CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207695
Priority or Standard	Standard
Submit Date(s)	01/07/2016
Received Date(s)	01/07/2016
PDUFA Goal Date	01/06/2017
Division/Office	DDDP
Reviewer Name(s)	Melinda McCord, MD
Review Completion Date	09/07/2016
Established Name	Crisaborole ointment, 2%
(Proposed) Trade Name	EUCRISA
Applicant	Anacor Pharmaceuticals Inc.
Formulation(s)	Ointment
Dosing Regimen	Apply twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of mild to moderate atopic dermatitis in patients 2 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AD	atopic dermatitis
ADSI	atopic dermatitis severity index
AE	adverse event
AN2728	EUCRISA (crisaborole) ointment, 2%
AR	adverse reaction
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
%BSA	percentage of subject's total body surface area
cAMP	Cyclic adenosine monophosphate
CBER	Center for Biologics Evaluation and Research
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDER	Center for Drug Evaluation and Research
CDLQI	Children's Dermatology Life Quality Index
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSRD	corticosteroid-responsive dermatoses
CSS	Controlled Substance Staff
DFI	Dermatitis Family Impact Questionnaire
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	End-of -Phase 2
ETASU	elements to assure safe use
FDA	Food and Drug Administration

FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice
hERG	the human Ether-à-go-go-Related Gene
Hgb	hemoglobin
ICH	International Conference on Harmonization
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISGA	Investigator's Static Global Assessment
ISS	integrated summary of safety
ITT	intent to treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent- to- treat population
MMF	mycophenolate mofetil
MRHD	maximum recommended human dose
NAI	no action indicated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDE-4	phosphodiesterase-4
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PeRC	Pediatric Review Committee
PREA	Pediatric Research Equity Act
PRN	as needed
PRO	patient reported outcome
PSUR	Periodic Safety Update report

QTIRT	QT Interdisciplinary Review Team
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TCI	calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment emergent adverse event
TQT	thorough QT
VAI	voluntary action indicated
WHO-DD	World Health Organization Drug Dictionary
WNL	within normal limits

1 Executive Summary

1.1. Product Introduction

EUCRISA (crisaborole) ointment, 2% is a low molecular weight, benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor. Crisaborole, the active moiety, is a new molecular entity which was developed for the proposed indication of the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. This product is a member of the pharmacological class of phosphodiesterase-4 (PDE-4) inhibitors. Although PDE-4 inhibition is known to increase intracellular cyclic adenosine monophosphate (cAMP) levels, the specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not known. The dosage form of the proposed product is an ointment and the dosing regimen is twice daily to affected areas.

The Agency concluded that the proposed proprietary name, EUCRISA, was acceptable from both a promotional and safety perspective under the NDA 207695. (Proprietary Name Review by Carlos M Mena-Grillasca, RPh., Division of Medication Error Prevention and Analysis (DMEPA) dated 3/10/2016).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted data from 2 adequate and well controlled clinical trials (AN2728-AD-301 and AN2728-AD-302) which provided evidence of the effectiveness of EUCRISA (crisaborole) ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. The primary efficacy endpoint for both trials was the proportion of subjects achieving success on Investigator's Static Global Assessment (ISGA) at Day 29 where success was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. EUCRISA was statistically superior to vehicle (P- value $\leq$ 0.038) on the primary and 2 secondary efficacy endpoints in both trials. The applicant demonstrated that EUCRIA is effective for its intended use in the target population. In my opinion, the applicant provided the substantial evidence of effectiveness required under 21 CFR 314.126 (a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

EUCRISA (crisaborole) ointment, 2%, a new molecular entity, is a topical phosphodiesterase-4 (PDE-4) inhibitor. Crisaborole was developed for the proposed indication of the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. The proposed dosing regimen is to apply a thin layer twice daily to affected areas. Data from 2 adequate and well-controlled trials established the safety and efficacy of EUCRISA for its intended use. Therefore, I recommend approval of EUCRISA, pending successful labeling negotiations and favorable final results of site inspections.

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease that occurs predominantly in children. An estimated 11-15% of children are affected in the United States. Atopic dermatitis or atopic eczema is characterized by severe itching and red, dry, scaly papules and plaques. Associated disorders include allergies, asthma, hay fever, allergic rhinitis and hypersensitivity reactions. The disease is characterized by a remitting and recurring course. The development of atopic dermatitis is influenced by genetic, immunologic and environmental factors.

The onset of atopic dermatitis commonly occurs between 3 and 6 months of age. Approximately 60% of patients develop AD within the first year of life and 90% by age 5 years. Most patients observe improvement in their skin disease with age; however, 10 to 30% experience symptoms that persist into adulthood. A small proportion of patients develop the disease as adults.[1]

Two identically-designed, adequate, well- controlled, trials provided data to support the efficacy of EUCRISA for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. In both trials, EUCRISA ointment, 2% was statistically superior to vehicle ointment on the primary endpoint, success in Investigator's Static Global Assessment (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 development program. 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.

