scalp
Source: Reviewer's table

7.1.2. Review Strategy

The focus of this review was the local and systemic safety of EUCRISA for the treatment of mild to moderate AD in subjects age 3 months to 2 years. Efficacy in this population was extrapolated from data in the adult population and older pediatric age groups.

Data Sources
The sources of data used for the evaluation of the safety and treatment effects of EUCRISA for the proposed indication included a final study report submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)], bioanalytic reports and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including the protocol, clinical study reports, SDTM, and Analysis Data Model (ADaM) format are located in the following network path:

\\CDSESUB1\evsprod\nda207695\0492.enx

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Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of EUCRISA for the proposed indication appeared adequate.

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial C3291002
This was a multicenter, open- label trial to evaluate the safety of EUCRISA (crisaborole) Ointment, 2% applied twice daily for 28 days in infants aged 3 months to less than 2 years with mild to moderate AD. Exploratory objectives included the evaluation of PK and efficacy.

Study Population
At least 100 evaluable subjects for safety and at least 16 evaluable subjects for pharmacokinetics of crisaborole under maximal use conditions. The key entry criteria were as follows:

- Inclusion criteria
  - Male and female subjects 3 months to less than 2 years of age
  - ISGA Score of mild (2) or moderate (3)
  - at Baseline/Day 1
  - Subject meets one of the following:
    - ✓ PK cohort: has moderate atopic dermatitis according to the Investigator's Static Global Assessment (ISGA of 3) and at least 35% treatable % BSA, excluding the scalp, and adequate venous access to permit repeated PK sampling; Of these subjects, at least 3 subjects are less than 9 months of age.
    - ✓ Non-PK cohort: has mild to moderate atopic dermatitis according to ISGA (2 or 3) and at least 5% treatable % BSA, excluding the scalp.

- Exclusion criteria
  - Any clinically significant dermatological condition or disease including Netherton syndrome
  - Premature at birth, defined as less than 37 gestational weeks.
  - Creatinine clearance (age appropriate) that is below the lower limit of normal (LLN), or serum creatinine greater than the upper limit of normal (ULN).
  - Aspartate aminotransferase or alanine aminotransferase values greater than the ULN
  - Has a history of:
    - ✓ angioedema or anaphylaxis
    - ✓ hyperactive airway disease requiring corticosteroid therapy
    - ✓ significant active systemic or localized infection, including known actively infected AD
    - ✓ biologic therapy including intravenous immunoglobulin at any time prior to study

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- ✓ treatment for any type of cancer
- ✓ previous treatment with crisaborole

Study Design

Investigators/ study staff instructed parents/guardians to apply EUCRISA in a thin layer to all areas affected with AD ("treatable AD lesions") except the scalp twice daily for 28 days. Investigators/ study staff demonstrated the application technique and emphasized that doses needed to be administered 8 to 10 hours apart with avoidance of mucous membranes. For subjects in the PK cohort, study staff carefully calculated the dose for each subject according to the %BSA affected with AD at Baseline/Day 1. In addition, Investigators/ study staff instructed parents/guardians of subjects in the PK cohort to avoid application of EUCRISA to the distal hands and feet and perioral area. Per Agreed Pediatric Study Plan, the Applicant evaluated the approved formulation of EUCRISA in the pediatric population age 3 months to less than 2 years.

Assessments occurred at the study site or via telephone contacts at Screening (up to 28 days prior to Baseline/Day 1), Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (end of treatment/early termination), Day 36, and Day 57 (end of study). Investigational staff conducted visits on Day 22, 36 and 57 as telephone interviews with parents or guardians. Parents/guardians of subjects enrolled in the PK cohort scheduled twice daily visits on Days 2 through 7 to ensure consistent application of the study product and allow PK sampling. However, following Baseline, some of the applications and blood sampling (except Day 8 procedures) could be performed by a qualified healthcare professional in the home. Parents or legal guardians of all subjects recorded each application of the study product in a dosing diary to monitor compliance. Investigational staff queried parents/ legal guardians on compliance with the lifestyle requirements.

An External Data Monitoring Committee led by prominent pediatric dermatologist, (b) (4) MD, provided recommendations to ensured timely review of blinded safety data and overall study integrity.

Assessments of Safety

- Safety laboratory tests (see section 7.3.3 of this review): Screening and end of treatment
- Physical examinations, including height/length, and weight: Screening and end of treatment
- Vital signs (temperature, respiratory rate, pulse rate, and blood pressure): all site visits
- Electrocardiograms: Screening/Baseline, Day 8 and end of treatment
- Adverse event reporting: all visits

Assessments of treatment effect included:

- "Treatable" %BSA excluding the scalp using the "hand print" method
- Investigator's Static Global Assessment (See section 7.2.2 of this review.)

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- Eczema Area and Severity Index (EASI) which quantifies the severity of AD based on the severity of the clinical signs (erythema, induration/papulation, excoriation, and lichenification on 4-point scales) and the percent BSA affected.
- Patient-Oriented Eczema Measure (POEM) (See section 2.3 of this review.)

Efficacy in subjects age 3 months to <2 years will be supported by extrapolation of efficacy from adequate and well controlled studies in the population age 2 years and older.

Other Assessments

- PK sampling for plasma concentrations of crisaborole and its metabolites (AN7602 and AN8323) occurred on Day 8 prior to the dose and 3 and 12 hours after the dose.
- Sampling for the assessment of propylene glycol concentration occurred at Screening and Day 28 prior to the dose. Subjects in the PK cohort provided an additional pre-dose sample on Day 8. A topical lidocaine-based anesthetic which did not contain propylene glycol could be used prior to blood sampling.

Concomitant Medications

Medications/therapies prohibited during the trial (Day 1 through Day 29 Visit):

- Systemic corticosteroids.
- Systemic immunosuppressive agents (e.g., methotrexate, ciclosporin, azathioprine, hydroxychloroquine, mycophenolate mofetil).
- Use of high-or-mid-potency topical corticosteroids or calcineurin inhibitors anywhere on the body.
- Systemic antihistamines.
- Light therapy (ultraviolet light therapy).
- Systemic antibiotics for the treatment of new onset infections that require use longer than 14 days.
- Systemic leukotriene receptor antagonist agents (e.g., montelukast).
- Wet wrap therapy.
- Use of topical medications or products on AD lesions, including, but not limited to:
- Antibacterial soaps (for bathing);
- Bleach baths;
- Topical sodium hypochlorite-based products;
- Topical antihistamines;
- Topical antibiotics (unless required for adverse event (AE) treatment)
- Emollients;
- Topical low potency corticosteroids (including hydrocortisone $\leq$1%);
- Diaper rash creams, lotions, ointments, powders, etc. where lesions are present

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Medications/therapies permitted during the trial (Day 1 through Day 29 Visit):

- Use of intranasal, ophthalmic and inhaled corticosteroids.
- Use of bland emollient(s) of choice to manage dry skin in areas surrounding, but not on or overlapping with treatable AD-involved areas.
- Use of bland emollient(s) of choice (not containing urea) in AD skin areas where crisaborole is not applied (e.g., scalp).
- Use of sunscreen, but not on or overlapping with treatable AD-involved areas.

Investigators advised parents/guardians to avoid bathing/ washing treatment sites within 4 hours of application or wiping or occluding the treatment sites. If the product was inadvertently removed, it should not be reapplied until the next scheduled dose. Investigators instructed parents/guarding to avoid the use of any other products containing propylene glycol. Pregnant caregivers should wear gloves to apply the product.

Endpoints

Safety:

- The primary endpoints were the incidence of treatment emergent AEs (TEAEs) (including application site reactions), SAEs, and clinically significant changes in height, weight, vital signs, electrocardiogram (ECG) and clinical laboratory parameters.

Exploratory endpoints were the following:

Efficacy:

- Change from baseline in %BSA;
- Proportion of subjects who achieve treatment success (defined as a score of Clear or Almost Clear with a 2-grade improvement from baseline) based on ISGA;
- % Change from baseline in EASI at each scheduled time point;
- Change from baseline in POEM at each scheduled time point.

PK [crisaborole, metabolites (AN7602 and AN8323)]:

- C_{max} (Day 8);
- T_{max} (Day 8);
- AUC_{0-12} (Day 8).

Subject Stopping Criteria

Parent/legal guardians could withdraw subjects at any time for any reason; Investigators could withdraw subjects at any time for their own safety. The following criteria were potential considerations for the withdrawal of subjects from the trial:

- The occurrence of adverse events that require the subject to stop participation in the study, due to availability for, or intolerance to, the study procedures.
- Adverse effects of the study active ingredient that are considered to be clinically significant by the physician in charge, and/or might be harmful to the subjects' health.
- Abnormal laboratory tests considered to be clinically relevant.
- Concurrent diseases that require use of a prohibited medication.

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- Adverse events consistent with propylene glycol or systemic PDE-4 inhibition toxicity such as clinically significant ECG abnormalities, acidosis, dehydration, diarrhea, seizure, signs of central nervous system depression and/or significant changes in mood or behavior.
- Clinically significant hypersensitivity reactions.

Investigator(s)

The Applicant identified 32 investigational sites located in three countries (Australia, Canada and the United States). A total of 137 subjects enrolled in the trial from 209 subjects who were screened.

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Table 2: Study Sites and Enrollment

Site Number	Principal Investigator	Site Name and Location	Subjects Screened (N)	Subjects Enrolled (N)
		AUSTRALIA		
1016	Ktut Arya	Australian Clinical Research Network, New South Wales	11	6
1021	Lynda Spelman	Veracity Clinical Research, Queensland	2	1
1022	John Su	The Royal Children's Hospital, Victoria	4	3
1023	Rodney Sinclair	Sinclair Dermatology, Victoria	4	2
1024	Michael Freeman	The Skin Centre, Queensland	1	1
1038	Johannes Kern	Eastern Health, Victoria	4	2
		CANADA		
1020	Danielle Marcoux	Centre hospitalier universitaire Sainte-Justine, Quebec	0	0
1025	Charles Lynde	Lynderm Research Inc, Ontario	9	5
1026	Melinda Gooderham	SKiN Centre for Dermatology, Ontario	3	1
1036	Loretta Fiorillo	Stollery Children's Hospital, Alberta	4	4
		UNITED STATES		
1001	Paul Wisman	Pediatric Research of Charlottesville, PLC, Virginia	7	5
1002	Sarah Field	Cummins, Kozak, Gillman & Ellis, Inc, California	0	0
1003	Robert Call	Clinical Research Partners, LLC	0	0
1004	Edward Kent	Timber Lane Allergy & Asthma Research, LLC	7	3
1005	Joe Williams	IMMUNOe Research Centers	6	1
1006	Colony Fugate	Houston Center Pediatrics, Oklahoma	3	3
1007	Richard Gower	Dermatology Specialists of Spokane, Washington	16	10
1008	William Rees	PI-Coor Clinical Research, LLC, Virginia	19	13
1009	Julie Shepard	Ohio Pediatric Research Association, Inc., Ohio	25	23
1010	Sarah Arron	University of California, San Francisco, California	16	8
1012	Joel Schlessinger	Skin Specialists, PC, Nevada	7	7
1018	Wynnis Tom	Rady Children's Hospital, California	2	2
1019	Eric Simpson	Oregon Health & Science University, Oregon	1	1
1027	Craig Spiegel	Craig A. Spiegel, M.D., Missouri	2	0
1028	John Browning	Texas Dermatology and Laser Specialists, Texas	3	1
1029	Janet DuBois	DermResearch, Inc., Texas	4	2
1031	Joseph Fowler	DS Research, Kentucky	2	1
1032	Douglass Forsha	Jordan Valley Dermatology Center, Utah	10	9
1033	Leslie Baumann	Baumann Cosmetic and Research Institute, Florida	12	7
1035	Dowling Stough	Burke Pharmaceutical Research, Arizona	2	2
1037	Nathan Forbush	Tanner Clinic, Utah	20	12
1040	Andrea Zaenglein	Penn State Hershey Medical Center, Pennsylvania	3	2

Source: NDA 207695, List Description Investigator Site, section 16.1.4.1

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Table 3: Schedule of Assessments Trial C3291002: All Subjects

Day		1	8	15	22	29	36	57
Window	-28 to -2 day(s)		±1 day	±3 days	±3 days	±3 days	±3 days	+3 days
Visit	Screening	Baseline			Telephone Contact	End of Treatment/Early Termination	Telephone Contact	Follow-up Contact[a] (End of Study)
Informed Consent	X							
Demographics	X							
Review Inclusion/Exclusion Criteria	X	X						
Medical History	X	X						
Confirmation of Diagnosis of AD	X	X						
Height/Length and Weight	X	X				X		
Vital Signs[b]	X	X	X	X		X		
Full Physical Examination	X[c]					X		
12-Lead Electrocardiogram (ECG)	X or	X	X			X		
Limited Physical Examination		X[d]						
ISGA[e]	X	X	X	X		X		
Eczema Area and Severity Index (EASI) (incl. % BSA total)		X		X		X		
Body Site checklist of AD lesions		X	X	X				
Patient-Oriented Eczema Measure (POEM)		X	X	X		X		
Calculate Treatable %BSA for eligibility assessment[f]	X	X						

Day		1	8	15	22	29	36	57
Window	-28 to -2 day(s)		±1 day	±3 days	±3 days	±3 days	±3 days	+3 days
Visit	Screening	Baseline			Telephone Contact	End of Treatment/Early Termination	Telephone Contact	Follow-up Contact[a] (End of Study)
Blood collection for serum chemistry and hematology	X[g]					X		
Blood sampling for assessment of propylene glycol concentration in plasma	X					X[h]		
Record treatable AD areas (excluding scalp) in source and provide parent(s)/legal guardian with documentation of the designated treatment areas		X						
Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use		X	X	X				
Dispense and weigh the investigational product tube(s) and apply first dose. First dose applied in office by study staff		X						
Dispense and weigh new investigational product tube(s) and provide for at-home dosing		X[i]	X	X				
At-home dosing, applied by parent(s)/legal guardian[i,j]		**2nd dose (PM) on Day 1, then BID up to PM dose prior to Day 29 visit**						
Review dosing diary; assess compliance; re-train parent(s)/legal guardian if doses missed			X	X	X	X		
Collect and weigh empty, partially used and unused investigational product tubes			X[i]	X		X		
Review and record prior and concomitant medications	X[k]	X	X	X	X	X	X	X

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Day		1	8	15	22	29	36	57
Window	-28 to -2 day(s)		±1 day	±3 days	±3 days	±3 days	±3 days	+3 days
Visit	Screening	Baseline			Telephone Contact	End of Treatment/Early Termination	Telephone Contact	Follow-up Contact[a] (End of Study)
Assess for AEs (including application site reactions) and SAEs	X	X[l]	X	X	X	X	X	X
Review lifestyle requirements	X	X	X	X	X	X		
Schedule/reconfirm next study visit/contact	X	X	X	X	X	X	X	
Remind parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to the next visit		X	X	X	X			

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

a Follow-up contact will be completed 28+3 calendar days after the last administration of the investigational product to capture any adverse events.

b Vital signs (temperature, respiratory rate, pulse rate, and BP) taken in seated or supine position after subject has been seated or lying face up for 5 minutes.

c A full physical examination will be performed at the Screening visit. If the full examination cannot be completed during screening, an unscheduled visit may be performed prior to Baseline/Day 1 to complete the full assessment.

d A limited physical examination will be performed at Baseline/Day 1.

e ISGA should be completed prior to assessment of EASI, whenever possible.

f Treatable percent body surface area (%BSA) is defined as the percent of a subject's total body surface area that is AD-involved, excluding the scalp.

g Blood draw for clinical labs may be completed any time during the screening period, (Day -28 to Day -2) however the results must be available and reviewed by the PI prior to the Baseline/Day 1 visit and investigational product application. If the laboratory sample cannot be obtained due to an upset child, parent or other collections issues, the subject will not be enrolled into the study. Serum chemistry laboratory assessments include lactate and parameters needed to perform calculation of osmolal gap and anion gap.

h Sample for propylene glycol concentration should be collected within 12 ±3 hours of the final Day 28 evening application. Investigational product should not be applied before this collection.

i Not applicable to subjects in PK cohort through Day 8.

j In the event the scheduled Day 29 visit does not fall exactly on Day 29, instruct parent(s)/legal guardian to keep dosing BID until the evening dose prior to the Day 29 visit.

k All medications and non-medication therapies used within 30 days prior to Screening.

l Assess for AEs (including application site reactions) /SAEs before and after in clinic dose at Baseline/Day 1.

Source of Schedules of Assessments: Final Protocol Amendment 1, 01 May 2018 page 14

Table 4: Schedule of Assessments Trial C3291002: Pharmacokinetics (PK) Cohort

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

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

Data Analysis

The analysis data sets included:

- Full analysis dataset: all subjects assigned to treatment (137 subjects)
- Safety analysis dataset: all subjects receiving ≥1 dose of the investigational product (137 subjects)
- PK dataset: all subjects participating in pharmacokinetic assessments (21 subjects)
- Non-PK dataset: all subjects not participating in pharmacokinetic assessments (116 subjects)

Treatment effects (e.g., ISGA,EASI, POEM, %BSA) were exploratory endpoints which were evaluated in all subjects who received ≥1 dose of study product and had at least one post-baseline assessment for that endpoint. The protocol specified that the data would be

summarized using descriptive statistics.

Protocol Amendments
The Applicant submitted one amendment to Protocol C3291002 as described below. These changes were implemented to address recommendations made by the Food and Drug Administration (FDA), to correct inconsistencies and to clarify procedures. In addition, the Applicant notified investigators (Letter dated 05-September-2018) of changes which were not considered substantial by Pfizer Inc. which provided for administrative changes and corrected additional inconsistencies in the text.

Amendment 1: Protocol dated 01 May 2018-Key changes

- Specified that at least 3 subjects less than 9 months of age will be enrolled in the Pharmacokinetic (PK) cohort
- Added instructions for investigators to monitor for potential hypersensitivity reactions at all visits;
- Added that any subject with a new or ongoing adverse event at the time of the Day 57, should be seen in the clinic for evaluation of that adverse event;
- Provided more specific withdrawal criteria related to known and potential toxicities associated with systemic PDE4 inhibition and propylene glycol (PG);
- Added guidance to standardize the method for measuring both height (length) and weight, including that three reproducible measurements should be recorded and the average entered onto the electronic case report form (eCRF);
- Added assessment of subject height/length and weight and ECG at Screening and required that investigators update of the treatable Atopic Dermatitis (AD) areas and the body map at clinic visits Day 8 and Day 15.
- Modified the exploratory objectives to include the evaluation of changes in Eczema Area and Severity Index (EASI) and Patient-Oriented Eczema Measure (POEM) from baseline at each scheduled time point;
- Clarified the entry criteria to exclude subjects with a creatinine clearance below the LLN, or serum creatinine that is greater than the ULN according to “age-appropriate” reference ranges.
- Clarified that investigators should use the handprint method to assess % Body Surface Area (%BSA)

7.2.2. Results of Efficacy Assessment

Efficacy in the population age 3 months to 2 years was extrapolated from data in the adult population and older pediatric age groups because the pathophysiology of mild to moderate AD and response to treatment are similar in both populations. In view of the limited utility of efficacy data from an open-label trial to inform labeling, the Applicant did not develop outcome measures that were specific for this population. Investigators documented treatment effects based on ISGA, EASI, POEM and treatable %BSA on Day 8, Day 15 and Day 29. The results support a trend toward improvement in AD severity over time.