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 did not support a causal link with EUCRISA. The primary methods for further assessment of these potential safety issues will be ongoing monitoring through pharmacovigilance in the post market setting (b) (4)

Safety and effectiveness of EUCRISA in pediatric patients below the age of 2 years have not been established. However, studies in the pediatric population age 3 months to less than 2 years were deferred because EUCRISA was ready for approval for use in adults. The following post marketing assessment will be required:

Conduct an open-label safety trial in 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 (b) (4) in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).

The available evidence of safety and efficacy supports the approval of EUCRISA for the topical treatment of mild to moderate atopic dermatitis (AD) in patients 2 years of age and older. Although there are safe and effective FDA approved products for the treatment of this disorder, EUCRISA provides an effective treatment option without the safety concerns associated with chronic use of topical corticosteroid products or calcineurin inhibitors. In view of favorable benefit/ risk assessment, I recommend approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atopic dermatitis (AD) is a common, chronic, pruritic inflammatory disorder which generally arises in childhood before the age of 5 years and is frequently associated with a personal or family history of other atopic conditions (asthma, allergic rhinitis.) An estimated 11-15% of the pediatric population in the United States is affected as well as a small percentage of the adult population. • Although not life-threatening, AD is associated with significant	Atopic dermatitis is a common condition which has a substantial emotional and economic impact on patients and their families. Additional safe and effective treatment options are needed to reduce the burden of this chronic disease on patients and families.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reduction in the quality of life for patients and their families. The impact of AD on quality of life is reported to be comparable with other chronic medical conditions such as diabetes.	
Current Treatment Options	• The management of atopic dermatitis involves both medical therapies and education of patients and their families about the use of emollients, gentle cleansers and the avoidance of factors which worsen the disease. • FDA approved products for the treatment of mild to moderate atopic dermatitis include a variety of topical corticosteroid (TCS) products and 2 topical calcineurin inhibitors (TCI). Although not curative, these anti-inflammatory products are effective at reducing the signs and symptoms of atopic dermatitis. However, both classes of products are associated with adverse events which prohibit chronic continuous use. • Generally, the initial treatment of mild to moderate atopic dermatitis includes the intermittent use of a topical corticosteroid product. However, the duration of therapy with TCS is limited by local and systemic adverse reactions. Potential local reactions observed with exposure to TCS include atrophy, stria, telangiectasia, irritation, folliculitis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, and secondary infection. Potential systemic adverse reactions observed with exposure to TCS include hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus.	There are safe and effective FDA approved products for the treatment of mild to moderate atopic dermatitis. However, these drug products are associated with local and systemic adverse events that which prohibit chronic, continuous use. Thus, there is a role for additional efficacious drug products with acceptable safety profiles.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Currently, there are 2 approved topical calcineurin inhibitors (TCI): ELIDEL® (pimecrolimus) Cream, 1% and PROTOPIC® (tacrolimus) Ointment. They are considered to be equivalent to a medium potency corticosteroid in the strength of their anti-inflammatory effects. Both TCIs carry a boxed warning regarding rare cases of malignancy (e.g., skin and lymphoma) and are labeled as second-line therapy. Topical calcineurin inhibitors are indicated for the short-term and non-continuous chronic treatment of AD in the population age 2 years and older and not indicated for immunocompromised patients or patients less than 2 years of age.	
Benefit	• The applicant submitted efficacy data from 2 adequate and well-controlled Phase 3 trials (AN2728-AD-301 and AN2728-AD-302) to support the approval of EUCRISA (crisaborole) ointment, 2% for the topical treatment of mild to moderate atopic dermatitis (AD). Enrolled subjects were ≥ 2 years of age with a body surface area (BSA) involvement ≥ 5% (excluding scalp) and an Investigator's Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate). • The pre-specified primary efficacy endpoint for both trials was the proportion of subjects who achieved success on the Investigator's Static Global Assessment (ISGA) at Day 29. Success was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. • EUCRISA ointment, 2% was statistically superior to vehicle ointment on the primary and secondary efficacy endpoint in both trials. In addition, a greater proportion of subjects in the EUCRISA arm experienced improvement in all signs and symptoms of AD at Day	The trials were adequate and well-controlled. The effect size was sufficient to represent clinically meaningful benefit. The evidence submitted by the applicant to support the approval of crisaborole has met the statutory evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	29 than subjects in the vehicle arm.	
Risk	• The primary safety database was comprised of pooled data from 2 identical Phase 3 trials, AN2728-AD-301 and AN2728-AD-302. Among 1511 subjects included in the safety population, 1012 subjects received crisaborole ointment and 499 received vehicle ointment. The applicant evaluated long-term safety in an open-label 48-week trial (Trial AN2728-AD-303) enrolling 517 subjects. The size of the safety database was adequate to identify relevant safety issues. • 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. • Adverse events of special interest which were identified and analyzed included class effects associated with the use of oral PDE-4 inhibitors (weight loss, gastrointestinal events and psychiatric disorders). There was no imbalance the incidence of gastrointestinal adverse events in the crisaborole treatment arm compared with the vehicle treatment arm. Weight loss was not correlated with exposure to crisaborole. However, interpretation of the data was limited by the small number of assessments and the study design which included only a 28-day vehicle controlled period. Identification of weight loss in the pediatric population were expected to gain weight, of a small amount of weight loss may be obscured. Additional uncertainty resulted from the evaluation of weight loss among pediatric subjects who are expected to gain weight. Cases of	The safety profile of EUCRISA (crisaborole) ointment, 2% was well characterized in the population age 2 to 79 years with mild to moderate atopic dermatitis. Generally, the adverse events observed with exposure to crisaborole were not unexpected for the pediatric age groups in which the disease commonly occurs. Many of these events related to ocal safety, common pediatric illnesses and disorders associated with atopic dermatitis such as asthma and allergies. The only adverse reaction observed in greater than 1% of subjects compared with vehicle was application site pain. The clinical trial data is insufficient to support a causal link between EUCRISA and adverse events related to suicidal ideation and behavior or weight loss.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	suicidal ideation and behavior were rare and assessed as confounded or not temporally related.	
Risk Management	• Not applicable.	The risks associated with this drug can be adequately managed through product labeling and pharmacovigilance in the post-marketing setting.

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) is a chronic, pruritic 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. The disease is characterized by a remitting and recurring course. The pathogenesis is complex involving genetic, immunologic and environmental factors.

The onset of atopic dermatitis commonly occurs between 3 and 6 months of age. Approximately 60% of patients develop AD within the first year of life and 90% by age 5 years. Most patients observe improvement in their skin disease with age. However, 10 to 30% experience signs and symptoms that persist into adulthood. A small proportion of patients develop the disease as adults.[1]

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.

Atopic dermatitis is a clinical diagnosis based on the signs and symptoms of the disease, the morphology and distribution of the lesions, the age of onset and personal and family history. Hanifin and Rajka (1980) developed a comprehensive set of diagnostic criteria which are frequently used in clinical trials. Pruritus is almost universally present. Among the minor criteria are a number of nonspecific cutaneous findings such as ichthyosis, palmar hyperlinearity, keratosis pilaris, cheilitis, Dennie-Morgan infraorbital folds, facial pallor and other atypical vascular responses. The diagnosis of AD requires the presence of 3 out of 4 major criteria and 3 out of 23 minor criteria. Due to the complexity of this diagnostic approach, the Hanifin and Rajka criteria are rarely used in clinical practice.[1]

[1] Eichenfield, LF et al. Guidelines of care for the management of atopic dermatitis Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51

The majority of patients are diagnosed with AD of mild severity. Among 91,642 children age 0 to 17 years who participated in the 2007 *National Survey of Children's Health (NSCH), the* overall prevalence of AD was 13% with 67% reporting their disease severity as mild, 26% as moderate and 7% as severe.[2] Epidemiologic data suggests that genetic, environmental and socioeconomic factors impact disease severity.[2,3]

Atopic dermatitis (AD) affects up to 25% of children worldwide[1] and 11-15% of children in the United States.[3] The epidemiologic data in adults is limited but prevalence estimates are substantially lower than in children. Population- based studies conducted in the US indicate that prevalence rates vary by state and population density.[4]

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. [5] 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.[3]

2.2. Analysis of Current Treatment Options

The management of atopic dermatitis involves both pharmacologic and non-pharmacologic interventions. Important measures include patient education, cutaneous hydration, the elimination of exacerbating factors, restoration of normal skin barrier function as well as the pharmacologic treatment of inflammation and pruritus.[6] Education of patients and their families is a key component of successful disease management. One of the first issues to address with the patient and family is skin hydration. Emollients containing high oil content which are applied immediately after bathing or hand washing impede water loss which occurs