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The protocol defined treatment success based on ISGA as a score of clear or almost clear with a 2-grade improvement from baseline. Results at Day 29 (success rate of 30%) were similar to labeled findings in the population age 2 years and older (success rate of 31-33% in EUCRISA arms with a success rate of 18-25% in the vehicle arms).

Table 5: **Assessment Scale**

Score	Grade	Description
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: Final Protocol Amendment 1, 01 May 2018 Table 3

Table 6: Success on Investigator's Static Global Assessment (ISGA)

	Crisaborole 2% BID (N=137)	
Visit	N	N (%)
Day 8	135	27 (20)
Day 15	134	29 (22)
Day 29	129	39 (30)

Abbreviation: BID = twice a day
Source: Final Study Report C3291002; Table 14.2.1.1

POEM scores range from 0 (least severe) to 28 (most severe) and include domains related to pruritus and sleep. Total mean POEM scores decreased by Day 8 compared with baseline.

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of EUCRISA in the pediatric population age 3 months to 2 years focused on data from a single trial, Trial C3291002. The analyses included TEAEs, serious AEs (SAEs), AEs leading to discontinuation, adverse reactions (ARs) and AEs associated with the product class, PDE-4 inhibitors. Class effects associated with the use of PDE-4 inhibitors include gastrointestinal disorders such as diarrhea, nausea, vomiting, dyspepsia, and gastrointestinal reflux disease and psychiatric disorders.

A potential safety issue specified by FDA in the WR was propylene glycol (PG) toxicity. EUCRISA contains propylene glycol (PG) (b) (4). Propylene glycol is a commonly used (b) (4) in food, drugs, cosmetics, and tobacco products. High exposures may result in accumulation of PG causing lactic acidosis, central nervous system depression, coma, hypoglycemia, seizures, hemolysis, agitation and cardiac arrhythmias. At risk

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populations include infants, especially those with low birth weight (Lim et al. 2014). Clinical findings related to PG toxicity and abnormalities in related laboratory parameters for PG (PG levels, osmolality, lactate, bicarbonate, creatinine, and anion gap) were a component of the safety analysis.

Other potential safety signals which were the subject of specific assessment in this review were AEs which were discussed in the Postmarket Drug Safety Surveillance Summary (Review by Jessica Weintraub, PharmD dated 6/18/2019). These AEs included contact dermatitis (identified as a new safety signal), weight loss, psychiatric AEs and gastrointestinal AEs (class effects observed in the postmarketing data but without sufficient frequency or information to allow a conclusion) and pigmentary changes (causality confounded by post inflammatory changes related to AD itself). The results of the Postmarket Drug Safety Surveillance Summary and additional findings from Division of Pharmacovigilance I (DPV I) will be included in Section 6.2 Postmarketing Experience of labeling for EUCRISA.

The applicant submitted narratives for adverse events of special interest which included AEs related to PG toxicity (e.g., seizure disorders, and cardiac conduction abnormalities), class effects and significant hypersensitivity reactions (e.g., anaphylactic and anaphylactoid responses).

7.3.2. Review of the Safety Database

Exposure

Extent of Exposure

The protocol defined compliance by the number of applications and the duration of exposure. To be compliant, a subject needed to complete between 80-120% of the expected doses. Overall, the majority of subjects were compliant, (126/137, 92%). The Applicant provided data regarding compliance for subjects in the PK cohort and non-PK cohort separately.

Table 7: **Extent of Exposure**

Statistic	Overall (N=137)	PK Cohort (N=21)
Duration of Treatment (days)		
Mean (SD)	27 (5)	26 (7)
Median (min/max)	28 (2-37)	28 (7-32)
Total Number of Applications		
Mean (SD)	53 (10)	52(13)
Median (min/max)	56 (4-74)	56 (13-64)
Number and Percentage of Compliance		
No	11 (8)	3 (14)
Yes	126 (92)	18 (86)

Source: Modified from Final Clinical Study Report, Protocol C3291002; Table 14.4.1.1, 14.4.1.2

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Characteristics of the Safety Population

Demographic and Baseline Characteristics

Investigators from three countries enrolled subjects in Trial C3291002: United States (112/137; 82%), Canada (15/137; 7%) and Australia (15/137; 11%). Per Applicant, there were no documented differences in the findings of safety or efficacy that varied with ethnicity (SDN 527 dated 1/8/2020).

Overall, subjects enrolled in the PK cohort and Non-PK cohort had comparable demographic characteristics. The majority of subjects in both cohorts were male, white and not Hispanic/ Latino. More than 60% of the subjects were 9 months to 24 months of age. Per protocol subjects who participated in PK assessments had moderate AD with higher baseline ISGA, POEM, EASI and BSA affected with AD.

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Table 8: Demographic and Baseline Characteristics

	Crisaborole 2% BID		
	Non-PK Set (N=116)	PK Set (N=21)	Total (N=137)
Age (months):			
3 - < 9	36 (31.0%)	7 (33.3%)	43 (31.4%)
9 - < 24	80 (69.0%)	14 (66.7%)	94 (68.6%)
Mean	13.7	12.7	13.6
Std Dev	6.41	6.58	6.42
Median	13.5	13.0	13.0
Range(min,max)	(3, 23)	(3, 23)	(3, 23)
Weight (kg)			
Mean	10.2	9.5	10.1
Std Dev	2.29	1.94	2.25
Median	10.2	9.8	10.1
Range(min,max)	(4.9, 16.0)	(6.2, 12.7)	(4.9, 16.0)
Body Length (cm)/Height (cm)			
Mean	77.0	75.5	76.7
Std Dev	8.39	8.56	8.40
Median	76.2	76.5	76.2
Range(min,max)	(58.0, 96.6)	(59.5, 90.0)	(58.0, 96.6)
BMI (kg/m^2)			
Mean	17.13	16.59	17.05
Std Dev	1.935	2.380	2.010
Median	16.97	15.72	16.79
Range(min,max)	(12.6, 23.3)	(14.2, 24.8)	(12.6, 24.8)
Gender			
Male	75 (64.7%)	13 (61.9%)	88 (64.2%)
Female	41 (35.3%)	8 (38.1%)	49 (35.8%)
Race			
White	71 (61.2%)	13 (61.9%)	84 (61.3%)
Black or African American	9 (7.8%)	2 (9.5%)	11 (8.0%)
Asian	23 (19.8%)	4 (19.0%)	27 (19.7%)
American Indian or Alaska Native	1 (0.9%)	0	1 (0.7%)
Native Hawaiian or Other Pacific Islander	1 (0.9%)	0	1 (0.7%)
Other	0	0	0
Unknown	0	0	0
Multiracial	11 (9.5%)	2 (9.5%)	13 (9.5%)
Ethnicity			
Hispanic or Latino	14 (12.1%)	2 (9.5%)	16 (11.7%)
Not Hispanic or Latino	99 (85.3%)	19 (90.5%)	118 (86.1%)
Unknown	0	0	0

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

Abbreviations: Std = standard deviation; min = minimum; max = maximum
Source: Final Clinical Study Report Protocol C3291002; Table 7 page 32

Concomitant Medications

The Applicant documented concomitant medications according to the WHODrug v201803 coding dictionary. At Baseline, 95% (130/137) of subjects used concomitant medications. The most common prior and concomitant treatments reported by parents/ legal guardians included other dermatological preparations (e.g., baby wipes) and emollients and protectives. Other common concomitant medications at Baseline included topical corticosteroids (TCS) (e.g., hydrocortisone, triamcinolone), pain relievers (e.g., ibuprofen, acetaminophen)), oral antihistamines (e.g., cetirizine, diphenhydramine), vaccines and vitamins/supplements. The most common TCS treatment used prior to the trial for treatment of AD was hydrocortisone (35.8%). There was limited use of topical calcineurin inhibitors. During the trial 97% (133/137) used concomitant treatments.

Disposition

Of the 209 subjects who were screened for participation in Trial C3291002, investigators deemed 79 subjects as screening failures and enrolled 137 subjects in the trial. All enrolled subjects received treatment and we included in the safety analysis set. Of these, 128 subjects

completed the treatment phase per protocol. A total of 4 subjects discontinued the study product due to TEAEs. However, all four subjects entered the follow-up phase and completed the trial. Five subjects were withdrawn by parent/guardian or were lost to follow-up.

Table 9: Trial C3291002-Disposition

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

Source: Final Clinical Study Report Protocol C3291002; Table 5

Protocol Deviations

The Applicant stated that the protocol deviations did not impact the safety of the participants or lead to withdrawal from the trial per protocol.

The key protocol deviations were:

- 12 deviations related to concomitant medications: Ten subjects used a prohibited medication; 2 subjects used a prohibited medication twice.
- 13 deviations related to inclusion/exclusion criteria: The blood collection supplies impeded sampling in this age group. Five participants (9 deviations) had incomplete laboratory assessments at screening. Study recruitment was placed on hold temporarily until the sites received redesigned equipment. One subject had ISGA score of severe at Screening. One subject used a TCS and systemic antihistamine within the washout period.
- 4 deviations related to the dose of the investigational product: 2 subjects received the wrong dose (1 received a larger total volume and 1 received doses for an additional 7 days). Two subjects did not receive 80-120% of the expected doses.
- 54 deviations related to clinical laboratory issues: 41 subjects had incomplete laboratory assessments or samples which were collected but could not be processed.