[2] Silverberg JI and Simpson EL. Associations of childhood eczema severity: A US population based study. Dermatitis. 2014; 25(3): 107–114
[3] UpToDate. Weston WL and Howe, W.Pathogenegis, clinical manifestations, and diagnosis of atopic dermatitis (eczema). Updated Jan 28, 2016. Accessed Sept 7, 2016.
[4] Carroll CL et al. The Burden of Atopic Dermatitis: Impact on the Patient, Family, and Society. Pediatric Dermatology. 2000; 22 (3) 192–199
[5] Hanifin JM et al. A Population-Based Survey of Eczema Prevalence in the United States. Dermatitis. 2007; 82(2):82-91.
[6] UpToDate. Weston WL and Howe, W. Treatment of atopic dermatitis (eczema). Updated July 18, 2016. Accessed on Aug 8, 2016.

through evaporation. Avoidance of exacerbating factors such as stress, exposure to detergents and solvents, environments with low humidity and/ or excessive heat, frequent bathing without the use of emollients are important for maintenance of treatment benefit. [7]

The standard approach to the initial treatment of mild to moderate atopic dermatitis is intermittent topical corticosteroid therapy with consistent use of emollients. Other agents which may be included in a treatment regimen to minimize adverse events from chronic use of topical corticosteroids are topical calcineurin inhibitors (TCI). FDA approved products for the treatment of atopic dermatitis include a variety of topical corticosteroid (TCS) products and 2 topical calcineurin inhibitors (TCI) as summarized in Table 1.

Topical corticosteroids (TCS) are immunomodulating agents which reduce the signs and symptoms of atopic dermatitis. TCS affect antigen processing and reduce the release of pro-inflammatory cytokines. Multiple formulations, dosage forms and potencies allow treatment to be individualized according to patient age, preference and location of use. However, the duration of therapy with TCS is limited by local and systemic adverse reactions. Potential local reactions observed with exposure to TCS include atrophy, stria, telangiectasia, irritation, folliculitis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, and secondary infection. Potential systemic adverse reactions observed with exposure to TCS include hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus.

Another class of immunomodulating agents with a different safety profile is topical calcineurin inhibitors (TCI). Their strength is considered to be equivalent to a medium potency corticosteroid. The precise mechanism of action of calcineurin inhibitors in the treatment of atopic dermatitis is not well established. However, it is known that these agents bind with high affinity to macrophilin-12 (FKBP-12) and inhibit the calcium-dependent phosphatase, calcineurin. As a result, these products inhibit T cell activation by blocking the transcription of inflammatory cytokines. [8, 9] Labeling for both TCIs includes a boxed warning regarding reports of rare cases of malignancy (e.g., skin and lymphoma). As a result, TCIs are indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

Adjunctive therapy with antihistamines and topical and oral antibacterial agents may be

[7] Eichenfield et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116-32
[8] ELIDEL® (pimecrolimus) Cream, 1% labeling. Section 12.1 Mechanism of Action.
[9] PROTOPIC® (tacrolimus) Ointment, 0.03%, 0.1% labeling. Section 12.1 Mechanism of Action

needed to address the intense pruritus and the infections that arise from scratching. Both non-pharmacologic and pharmacologic measures may be employed to alleviate pruritus. Strategies to control pruritus include oral antihistamines, tepid baths or wet dressings and moisturizers with antipruritic ingredients, camphor, menthol or phenol.

Examples of the currently available products approved by the FDA for the treatment of mild to moderate atopic dermatitis with their major associated safety issues are tabulated below.

Table 1: Currently available products approved by the FDA for the treatment of Atopic Dermatitis

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety Issues
Examples of Topical Corticosteroids Approved for the Treatment of AD in the Pediatric Population				
Fluticasone propionate (Cutivate Cream, 0.05%) Fougera NDA 019957	Relief of the inflammatory and pruritic manifestations of CSRD in patients 3 months and older.	Dec 18, 1990	AD: Apply a thin film of CUTIVATE® Cream to the affected skin areas once or twice daily. Rub in gently. Safety and efficacy of drug use for longer than 4 weeks, or in pediatric patients below 3 months of age, have not been established.	HPA axis suppression observed in 2/43 (4.7%) pediatric patients ages 2 years to 5 years old who were treated for 4 weeks covering at least 35% BSA
Hydrocortisone butyrate (Locoid Lipocream 0.1%) Valeant Pharm NDA 20769	Treatment of mild to moderate AD age 3 months to 18 years of age; Relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in adults	Sept 8, 1997	Apply a thin layer to the affected skin areas two times daily for AD in patients 3 months of age and older. Safety and efficacy of drug use for longer than 4 weeks, or in pediatric patients below 3 months of age, have not been established.	HPA axis suppression observed in 5/82 (6.1%) pediatric patients ages 5 months to 18 years who were treated with Locoid Lipocream three times daily for up to 4 weeks at least 25% of body surface area (BSA)
Mometasone furoate (Elocon Cream 0.1%) Merck Sharp Dohme Corp NDA- 019625	Relief of the inflammatory and pruritic manifestations of CSRD in patients ≥ 2 years of age.	May 6, 1987	Apply a thin film of ELOCON Cream to the affected skin areas once daily. ELOCON Cream may be used in pediatric patients 2 years of age or older. Since safety and efficacy of ELOCON Cream have not been established in pediatric patients below 2 years of age; use in this age group is not recommended	HPA axis suppression observed in 16/97 (16.5%) age 6 to 23 months applied once daily for approximately 3 weeks over a mean body surface area of 41% (range 15%-94%)
Mometasone furoate (Elocon Lotion	Relief of the inflammatory and pruritic	Mar 30, 1989	Apply a few drops of ELOCON Lotion to the affected skin areas once daily and massage	HPA axis suppression observed in 19/65 (29.2%) pediatric subjects ages 6 to

0.1%) Merck Sharp Dohme Corp NDA 019796	manifestations of CSRD in patients ≥12 years of age		lightly until it disappears. Therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary	23 months, with atopic dermatitis, who applied ELOCON Lotion applied once daily for approximately 3 weeks over a mean body surface area of 40% (range 16-90%).
Halobetasol propionate (Ultravate Cream/ Ointment 0.05%) Ranbaxy NDA 019967 NDA 019968	Relief of the inflammatory and pruritic manifestations of CSRD in patients 12 years and older.	Dec 27, 1990 Dec 17, 1990	Apply a thin layer of Ultravate Cream or Ointment to the affected skin once or twice daily. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.	no studies listed
Desonide (Desonate Gel, 0.05%) Bayer HealthCare Pharma NDA 021844	Treatment of mild to moderate AD in patients 3 months of age or older	Oct 20, 2006	Applied as a thin layer to the affected areas two times daily and rubbed in gently. Therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, reassessment of diagnosis may be necessary. Treatment beyond 4 consecutive weeks is not recommended.	The effect of Desonate on HPA axis function was investigated in pediatric subjects, 6 months to 6 years old, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test.
Desonide (Verdeso Foam 0.05%) Aqua Pharm NDA 021978	Treatment of mild to moderate AD in patients 3 months of age or older	Sept 19, 2006	A thin layer of VERDESO Foam should be applied to the affected area(s) twice daily. Shake the can before use. Dispense the smallest amount of foam necessary to adequately cover the affected area(s) with a thin layer.	In an HPA axis suppression trial, three of 75 (4%) pediatric subjects with mild to moderate AD covering at least 25% BSA, who applied VERDESO Foam twice daily, experienced reversible suppression of the adrenal glands following 4 weeks of therapy
Fluocinonide (Vanos Cream 0.1%) Medicis Pharmaceutical Corp	Relief of the inflammatory and pruritic manifestations of CSRD in patients 12 years and older	Feb 11, 2005	apply a thin layer of VANOS Cream once daily to the affected skin areas as directed by a physician. Once daily application for the treatment of atopic dermatitis has been	HPA-axis suppression following application of VANOS Cream, 0.1% (once or twice daily) was also evaluated in 123 pediatric patients from 3 months to <

NDA 021758			shown to be as effective as twice daily treatment in achieving treatment success during 2 weeks of treatment	18 years of age with atopic dermatitis (mean BSA range 34.6 % - 40.0 %). HPA-axis suppression was observed in 4 patients in the twice daily groups. 4/123 (3.3%)
Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety Issues Warnings
Other Treatments – Topical Calcineurin Inhibitors Approved for the Treatment of AD in the Pediatric Population				
Tacrolimus (Protopic Ointment, 0.03% and 0.1%)	Second-line therapy for the short-term and non- continuous chronic treatment of moderate to severe AD in non-immuno-compromised adults and children who have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable	Dec 8, 2000	Adults: 0.03% and 0.1% 2-15 years of age: 0.03% Twice daily	Long-term safety of topical calcineurin inhibitors has not been established. -rare cases of malignancy -continuous long-term use in any age group should be avoided -not indicated for use in children less than 2 years of age -should not be used in immunocompromised adults and children. -If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined -safety not established beyond one year of non-continuous use.
Pimecrolimus (Elidel Cream 1%)	Second-line therapy for the short-term and non- continuous chronic treatment of moderate to severe AD in non-immuno-compromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable	Dec 13, 2001	Apply a thin layer of ELIDEL (pimecrolimus) Cream, 1% to the affected skin twice daily -stop using ELIDEL Cream, 1% when signs and symptoms (e.g., itch, rash and redness) resolve - Continuous long-term use of ELIDEL Cream, 1% should be avoided - Avoid use of ELIDEL Cream, 1% with occlusive dressings.	Long-term safety of topical calcineurin inhibitors has not been established -rare cases of malignancy -continuous long-term use in any age group should be avoided -not indicated for use in children less than 2 years of age