- 9 deviations related to procedures/tests: Limited physical examinations were not performed in 2 subjects and ECGs were not performed in 3 subjects (2 subjects with 1 deviation each and 1 subject with 3 deviations). The dosing diary was not issued to 2 subjects.
- 6 deviations related to scheduled visits: 3 subject families did not receive telephone contact visits. Two subjects (3 deviations) did not complete their scheduled clinic visit.
- After database lock, one site (1009) reported that investigational staff prepared phlebotomy sites with alcohol (not soap and water per protocol) and subsequently 5 subjects had crisaborole plasma concentrations that were out of the expected range on Day 8.

Adequacy of the Safety Database
The size of the safety database exceeded the number specified in the PMR and was sufficient for the evaluation of EUCRISA applied once twice daily for up to 4 weeks in the pediatric population. The demographics of the study population are adequately representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the pharmacokinetics (PK) and safety profile of EUCRISA for the treatment of mild to moderate AD in the pediatric population age 3 months to 2 years.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall, the quality of the data submitted was adequate to characterize the safety of EUCRISA applied twice daily for up to 4 weeks. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
Per ICH E6 (R1), the Applicant defined an adverse event (AE) as "any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage." Therefore, an AE may be any unfavorable and unintended sign (including an abnormal laboratory finding) or symptom. Per protocol, investigators documented all AEs occurring after signing of the informed consent through the final study visit. Treatment-emergent adverse events were defined as, 1) AEs which occurred on or after the first dose or, 2) AEs which represented a worsening of a pre-existing condition on or after the first dose of the study product.

On the case report form (CRF), investigator recorded all AEs that were directly observed, spontaneously disclosed by parents/legal guardians and elicited by non-leading questioning. The Applicant coded AEs using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1) and categorized AEs, TEAE and serious adverse event (SAEs) by SOC and preferred term (PT). Applicant provided summaries of the number of subjects reporting any TEAE, SAEs by SOC, PT, severity, relationship to study product and seriousness.

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Routine Clinical Tests
Safety monitoring included physical examinations with vital signs, ECGs, a safety laboratory assessments and documentation of adverse events. Investigational staff conducted safety laboratory testing (serum chemistry and hematology) at screening and Day 29. See below for the specific laboratory tests.

Table 10: Trial C3291002-Clinical Laboratory Test Parameters

Hematology	Chemistry	Other Bioanalytical Laboratory Assessment
Hemoglobin Hematocrit Red blood cell count Platelet count White blood cell count (% and absolute) • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes	Blood urea nitrogen Glucose (non-fasting) Creatinine Sodium Potassium Chloride Bicarbonate Alanine aminotransferase Aspartate aminotransferase Total bilirubin Alkaline phosphatase Albumin Total protein Lactate Calculation of osmolal gap Calculation of anion gap	Propylene glycol systemic levels

Source: Protocol Section 7.1.1 Table 3

To monitor the plasma concentrations of propylene glycol, the investigational staff conducted blood sampling at screening and Day 28 (12 hours post dose). Subjects in the PK cohort provided an additional pre-dose sample for determination of propylene glycol concentration on Day 8 at the first of 3 PK sampling timepoints.

7.3.4. Safety Results

Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events
There were no deaths during this pediatric development program. Investigators did not withdraw any subjects from the trial due to TEAEs. One subject from the PK cohort experienced a serious adverse event (SAE) of "febrile convulsion" which resulted in the withdrawal of the study drug. A brief narrative is provided below:

- A 22-month-old white female (b) (6)) with a history of recurrent otitis media and an 8-month history of AD experienced a seizure on Day 6 after receiving EUCRISA twice daily. The caregiver reported that that when the infant woke up from a nap, she stiffened, "jerked a couple times," began trembling and "her face turned blue." The seizure resolved after 2 to 3 minutes. In the emergency room, the infant had a temperature of 103º F and adenovirus positivity on a respiratory panel. Anion gap, lactic acid, glucose and other chemistry parameters were normal. Propylene glycol level was

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1810 ng/mL (no reference range) on Study Day -13, 1980 ng/mL on Study Day 8, and 396 ng/mL on Study Day 32. Concomitant products at the time of the event included ibuprofen and Pampers baby wipes. The TEAE of moderate seizure was considered to be not related to the study product or PG concentration but due to the occurrence of an infection and fever.

For seven subjects, investigators reduced the dose or withdrew the study product due to TEAE. Four subjects discontinued the study product permanently (febrile convulsion, dermatitis infected, application site pain and application site discomfort); three subjects reduced the dose (application site erythema) or temporarily withdrew the study product (dermatitis atopic, application site reaction/contact dermatitis). Brief narratives of the three subjects from the non-PK cohort who experienced TEAEs of moderate severity, discontinued EUCRISA permanently but remained in the trial are below:

- a 23-month-old Asian male ((b) (6)) with a 17 -month history of AD and no other significant past medical history experienced application site stinging (reported term) on Day 1 after receiving EUCRISA twice daily. Concomitant products at the time of the event included Little Ones Wipes and Sorbolene Cream (bland emollient containing paraffin and glycerin). The TEAE of application site pain was considered to be related to the study product.

- an 8-month old Asian male ((b) (6)) with a 7- month history of AD and no other significant past medical history developed infected dermatitis (reported term) on Day 13 and received EUCRISA twice daily for 14 days. Concomitant products at the time of the event included Huggies Wipes, QV Baby Sensitive Skin Emollient and Secalia AHA Body Emollient (containing glycerin, alpha hydroxy acids, shea butter and inca inchi oil). The infant received oral cephalexin and hydrocortisone acetate ointment and recovered in 7 days. The TEAE of dermatitis infected was not considered to be related to the study product.

- a 12- month old white male ((b) (6)) with a 10-month history of AD and no other significant past medical history experienced application site discomfort (reported term) on Day 2 after receiving EUCRISA twice daily for 2 days. Concomitant products at the time of the event included Dermeze Ung and Wipes – Coles Comfy Bots. The infant recovered on Day 9. The TEAE of application site discomfort was considered related to the study product.

Adverse Events
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%). After pooling of related PTs, the most frequent TEAE were: upper respiratory tract

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infection (includes nasopharyngitis, viral upper respiratory infection), dermatitis atopic (includes eczema), pyrexia, ear infection (includes otitis media, acute otitis media), diarrhea, and application site pain (includes application site discomfort).

TEAEs which occurred in more than 4 subjects are tabulated below.

Table 11: Treatment Emergent Adverse Events (TEAEs) by Severity in ≥4 Subjects by Preferred Term (PT)

Number of evaluable subjects	N=137			
Severity per Investigator	Mild	Moderate	Severe	Total
Total number of subjects with any TEAE	48 (35)	39 (29)	1 (1)	88 (64)
Number (%) subjects with TEAE by SOC, PT & severity				
Skin and Subcutaneous Tissue Disorders				
Dermatitis atopic	5 (4)	3 (2)	1 (1)	9 (7)
Dermatitis diaper	6 (4)	3 (2)	0	9 (7)
Eczema	3 (2)	2 (2)	0	5 (4)
Dermatitis contact	2 (2)	2 (2)	0	4 (3)
Erythema	4 (3)	0	0	4 (3)
Rash	3 (2)	1 (1)	0	4 (3)
General Disorders and Administration Site Conditions				
Pyrexia	10 (7)	3 (2)	0	13 (10)
Application site pain	3 (2)	2 (2)	0	5 (4)
Application site discomfort	3 (2)	1 (1)	0	4 (3)
Application site erythema	1 (1)	3 (2)	0	4 (3)
Infections and Infestations				
Upper respiratory tract infection	6 (4)	4 (3)	0	10 (7)
Otitis media	1 (1)	5 (4)	0	6 (4)
Conjunctivitis)	4 (3)	1 (1)	0	5 (4)
Ear infection	2 (1)	2 (1)	0	4 (3)
Nasopharyngitis	4 (3)	0	0	4 (3)
Gastrointestinal Disorders				
Diarrhea	9 (7)	1 (1)	0	10 (7)
Teething	2 (2)	2 (2)	0	4 (3)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	6 (4)	1 (1)	0	7 (5)
Rhinorrhea	4 (3)	1 (1)	0	5 (4)
Total Preferred Term Events	124	67	1	192

Source: Adapted from Table 14.3.1.2.2.1

A total of 43 subjects (31%) experienced 59 adverse events localized to the application site. One subject (1%) experienced a severe TEAE (dermatitis allergic) and 4 subjects (3%) experienced contact dermatitis at the application site. The majority of TEAEs occurring at the application site were considered to be related to the study product. Some of the TEAEs which were not considered to be related included some AEs in the Infections and infestations SOC (e.g., roseola, molluscum contagiosum, dermatitis infected, impetigo, and rash pustular) and some AEs in the Skin and subcutaneous disorders SOC (e.g., dermatitis allergic, diaper dermatitis, some cases of contact dermatitis, rash, rash popular) and a therapeutic procedure. Local TEAE were most

commonly observed on the face (17 subjects), leg and back (8 subjects each, and abdomen and arm (7 subjects each).

Adverse Reactions (AR)
A total of 22 subjects (22/137; 16%) experienced 32 TEAE which were determined to be related to the study product. Among the subjects experiencing related TEAEs, 2 subjects discontinued the study product permanently and 2 subjects reduced the dose or temporarily discontinued the study drug due to a TEAE. These subjects remained in the trial. Most of these TEAE were application site reactions. The PTs are listed below by severity without pooling. All ARs were mild or moderate.

In this population, reports of application site pain/discomfort, application site pruritus and pruritus are indirect assessments by an observer. Therefore, data regarding these AEs should be interpreted with caution.