CSRD= corticosteroid-responsive dermatoses
AD=atopic dermatitis

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Crisaborole is a new molecular entity which is not currently approved or marketed in any jurisdiction. The applicant developed EUCRISA (crisaborole) ointment, 2% for the treatment of inflammatory disorders such as mild to moderate atopic dermatitis and psoriasis.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant initiated the development of crisaborole for the treatment of atopic dermatitis on 4/30/2008 under IND 102317 (b) (4) the ointment formulation (b) (4) was being evaluated for the treatment of subjects with psoriasis. In accordance with Agency advice, the applicant pursued further investigation of Crisaborole for the indications of atopic dermatitis and psoriasis with the ointment dosage form under IND 77537.

The applicant sought Agency advice early in the development of crisaborole for the indications of atopic dermatitis and psoriasis. On February 13, 2008, the Agency provided initial guidance regarding the information needed to support a proposed Investigational New Drug Application under 21 CFR 312 for crisaborole (b) (4) (Pre-IND Meeting under IND 77537). The applicant considered the relevant general comments in their approach to the investigation of crisaborole in subjects with atopic dermatitis.

The applicant initiated IND 102, 317 on April 30, 2008 (b) (4) After concluding that the ointment dosage form provided an improved benefit risk profile, the applicant conducted 3 Phase 2 trials and a Phase 1 trial to evaluate the pharmacokinetics, safety and treatment effect of crisaborole ointment in the pediatric and adult populations with AD (IND 102317). The applicant conducted these trials using open-label designs or within- subject, bilateral lesion comparisons.

The key comments communicated to the applicant at the End-of -Phase 2 (EOP2) and Pre-NDA meetings (conducted under IND 77537) are the following:

EOP2 Meeting (February 26, 2014)

- The Division conveyed concern that within-subject, bilateral comparison trials

are limited in assessing dose response and providing reliable safety and efficacy data due to the lack of control for systemic exposure. In addition, the estimates of treatment effect used for powering the Phase 3 trials are not based on Phase 2 trial(s) using the same study population, the same measure and the same definition of 'success/failure' that will be used in the Phase 3 trials.

- The applicant proposed to enroll only pediatric subjects age 2 to 17 years with mild to moderate atopic dermatitis (IGSA score 2 or 3) involving ≥ 5% treatable BSA (excluding the scalp). Because the target population includes adult and pediatric patients, the Division recommended that the study population include a sufficient number of adult subjects to be able to assess efficacy and safety in that subgroup.
- The Division also noted that the prevalence of atopic dermatitis is the highest in the 2 to 6 year age group and recommended that the sponsor should consider enrolling a greater proportion of subjects in this pediatric subgroup. The applicant proposed to include at least 20% (i.e. 300 subjects) in the 2 to 6 year age group .The Division agreed.
- The proposed primary efficacy endpoint of the proportion of subjects achieving treatment success which is defined as an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2- grade improvement from baseline is acceptable. However, the IGSA category descriptors should be modified so that the category "Clear" should represent the true absence of disease (e.g., no residual coloration other than hypo/hyperpigmentation).
- Regarding the proposed secondary endpoints, the Division recommended including an evaluation of the signs and symptoms of atopic dermatitis (e.g. erythema, induration/papulation, scaling and oozing/crusting) which should be evaluated globally on a 4-5 point scale and not by body region (as in the EASI score.) In addition, the assessment of pruritus in this trial has limited regulatory utility because the baseline pruritus score and PRO dossier were not included in the briefing package. The sponsor agreed not to use the EASI score or time to improvement of pruritus as secondary endpoints.

Pre-NDA Meeting (September 23, 2015)

- The non-clinical reviewer noted that the major metabolite AN7602 was not evaluated in vitro for potential to inhibit or induce cytochrome P450 enzymes. Results from Trial AN2728-AD-102 showed that the exposure to metabolite AN7602 was greater than 30% of the parent AN2728. Therefore, the Division asked the applicant to provide in the NDA results of in vitro enzyme inhibition and induction studies.
- (b) (4) hould be added to the drug product specification.

- Agency agreed that the applicant may submit updated drug product stability data for 100-g tubes (12-month data for 3 primary stability lots) within 30 calendar days of the original NDA submission.
- Results of photostability studies on the drug substance and drug product should be included in your NDA submission.

In an Advice Letter dated October 6, 2014, the Division confirmed their agreement with the Agreed initial Pediatric Study Plan (iPSP). The Division stated the following:

> "We acknowledge your plan to study AN2728 topical ointment, 2% in pediatric subjects ages 3 months to less than 2 years old and your request to waive studies in pediatric subjects ages birth to less than 3 months old."