Table 12: Drug-Related Treatment Emergent Adverse Events (Adverse Reactions)

Number of evaluable subjects	N=137			
Severity	Mild	Moderate	Severe	Total
Number of subjects with any adverse reaction (AR)	16 (12)	6 (4)	0 (0)	22 (16)
Number (%) subjects with AR by PT & severity				
Application site pain	3 (2)	2 (2)	0 (0)	5 (4)
Application site discomfort	3 (2)	1 (1)	0 (0)	4 (3)
Erythema	4 (3)	0 (0)	0 (0)	4 (3)
Application site erythema	1 (1)	2 (2)	0 (0)	3 (2)
Pruritus	3 (2)	0 (0)	0 (0)	3 (2)
Application site reaction	1 (1)	1 (1)	0 (0)	2 (2)
Eczema	2 (2)	0 (0)	0 (0)	2 (2)
Application site pruritus	1 (1)	0 (0)	0 (0)	1 (1)
Application site irritation	1 (1)	0 (0)	0 (0)	1 (1)
Dermatitis contact	0 (0)	1 (1)	0 (0)	1 (1)
Skin irritation	1 (1)	0 (0)	0 (0)	1 (1)
Otitis media	1 (1)	0 (0)	0 (0)	1 (1)
Rhinitis	1 (1)	0 (0)	0 (0)	1 (1)
Upper respiratory tract infection	1 (1)	0 (0)	0 (0)	1 (1)
Oral candidiasis	0 (0)	1 (1)	0 (0)	1 (1)
Defect conduction intraventricular	1 (1)	0 (0)	0 (0)	1 (1)
Total Preferred Term Events	24	8	0	32

Source: Modified from Table 14.3.1.2.4.1 Page 2 of 2

The Applicant proposed to include the term [redacted] (b) (4) " in section 6.2 Postmarketing Experience to encompass a number of local reactions reported by patients using EUCRISA after approval. However, because the term [redacted] (b) (4) " is insufficiently specific to inform healthcare providers in labeling, the Pharmacovigilance team recommended including only the term "allergic contact dermatitis" which was meaningful and supported by the data. The 3 cases from the literature and FDA Adverse Event Reporting System (FAERS)

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were confirmed by patch test findings. Refer to Section 10 of this review for a discussion of the labeling recommendations.

Laboratory Findings

Per WR, the trial included a routine laboratory evaluation and monitoring for propylene glycol toxicity by obtaining levels of PG and lactate and providing calculations of osmolar gap (difference between measured osmolality and calculated osmolality) and anion gap. In general, evaluation of shift tables indicated no clinically meaningful changes from Baseline to the end of treatment. Shift tables for parameters of renal and hepatic function and other chemistries showed shifts for 1 or 2 subjects. Shift tables of lactic acid levels showed almost equal numbers of subjects shifted from high levels at Baseline to normal levels at the end of treatment (22 subjects) as shifted from normal levels at Baseline to high levels at the end of treatment (23 subjects). Based on a normal range of osmolar gap of ±10 mOsm/kg, the majority of subjects had a normal osmolar gap at Baseline and end of treatment. A greater number shifted from normal to low (4) than shifted from normal to high (1). Among subjects with a high osmolar gap at Baseline most shifted to normal (4) at the end of treatment while only one remained high.

Physical Examinations and Vital Signs

There were no clinically meaningful abnormal findings on physical examination beyond the expected cutaneous findings. Investigational staff evaluated vital signs (temperature, respiratory rate, pulse rate, and blood pressure) at screening, baseline, Day 8, Day 15 and Day 29. Although there was variability in the recorded vital signs compared to reference ranges, investigators assessed these differences as not clinically meaningful.

Table 13: Reference Ranges for Vital Signs (PALS)

Age category	Infant (1 month -1 year)	Toddler (1 year -2 years)
Heart Rate (Awake) beats/minute	100-190	90-160
Heart Rate (Asleep) beats/minute	98-140	80-120
Respiratory rate breaths/minute	30-53	22-37
Systolic Pressure mmHg	72-104	86-106
Diastolic Pressure mmHg	37-56	42-63
Temperature varies with site not age		
Ear	35.8-38	
Axillary		36.5-37.5

Sources: See the literature in the References section of this review (Fleming et al. 2011; Novak and Gill 2018).

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Table 14: Summary of Post-Baseline Vital Signs Data

		Crisaborole 2% BID	
Parameter (units)	**Criteria**	**N**	**n (%)**
Diastolic Blood Pressure (mmHg)	Value <37 mmHg	136	0
	Value >63 mmHg	136	73 (53.7)
Pulse Rate (bpm)	Value <90 bpm	137	12 (8.8)
	Value >180 bpm	137	0
Respiratory Rate (breath/min)	Value < 22 breaths/min	137	17 (12.4)
	Value > 53 breaths/min	137	4 (2.9)
Systolic Blood Pressure (mmHg)	Value <72 mmHg	137	6 (4.4)
	Value >106 mmHg	137	31 (22.6)
Temperature (c)	Value >= 39 celsius	137	0

Source: Final Study Report C3291002 Table 14.3.5.2.1

In addition, investigational staff measured length and weight at screening, baseline and Day 29. Although the duration of the trial was limited, observed changes were consistent with expected changes on standard growth curves. One subject (1009 (b) (6)) had "weight loss" based on a telephone contact (weigh measured at home and compared with office values). See narrative in Section 7.3.5.

Electrocardiograms (ECGs) and QT
During the development of EUCRISA, the applicant performed cardiac safety monitoring during multiple trials and conducted a thorough QT (TQT) Study (AN2728-TQT -108). In a review of the TQT, the QT Interdisciplinary Review Team (QTIRT) team observed that no effect of crisaborole was seen on hERG receptors at a dose of 1 micromolar and no effect was seen in dogs at doses up to 300 mg/kg. After reviewing the TQT study results, the QT-IRT concluded crisaborole had no significant QTc prolongation effect up to supratherapeutic doses. [Review by Qianyu Dang 5/20/2014]. Upon review of the ECGs from phase 3 trials, QTIRT team stated, "It appears that there is no substantial increase in cardiac adverse events after application of crisaborole compared to that from vehicle in Phase 3 trials; however ECG monitoring in Phase 3 trials is mainly for patient safety and detecting outliers" (QTIRT Review by Jiang Liu dated 4/20/2016). See Clinical Review dated November 3, 2016.

In view of reports concerning cardiotoxicity (arrhythmia, hypotension, cardiorespiratory arrest) in neonates and infants who were exposed to PG as an excipient, the applicant performed ECGs during Trial C3291002 at screening/ baseline, Day 8 and Day 29. Per Applicant, prolongation of the QTcF interval >30 msec over baseline was observed in 10 subjects. However, no QTcF intervals were >500 msec and / or increased >60 msec. A Cardiovascular Safety and Advisory Council, employed by Pfizer but independent from study teams and Data Safety Monitoring Board reviewed the cardiograms. The Applicant stated that interpretation of findings was confounded by a lack of normal values for ECG intervals in this age group, movement artifact and uncorrected rapid heart rates. In addition, some procedural errors occurred such as misplaced limb leads (1 subject).

Shetarra Walker MD, Division of Cardiovascular and Renal Products, reviewed the cardiovascular safety data from the trial and provided the following comments:

> "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 provided a detailed discussion of the one potential case of cardiotoxicity:

- An 11- month old African American male ((b) (6)) with no significant past medical history other than AD was treated with crisaborole ointment, 2% twice daily for 26 days followed by completion of a post-treatment follow-up period. At baseline, this subject had a moderate ISGA severity score of 3 and treatable BSA of 94%. An ECG was performed on this subject at time of screening and on Study Day 8, both showing sinus tachycardia (heart rates 138-141 beats per minute) but no conduction abnormalities. The sinus tachycardia was not reported as a TEAE. On Study Day 27 (end of treatment (EOT)), his ECG showed sinus tachycardia (heart rate 102 beats per minute) and intraventricular conduction delay (IVCD). The IVCD (investigator term) was reported as a mild TEAE but not the sinus tachycardia. Otherwise, this subject had normal pulse rate and blood pressure measurements recorded throughout the study. At time of the event, the investigator reported concomitant use of baby wipes, mentholatum ointment, amoxicillin, montelukast, and Zarbees Baby Cough Syrup. Because of the ECG abnormality, the subject was referred to a cardiologist. However, information from that cardiology visit was not provided to the investigative site.

  This subject had abnormal lab assessments including elevated anion gap at baseline (27 mEq/L, reference range 7-18 mEq/L) and EOT (25 mEq/L). Lactic acid was normal at baseline but elevated to 21 mg/dL (reference range 4-20 mg/dL) at EOT. The osmolar gap was -15 mOsm/kg at Screening and -5 mOsm/kg at EOT (no reference range provided). PG levels were 3220 ng/mL (0.32 mg/dL) at baseline and 5130 ng/mL (0.51 mg/dL) at EOT. Serum sodium, potassium, and bicarbonate were within normal limits during the study. The IVCD TEAE was considered resolved by Study Day 37. The investigator considered the IVCD related to the study medication but the Applicant does not believe that PG played a causative role in the TEAE based on comparison of this subject's plasma PG levels to those associated with reported cardiac arrhythmias in published literature.

Dr. Walker provided the following comments:

> "According to one source, a normal osmolar gap is ±10 mOsm/kg. An osmolar gap of at least +20 mOsm/kg is indicative of the presence of other osmotically active particles such as PG. Subject (b) (6) did not have an elevated osmolar gap…The subject described in the narrative above had the most extensive treatable BSA, 94%, compared to average treatable BSA of 28%…Moreover, after reviewing all EOT PG levels, I could not find an obvious correlation between age and PG level…interpretation of PG levels in

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> this study are confounded by lack of control of other sources of PG such as those found in food and personal care products. In an otherwise healthy child with no significant cardiac family history and no new cardiac history, signs, or symptoms, there is a higher likelihood an ECG finding of IVCD is either a false positive or normal variant. is insufficient evidence in Study C3291002 to conclude that the ECG finding of IVCD in the subject described above can be attributed to PG toxicity. Moreover, there is insufficient evidence among all the safety data to conclude there is any cardiac safety signal due to PG toxicity…There are no published reports of isolated IVCD concerning for PG-induced toxicity nor are there reports of PG-induced toxicity from topical therapies in patients with AD. After review of cardiovascular safety data in Study C3291002, we did not find evidence of PG-induced cardiotoxicity. Therefore, we do not recommend adding a cardiotoxicity warning or precaution to product labeling for Eucrisa."