Refer to Section 8.8.3 Pediatrics and Assessment of Effects on Growth.

The applicant included a Request for Priority Review Designation in the NDA submission. The Division did not grant the priority review request because although atopic dermatitis (AD) may be a severe condition, it is not a serious condition since it does not result in increased mortality or permanent disability. Currently available treatments for AD mitigate the signs and symptoms of the disease but do not provide permanent remission. Although data provided in the NDA submission supported the efficacy of the proposed product in the treatment of AD, the data did not support the superiority of the proposed product to the available therapies with regard to the durability of response or benefit/risk assessment. The Agency notified the applicant that the review classification for this application was standard (Filing Communication Letter dated 3/21/2016).

3.3. Foreign Regulatory Actions and Marketing History

There are no relevant regulatory actions from foreign marketing experience as crisaborole ointment is not approved in any jurisdiction at the time of this review.

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 requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of 4 domestic sites based on the following criteria: sample size, treatment effect, response rate

and the presence of missing data. The rationale for the selection of each specific site is provided below:

- Site 138: large sample size, large treatment effect and 6 subjects with missing data for the active arm but no missing data for the vehicle arm.
- Site 150: large sample size, large treatment effect and 3 subjects with missing data for the vehicle arm and no missing data for the active arm.
- Site 211: large sample size, large treatment effect with low response rate for vehicle arm, and relatively large amount of missing data.
- Site 240: large sample size, large treatment effect with low response rate for vehicle, and no missing data.

Table 2: Results of Site Inspections

Site Number, Name, and Address	Protocol ID	Number of Subjects	Tentative Classification	Inspection Dates
Center 138 Joe Lynn Williams, Jr, MD IMMUNOe International Research Center 3240 E 104th Ave Thornton, CO 80233	AN2728-AD-301	39	VAI	Apr 20-28 2016
Center 150 Richard G. Gower, MD Marycliff Allergy Specialists PS 324 S Sherman St, A2 Spokane, WA 99202	AN2728-AD-301	30	NAI	May 10-13 2016
Center 211 William C. Rees, MD PI-Coor Clinical Research, LLC 8982 Fern Park Drive Burke, VA 22015	AN2728-AD-302	46	NAI	April 26, 2016
Center 240 Julie Shepard, MD Ohio Pediatric research Association 7200 Poe Avenue, Suite 200 Dayton, OH 45414	AN2728-AD-302	33	NAI	May 4-11 2016

Source: Reviewer's Table

NAI = **N**o **A**ction **I**ndicated. (No deviation from regulations. The applicant is in compliance and data is acceptable)
VAI = **V**oluntary **A**ction **I**ndicated. (Deviation(s) from regulations. The Agency requested voluntary correction and data or portions thereof may/may not appear acceptable).

OAI =**O**fficial **A**ction **I**ndicated (Serious non-compliance requiring regulatory or administrative action by FDA and data is unacceptable). 21 CFR 312.70 and 21 CFR part 50 & 312

Review of the study records included the delegation logs, IRB and CRO communications, source documents, adverse events, financial disclosure forms, personnel training, and study drug accountability records and storage information. The results indicated that some deviations from regulations occurred at Center 138. The Agency issued a Form FDA 483 at the conclusion of the inspection for the following two instances of failure to adhere to the protocol:

(1) Subject 021 used hydroxyzine as needed per the Concomitant Medication Log despite the protocol excluding subjects using systemic antihistamines on a non-stable basis.

(2) Subjects 013 used Mupirocin for the treatment of impetigo despite the restriction in the protocol regarding the use of topical antibacterial agents.

The reviewer concluded the following:

"The isolated protocol deviations noted above would not appear to have a significant impact on safety or efficacy considerations. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication. " (Review by Roy Blay, Ph.D. dated 10/6/2016)

Reviewer Comment:

The Statistical Reviewer, Matthew Guerra, PhD., analyzed the primary efficacy endpoint without data from Center 138 and observed only a minimal change in response rate. Refer to the Table 17 of the Statistical Review and Evaluation by Matthew Guerra, PhD dated 8/19/2016.

4.2. Product Quality

Drug Product

EUCRISA (crisaborole) ointment, 2%, a new molecular entity (NME), was developed as a non-sterile drug product for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. Crisaborole is a low molecular weight benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor.

The drug product is white to off-white, petrolatum based ointment. Each gram of the product contains 20 mg of crisaborole in an ointment vehicle containing white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium. EUCRISA is packaged in (b) (4) laminate tubes with a (b) (4) cap, (b) (4) tube head, and (b) (4) seal. The drug product is available in three packaging presentations with labeled content of 60 g, 100 g, and 2.5 g (physician sample). All

excipients are compendia and none of the excipients are of human or animal origin. The Quality Reviewer identified no quality microbiology deficiencies in the information provided.