Therefore, based on the review by Dr. Walker the recommended language to be included in labeling regarding the effects of EUCRISA on repolarization are as follows:

> 12.2 Pharmacodynamics
>
> Cardiac Electrophysiology
> At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent.

Negative outcomes are not generally included in labeling. However, Associate Directors for Labeling, Joseph A. Grillo, Pharm.D. and Eric Brodsky Pharm.D, recommended that the Division retain the pertinent negative QT statement under an Cardiac Electrophysiology heading in the Pharmacodynamics subsection of labeling (email communications 1/17/2020 and 1/21/2020). In view of the efforts of the FDA for more consistency across all labeling and adherence to current guidance, this statement regarding the outcome of the TQT evaluation will remain in labeling.

Immunogenicity
As the product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

7.3.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest
The WR required active monitoring for adverse events known to be associated with crisaborole and potential adverse events associated with exposure to PG. To address this requirement, the Applicant identified and analyzed AEs of special interest which were related to PDE-4 class effects, propylene glycol (PG) toxicity or hypersensitivity reactions.

Class Effects
Subjects experienced TEAEs that were potentially attributable to systemic PDE-4 inhibition (diarrhea, vomiting and weight decrease). However, investigators did not consider any of these

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TEAEs to be related to EUCRISA. No subjects experienced other TEAEs potentially associated with systemic PDE-4 inhibition (e.g., insomnia, nausea, serious infections, malignancy). The study design with a 4-week duration of exposure could have limited the detection of AEs with a long latency period. The key narratives are as follows:

- An 11- month old Asian male ([redacted]) with a 2-month history of AD and no other significant past medical history experienced mild "weight loss" on Day 29 after receiving EUCRISA twice daily for 27 days. Study staff documented the following weight: screening: 8.5 kg; baseline: 8.51 kg; Day 27: 8.58 kg; Day 29: 8.1 kg (telephone assessment) and Day 57: not recorded but weight loss documented as resolved. Albumin level was high (5.0 and 4.9g/dL) on Day 15 and 27; anion gap was elevated from screening to Day 27 and all other laboratory parameters were normal after screening. The subject experienced no other adverse events during the trial. Concomitant products at the time of the event included Lubriderm baby lotion and Tylenol. The subject recovered from the event on Day 57. Documentation of weight loss was inadequate because the parent/guardian reported weight loss in a follow-up telephone contact and subsequent weight measurement at the study site was not recorded. The AE of "weight loss" was assessed as not related to the study product but due to "inadequate caloric intake" (rationale not supported; SDN 524 dated 12/31/2019).

- A 15- month old white male ([redacted]) with a 12-month history of AD and no other significant past medical history experienced diarrhea (investigator term) on Day 6 after receiving EUCRISA twice daily. Concomitant products at the time of the event included Huggies Baby Wipes. Diarrhea resolved after 12 days (Day 6 to 18). The AE of diarrhea was considered unlikely related to the study product; anion gap and lactic acid levels were elevated from screening through Day 32; PG level was less than 100 at Baseline and 232 at the end of treatment. There were no other significant laboratory abnormalities with treatment. See below for additional details regarding subject [redacted].

Propylene Glycol (PG) Toxicity

Background:

EUCRISA contains propylene glycol (PG) [redacted] The US Food and Drug Administration (FDA) classified PG as a food additive that is generally regarded as safe. However, there are reports in the literature documenting the toxicity of PG and its acidic metabolites in young children who were exposed to PG when administered as excipient in a drug product. Generally, the pediatric subjects who experienced AEs received large doses of PG by continuous intravenous (IV) administration or by topical administration of products to substantial body surface areas affected with burns. Adverse events associated with PG toxicity include:

- Hyperosmolality, lactic acidosis, osmolar gap;
- Renal dysfunction, acute renal failure;

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- Cardiotoxicity (arrhythmia, hypotension, cardiorespiratory arrest);
- Central nervous system toxicity (depression, coma, seizures);
- Respiratory depression, dyspnea;
- Liver dysfunction;
- Hemolytic reaction and hemoglobinuria (Committee for Human Medicinal Products (CHMP) 2014).

PG is a highly water-soluble substance. Absorption of PG through the intact skin is expected to be low according to nonclinical studies and in vitro assessments using human biopsy specimens. However, dermal absorption may become a significant source of exposure once the barrier function of the skin is compromised (Committee for Human Medicinal Products (CHMP) 2017) as in infants with atopic dermatitis (AD). Results of population PK modeling using data from multiple trials in the crisaborole development program confirmed that disease status had a significant impact on systemic exposure. See the Clinical Pharmacology Review, pharmacometrics analysis by Da Zhang, PhD (dated 3/4/2020).

Per the Code of Federal Regulations (CFR) Title 21, propylene glycol is generally recognized as safe for use in multiple types of products and foods. The Inactive Ingredient Database (IID) includes topical products with a maximum potency per unit dose of >98% w/w. Propylene glycol is present in over-the-counter, topical products used to manage AD. In Trial C3291002, emollients and skin barrier enhancing products ("protectives") were among the most common prior and concomitant treatments reported by the parents/guardians of enrolled subjects. At baseline, the majority of subjects had detectable levels of PG. Da Zhang, PhD. conducted a regression analysis of PG systemic exposure and stated the following:

> "An examination of the plot of measured concentrations at the respective visits does not indicate any trend of increasing concentrations of propylene glycol that can be attributed to treatment with crisaborole ointment. Most subjects had measurable systemic concentrations of propylene glycol at screening and the source of the propylene glycol is not known. A likelihood ratio test conducted by comparing an intercept only model to a slope-intercept linear model utilizing %treated BSA as the independent variable identified no relationship between the changes in propylene glycol concentrations and %treated BSA on Day 8 (p-value=0.8627) or end of treatment (p-value=0.9565) visit (ePharm RA 16376868)." See the Clinical Pharmacology Review, pharmacometrics analysis by Da Zhang, PhD (dated 3/4/2020).

There is no consensus regarding the maximum dose of PG that can be safely administered to a neonate, infant or child. Per Mona Khurana, MD, Division of Pediatric and Maternal Health (DPMH), propylene glycol accumulation is potentially more likely in neonates and infants because adult levels of alcohol dehydrogenase are not reached until 5 years of age. In addition, there are reports of a prolonged half-life of propylene glycol in neonates (16.9 hours) compared with the half-life of propylene glycol in adults (5 hours). Other populations at greater risk for PG toxicity include patients in any age group with liver failure, acute kidney injury, or chronic kidney disease or in the presence of substrates with greater affinity to alcohol dehydrogenase

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(e.g., ethanol). [redacted] was insufficient data to determine a safe or acceptable level of propylene glycol for use in pediatric patients [redacted]. Nevertheless, modeling by De Cock et al. showed that standard safe dosing regimens had peak PG concentrations ranging between 2.8–21.8 mg /dL (Novak and Gill 2018). Other studies suggest that toxicity from PG is most likely to occur at serum concentrations above 18 to 25 mg/dL (Lim et al. 2014).

The highest PG concentration measured in any subject during the trial was [redacted] ng/mL [redacted] mg/dL) which is far below this threshold. This subject ([redacted]) experienced adverse events of mild application site discomfort and mild rhinorrhea. Six other subjects with PG concentrations exceeding [redacted] ng/mL (≥[redacted] mg/dl) at any timepoint had no or mild adverse events (application site discomfort, teething, upper respiratory tract infection (2), nasal congestion, pyrexia (2), allergy to animal and vomiting). No AEs suggestive of PG toxicity were identified among these subjects.

Osmolality is the number of solute particles in 1 kg of solvent whereas osmolarity refers to the number of solute particles per 1 L of solvent. The osmolality (osmolar) gap or osmolarity gap is the difference between the measured value and the estimated value and suggests the presence of other osmotically active, unmeasured particles (e.g., PG). Among the subjects who received crisaborole and had an osmolar gap of greater than 10 mOsm/kg during the trial, the majority had elevated values at Screening/Baseline. In four subjects, elevated osmolar gaps normalized by the end of treatment (# [redacted]). Among these subjects, only one subject had an elevated lactic acid level at end of treatment ([redacted]).

Three subjects had an increase in osmolar gap of greater than 10 mOsm/kg after Screening/ Baseline (# [redacted]). Two subjects participated in the PK assessments under maximal use conditions (# [redacted]). One of these subjects had an elevated lactic acid level (# [redacted]) at the end of treatment. This 4-month-old male subject (# [redacted]) had widely varying values for the osmolar gap at different timepoints (Screening: 0; Baseline: 19; Day 8: -4; and end of treatment: 13). The other subject in the PK cohort (# [redacted]), a 14-month-old white male subject may have had blood sampling through the treatment site. Laboratory values for this subject related to PG concentration were considered unreliable since contamination may have occurred during sampling. In addition, this subject had interruption of study treatment when he experienced moderate adverse events (application site reaction and contact dermatitis). The third subject with an elevated osmolar gap, an 11-month-old white male, had a normal lactic acid level and an unconfirmed adverse event of weight loss. Except for the subject with possible contamination (# [redacted]), the subjects with elevated osmolar gap had peak propylene glycol concentrations which remained below the mean value at baseline and at the end of treatment ([redacted] ng/mL, respectively). Investigators concluded that none of the lab abnormalities were clinically significant. Also, see Section 7.3.4 of this review.

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AEs of Special Interest

Per WR, the Applicant evaluated any AEs which were potentially associated with PG toxicity as AEs of Special Interest. There were 3 AEs which were considered in this category: irritability, intraventricular conduction delay (IVCD) and seizure. However, causality could not be linked to PG toxicity for any of the 3 events. Narratives for 2 of the AEs are included in section 7.3.4. The event of IVCD is discussed under *Electrocardiograms (ECGs) and QT*; the event of seizure is discussed under *Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to Adverse Events (AEs*). The narrative for the third subject who experienced transient irritability is provided below:

- A 15- month old white male ((b) (6)) with a 12-month history of AD and no other significant past medical history experienced moderate irritability (investigator term) on Day 14 after receiving EUCRISA twice daily. Concomitant products at the time of the event included Huggies Baby Wipes. Anion gap and lactic acid levels were elevated from screening through Day 32. There were no other significant laboratory abnormalities with treatment. The AE of irritability resolved on the following day and was considered not related to the study product. The subject also experienced diarrhea for 12 days (Day 6 to 18) after 7 days of treatment with EUCRISA. PG level was less than 100 at Baseline and 232 at the end of treatment; bicarbonate was normal and osmolality relatively unchanged at both timepoints. The AE of diarrhea was considered unlikely related to the study product.

Hypersensitivity

During the phase 3 trials, 4 subjects (≤1%) experienced adverse reactions of contact urticaria or hypersensitivity. The potential for hypersensitivity was included in labeling in sections 4 *Contraindications*, 5 *Warnings and Precautions* and section 6.1 *Clinical Trials Experiences*. See Clinical Review dated November 3, 2016. In the development program, there were no reports of adverse events of anaphylaxis, angioedema or serum sickness that were deemed to be related to the study product.

In Trial C3291002, one subject experienced urticaria and one subject experienced anaphylaxis. Investigators concluded that neither TEAE was related to the study product. Brief narratives of the cases of hypersensitivity reported during the trial are below:

- A 13-month-old Asian male ((b) (6)) with a 12-month history of AD and food allergies (egg and peanut) experience hives (investigator term) on Day 28 after receiving EUCRISA twice daily for 28 days. The AE resolved on the same day with oral Benadryl. This moderate AE of urticaria was assessed as not related to the study product but possibly related to a food allergy.

- An 8-month-old Asian female ((b) (6)) with AD since birth and food allergies (eggs and nuts) experienced anaphylaxis (investigator term) on Day 50 after receiving EUCRISA twice daily for 29 days. Concomitant products at the time of the event included topical Chinese herbal medicine, Pampers Sensitive Wipes and alcometasone

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diproprionate. In the emergency room, the subject received intravenous diphenhydramine, methylprednisolone, sodium chloride, and intramuscular epinephrine and recovered by the following day. The AE of the moderate anaphylactic reaction was assessed as not related to EUCRISA (probably related to exposure to nuts).

Local Tolerability

The Applicant assessed tolerability by evaluating AEs occurring at the application site. Most of the TEAE which occurred at the application site were considered to be related to the study product unless the investigator identified another causality. A total of 21 (15%) subjects experienced 27 ARs which were localized to the application site. The most common preferred terms were application site pain, application site discomfort and erythema. The majority of local ARs were mild in severity. However, two subjects discontinued the study product and two subjects reduced the dose or temporarily discontinued the study product due to a TEAE. These subjects modifying or discontinuing EUCRISA remained in the trial The most common location for a local AR was the face. Application site events by PT and severity are tabulated below.

Table 15: Adverse Reactions Localized to the Application Site

Number of evaluable subjects	N=137			
Severity	Mild	Moderate	Severe	Total
Number of subjects with any AR at the application site	16 (12)	5 (4)	0 (0)	21 (15)
Number (%) subjects with TEAE by PT & severity				
Application site pain	3 (2)	2 (2)	0 (0)	5 (4)
Application site discomfort	3 (2)	1 (1)	0 (0)	4 (3)
Erythema	4 (3)	0 (0)	0 (0)	4 (3)
Application site erythema	1 (1)	2 (2)	0 (0)	3 (2)
Pruritus	3 (2)	0 (0)	0 (0)	3 (2)
Application site reaction	1 (1)	1 (1)	0 (0)	2 (2)
Eczema	2 (2)	0 (0)	0 (0)	2 (2)
Application site pruritus	1 (1)	0 (0)	0 (0)	1 (1)
Application site irritation	1 (1)	0 (0)	0 (0)	1 (1)
Dermatitis contact	0 (0)	1 (1)	0 (0)	1 (1)
Skin irritation	1 (1)	0 (0)	0 (0)	1 (1)
Total Preferred Term Events	20	7	0	27

Source: Table 14.3.1.2.4.2

7.3.6. Safety Analyses by Demographic Subgroups

In view of the small sample size, the analysis of TEAE by demographic subgroup has limited utility. In addition, the disparity in the sizes of the subgroups confounds the interpretation of the results.

The majority of subjects (94/137; 69%) were in the older age group (9 to <24 months). A total of 62 subjects (66%) experienced 140 adverse events in the older age group while 26 subjects (61%) experienced 52 adverse events in the younger age group (3 to <9 months). Three subjects in the younger age group and 4 subjects in the older age group modified the dose or

discontinued the study drug due to an adverse event. A total of 31 subjects (33%) in the older age group and 12 subjects (28%) in the younger age group experienced infections or infestations. However, the types of infections appeared to be distributed in an age specific pattern (e.g., greater numbers of subjects with otitis media and other ear infections in subjects 9 months <24 months). The Applicant documented no cases of observer reported outcomes (application site pain, application site discomfort and application site pruritus) in subjects age 3 to <9 months.

The majority of subjects (88/137; 64%) were male. A total of 61 male subjects (69%) experienced 139 AEs while 27 female subjects (55%) experienced 53 AEs. Six male subjects and 1 female subject modified the dose or discontinued the study drug due to an adverse event. A greater number of male subjects (8 subjects; 9%) experienced diarrhea than female subjects (2 subjects; 4%). Similar proportions of males and females experienced application site reactions, 9 male subjects (10%) and 6 female subjects (12%), and infections and infestations, 27 male subjects (31%) and 16 female subjects (33%).

The majority of subjects (84/137; 61%) were white. The study population included Asians (27/137; 20%), African Americans (11/137; 8%) and other (15/137; 11%). A total of 60 white subjects (71%) experienced 138 AEs; 14 Asian subjects (52%) experienced 26 AEs; 6 African American subjects (55%) experienced 14 AEs; 8 other subjects (53%) experienced 14 AEs. One white subject experienced a serious AE and one white subject experienced a severe AE. Application site reactions were observed in white, Asian, African American and other subjects,12%, 7%, 9% and 13% respectively. Infections and infestations were observed in white, Asian, African American and other subjects, 30%, 26%, 46% and 40% respectively. The sizes of the subgroups prevented any definitive conclusions.

7.3.7. Supportive Safety Data From Other Clinical Trials

120-Day Safety Update
In accordance with 21 CFR 314.50(d)(5)(vi)(b), Pfizer, Inc. submitted a 4-month safety update report for NDA 207-695 S-010 for EUCRISA, 2% (SDN 1456 dated 02/07/2020). The Applicant stated that there were no ongoing nonclinical or clinical studies relevant to this sNDA (S-0010). Therefore, Pfizer provided no new nonclinical or clinical safety information that would reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in daft labeling.

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting
The analysis of the safety data from Trial C3291002 identified no additional safety signals in the population age 3 months to less than 2 years. Therefore, no additional safety signal are anticipated in the post market setting.

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7.4. Summary and Conclusions

7.4.1. Statistical Issues

This trial was not designed to establish efficacy. There were no statistical issues affecting the overall conclusions.

7.4.2. Conclusions and Recommendations

In this supplement, the Applicant submitted results from Trial C3291002 to support the safe use of EUCRISA for the treatment of pediatric subjects age 3 months to <2 years with mild to moderate atopic dermatitis. Trial C3291002 was an open-label, PK and safety trial enrolling 137 subjects with an ISGA Score of mild (2) or moderate (3) at Baseline/Day 1 and a BSA affected with AD of at least 5%. In a subset of 21 subjects with AD of at least moderate severity and at least 35% BSA affected, the Applicant evaluated the pharmacokinetics and potential for PG toxicity under maximal use conditions. All subjects received EUCRISA twice daily in a thin layer to all treatable lesions of AD (excluding the scalp) for 4 weeks.

There were no deaths, unexpected adverse events or safety signals. One subject experienced a serious adverse event (febrile seizure) which was assessed as not related. No subjects withdrew from the trial due to adverse events. However, investigators temporarily modified the dose or withdrew the study drug from 7 subjects who experienced AEs and 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, hypersensitivity reactions and propylene glycol (PG) toxicity. 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 albumen levels. There was no data to suggest that the subject was evaluated for other causes of weight loss (e.g., dehydration). In addition, two subjects experienced hypersensitivity reactions (anaphylaxis and urticaria); neither TEAE was assessed as related to EUCRISA.

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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. In a review of the current clinical and nonclinical data (European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) 2014), the authors were not able to establish correlations between PG exposure, patient characteristics and reported adverse events. On reexamination of the published safety data (EMA, CHMP 2017), the authors proposed a dose limit of PG of 50 mg/kg for children ≥ 1 month and < 5 years for products administered by any route (IV, oral or topical). Nevertheless, the authors noted that after cutaneous administration, PG penetrates the skin "to a variable extent difficult to predict depending on the severity of the skin damage."

As the pathophysiology of AD and response to treatment are similar in the adult and pediatric populations, efficacy in the population age 3 months to less than 2 years was extrapolated from data in the adult population.

PMR 3142-1 is fulfilled. The submitted PK and safety data in the pediatric population support approval of this sNDA which provided for the use of EUCRISA in the population 3 months and older with mild to moderate AD.

8. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile of the product in the population age 3 months to 2 years was expected to be similar to the safety profile in older pediatric age groups.

9. Pediatrics

The Applicant submitted the clinical study report (CSR) for Trial C3291002 to address the post marketing requirement (PMR) 3142-1 under the Pediatric Research Equity Act (PREA) and in response to a WR for Pediatric Studies under the pediatric exclusivity program for crisaborole. The Applicant submitted the CSR on September 23, 2019 which was consistent with the milestone dates and terms of the WR (e.g., submission required by 09/30/2020).

The Pediatric Exclusivity (PE) Board met on February 19, 2020 to determine whether the Applicant met the terms of the Written Request (issued on March 16, 2017). The Division agreed that the Applicant designed and conducted Trial C3291002 in accordance with the terms of the WR. The Applicant exceeded the required sample size, evaluated the specified study population and performed the assessments to evaluate the pharmacokinetics and safety of EUCRISA in the target population age 3 months to less than 2 years. The PE Board agreed that

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the Applicant had met the terms of the WR exactly (prong 1). The PE Board voted to grant pediatric exclusivity to this drug (Pediatric Exclusivity Determination Checklist dated 02/21/2020).

The Pediatric Review Committee (PeRC) agreed with the Division that PREA PMR 3142-1 was fulfilled and the data was sufficient to support amended labeling (PeRC Meeting held February 25, 2020.

Erica Radden, M.D., the Division of Pediatric and Maternal Health (DPMH), Pediatric Team, agreed with expanding the age group specified in the indication for EUCRISA to 3 months and older. Dr. Radden and the Pediatric Team provided recommendations for labeling (Sections 1, 6, and 8). The review team included the key findings from Trial C3291002 in section 8.4 Pediatric Use section. As the capture of observer reported outcomes such as pain and pruritus had limited precision in this case, the review team omitted quantitative data in favor of general statements regarding the absence of new safety signals in this population. See Review by Erica Radden, MD dated 3/2/2020.

The review team recommended the following language for section 8.4 Pediatric Use:

> 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 in this age group is supported by data from two 28-day adequate, vehicle-controlled safety and efficacy trials which included 1313 pediatric subjects ages 2 years to 17 years of whom 874 received EUCRISA. The most commonly reported adverse reactions in subjects 2 years and older was application site pain. Additionally, use of EUCRISA in pediatric patients ages 3 months to less than 2 years was supported by data from a 28-day open label, safety and pharmacokinetics (PK) trial in 137 subjects. No new safety signals were identified in subjects 3 months to less than 2 years of age [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].
>
> The safety and effectiveness of EUCRISA in pediatric patients below the age of 3 months have not been established.

At this time, no additional postmarketing requirements or commitments for deferred pediatric studies are needed under the PREA (21 CFR 314.55(b) and 601.27(b)).

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10. Labeling Recommendations

10.1. Prescribing Information

The Applicant submitted proposed prescribing information (PI) and patient package insert (PPI) for EUCRISA. Rhiannon Leutner, PharmD, MPH, MBA from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI for EUCRISA and did not identify areas of vulnerability that may lead to medication errors (Review dated 12/20/2019). In addition, Laurie Buonaccorsi, PharmD from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI and PPI. (Review dated 2/4/2020). Dr. Buonaccorsi indicated that OPDP had no comments on the proposed labeling. Erica Radden, M.D. from the Division of Pediatric and Maternal Health (DPMH), reviewed the proposed labeling and provided recommendations regarding the inclusion of pediatric data in labeling in accordance with 21 CFR 201.57(c)(9)(iv). Clinical comments regarding the content of labeling are integrated into the relevant sections of this review.

The members of the primary review team who provided recommendations regarding PI are tabulated below. Refer to the Reviews by Luke Oh, PhD (dated 3/4/2020) and Erica Radden, M.D. (dated 3/2/2020). Comments from the team will be reflected in the final labeling and the approval letter.

Table 16: Reviewers Providing Labeling Comments and Location in the Document

Section	Reviewers Providing Comments & Location in This Review
1 Indications and usage	Clinical team Section: 7.4.1
6 Adverse reactions	Clinical team Section: 7.3.4; Melissa Reyes / Jonn Bailey 10.1 Cardiovascular and Renal Products: Shetarra Walker 7.3.4
8 Use in specific Populations	DPMH: Erica Radden (Pediatrics): 9, 10.1 Clinical Pharmacology Reviewer: Luke Oh / Da Zhang Section 6 Clinical team 7.3.5
12 Clinical pharmacology	Clinical Pharmacology: Luke Oh/Chinmay Shukla: Section 6
13 Nonclinical toxicology	Pharmacology/Toxicology: 5 Kumar D. Mainigi/ Barbara Hill

Source: Reviewer's table

Postmarketing Experience

The Applicant submitted a tabulation of spontaneous post-marketing adverse event reports and proposed labeling to capture post-marketing experience information. Application site pain was the only event that was observed in clinical trials and met threshold (4.4%) for inclusion as an

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adverse drug reaction. Based on review of their pharmacovigilance database, the Applicant identified other application site reactions with signals of disproportionate reporting (Signal of Disproportionate Reporting with EB05>2). After pooling pain related terms (including application site paresthesia, application site warmth, application site burn, application site irritation, application site discomfort, application site hyperesthesia, and application site hypoesthesia) and hypersensitivity related events (including application site urticaria and application site hypersensitivity), the Applicant identified 10 unlabeled application site reactions: discoloration, dryness, erythema, exfoliation, inflammation, pruritus, rash, swelling, vesicles and reaction. In 36 cases, the relationship to EUCRISA was supported by positive dechallenge (resolution after withdrawal of the drug). Despite the limitations of the data, the Applicant proposed to include (b) (4) as post approval ARs in Section 6.2 of the PI due to the biologic plausibility.

Jonn Bailey, PharmD, BCACP, and LCDR Melissa Reyes, MD, MPH, DTMH, from the DPV I, conducted an analysis of the submitted data, an independent review of the literature and an evaluation of cases within the FAERS database for any potential safety signals to be conveyed in labeling. The results of the Postmarket Drug Safety Surveillance Summary (Review by Jessica Weintraub, PharmD, BCPS dated 6/18/2019) provided a focus for the current review. No adverse reactions which were discussed in the Postmarket Drug Safety Surveillance Summary met the Center for Drug Evaluation and Research (CDER) Newly Identified Safety Signal criteria; however, DPV I identified one AE, contact dermatitis, for further evaluation. Other adverse events of continued interest were application site reactions, allergic contact dermatitis, anaphylaxis/ angioedema, and pigmentation changes.

The reviewers identified 3 cases of contact dermatitis which were confirmed by patch testing [a FAERS case associated with an excipient in EUCRISA (propylene glycol) and 2 cases in the medical literature to the active pharmaceutical ingredient.] There was insufficient evidence to support a causal association between the use of crisaborole and the development of anaphylaxis, angioedema or pigmentation changes.

Based on this review, DPV recommended revision of the proposed section 6.2 Postmarketing Experience subsection of the PI to reflect the potential risk of allergic contact dermatitis with the use of EUCRISA.

> 6.2 Postmarketing Experience
> The following adverse reactions have been identified during postmarketing postapproval use of EUCRISA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:
>
> *Skin and Subcutaneous:* allergic contact dermatitis

See the Pharmacovigilance Review dated January 21, 2020.

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10.2. Patient Labeling

The Applicant submitted a proposed patient package insert (PPI). Shawna Hutchins, MPH, BSN, RN from the Division of Medical Policy Programs (DMPP) and Laurie Buonaccorsi, OPDP reviewed the PPI and concluded that the proposed PPI was acceptable. Refer to the Patient Labeling Reviews by Shawna Hutchins (dated 1/31/2020) and Laurie Buonaccorsi (dated 2/4/2020).

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12. Financial Disclosure

In compliance with 21 CFR Part 54 and *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators* (Final, February 2013), the Applicant provided Disclosure Forms from clinical investigators and sub-investigators who participated in the covered clinical trial for EUCRISA. Prior to trial initiation, all investigators were required to certify the absence of certain financial interests or arrangements or disclose those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv). Per Applicant, none of the investigators/ sub-investigators were employees of the Applicant or had equity interest or had propriety interests to disclose. However, a total of 4 investigators of 124 (3%) investigators (Dr. (b) (6)) had significant payments of other sorts to disclose which exceeded $24,999.00. The Applicant listed all payments to the 4 investigators and the reasons for the payments (consulting, committee participation and education).

Table 17: Clinical Trial C3291002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 32 principal investigators (124 investigators and sub-investigators)		
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):		
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: Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
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:	Yes ☒	No ☐ (Request explanation from Applicant) NA

Forms: 3454 and 3455

The Applicant performed the following procedures to minimize potential bias (NDA 207695 SN 0522 dated 1/8/2020):

- Conducted the trial according to the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origin in the Declaration of Helsinki, and applicable privacy laws and Pfizer standard operating procedures in place at that time.
- Consulted the current FDA Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators.
- Public Health System Administrative Actions Listing was checked for researchers who have had administrative actions imposed against them by the Office of
- Research Integrity: http://www.ori.dhhs.gov.
- Frequent monitoring of investigator trial sites, confirmation of data validity per clinical monitoring plan and "cleaning checks" (e.g., querying data though electronic edit checks) were utilized to ensure that errors were identified and corrected
- Review of data and investigation of inconsistencies.
- Review of the study report by members of the project team and Quality Control prior to issue.
- Pre-specification of statistical methods.
- Review of the certification, historical performance and/or qualifications and credentials of site and facilities performing safety and pharmacokinetic evaluations.
- Audit of study sites.
- Conduct trial at multiple site.

Melinda McCord, M.D.
Medical Officer/Dermatology

Reference ID: 4576066

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
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