Drug Substance [USAN Name] Quality Summary

The active pharmaceutical ingredient (API), crisaborole, is well characterized. The chemical name of crisaborole is: 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole.

The quantitative composition is presented in Table 3.

Table 3: Composition of EUCRISA

Components	Function	Concentration (% w/w)
Crisaborole	Active	2.0000
White petrolatum	Ointment base	(b) (4)
Propylene glycol	(b) (4)	
Mono- and di- glycerides		
Paraffin		
Butylated hydroxytoluene		
Edetate calcium disodium		

Source: Modified from Quality Assessment page 73

Impurities

The applicant provided a thorough discussion of the potential and actual impurities found in the crisaborole drug substance including organic and inorganic impurities, heavy metals and residual solvents. All were adequately controlled in the drug substance. Although 2 organic impurities were identified, they were not detected in batches manufactured using the proposed commercial process.

The drug substance specifications were acceptable and data from all stability studies demonstrated that crisaborole is chemically and physically stable under ICH Q1A(R2) conditions at all tested time points within a container closure system representative of the commercial container closure.

Expiration date

Based on the long-term primary stability data submitted, the quality reviewer concluded that the proposed expiration dating period of 24 months for the 60 g and 100 g presentations and 22 months for the physician sample presentation was acceptable.

LABELING/LABELS

Package Insert

Recommendations

Product title, Drug name (201.57(a)(2))

- The word "TRADENAME" needs to be replaced by "EUCRISA" throughout the document.
- "(b) (4)" should be changed to "ointment, for topical use"

Dosage Forms and Strengths (21CFR 201.57(c)(4))

- The phrase "(b) (4)" needs to be removed because it is not justified in the drug product section of the NDA.

The Division and CMC Review team recommended the following to be included in labeling:

2 DOSAGE AND ADMINISTRATION

Apply ~~TRADENAME~~ **a thin layer of EUCRISA** twice daily to affected areas. (2)
~~TRADENAME~~ **EUCRISA** is for topical use only and not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

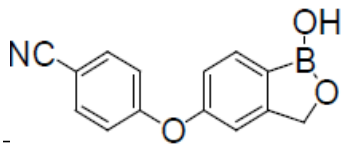
Ointment: 20 mg (2%) of crisaborole per gram of white to off-white ointment.
(b) (4)

11 DESCRIPTION

~~TRADENAME~~**EUCRISA**, contains 2% crisaborole (w/w) in a petrolatum-(b) (4) **based, white to off-white** ointment~~,~~ **and** is for topical use. The active ingredient, crisaborole, is a (b) (4) **phosphodiesterase-4** (PDE-4) inhibitor. (b) (4)

Crisaborole is described chemically as 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole. The empirical formula is C14H10BNO3 and the molecular weight is 251.1 **g/mol**.

The structural formula is represented below:



Crisaborole drug substance [redacted] is freely soluble in common organic solvents such as isopropyl alcohol and propylene glycol, and insoluble in water.

[redacted] **EUCRISA** contains 20 mg of crisaborole in an ointment containing white petrolatum [redacted] propylene glycol [redacted], mono- and di-glycerides [redacted], paraffin [redacted] butylated hydroxytoluene [redacted] and edetate calcium disodium [redacted]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

~~TRADENAME~~ **EUCRISA** is **a white to off-white** [redacted] ointment containing 2% crisaborole and is supplied in 60 g and 100 g laminate tubes.

60 g tube: NDC 55724-211-21
100 g tube: NDC 55724-211-11

16.2 Storage and Handling
Store at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F).
[see USP Controlled Room Temperature].

[redacted]
Keep tube tightly closed.
[redacted]

Container and Carton Labels (2.5 g, 60 g, 100 g)

Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))

- The word "TRADENAME" needs to be replaced by "EUCRISA"
- Since the product is a topical ointment, as per the guidelines provided on Dec. 1, 2014 by USP Expert Committee on Nomenclature, Safety and Labeling, the established name should be given as "(crisaborole) Ointment, 2%"

Lot number per 21 CFR 201.18

- The lot number needs to be provided.

Expiration date per 21 CFR 201.17

- The expiration date needs to be provided.

CMC Recommendation and Conclusion on Approvability

The applicant of this NDA provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities involved in this application.

No Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps are needed.

However, the issues on labels/labeling are not completely resolved at this time.

Per 21CFR 314.125(b)(6), the Quality Review Team does not deem NDA 207695 to be ready for approval until the applicant addresses the deficiencies that were identified in the labels and package insert.

Additional Issues
On 9/9/2016 (SD 11), the applicant informed the Agency of the presence of potential mutagenic impurities in the crisaborole (b) (4). These impurities included:

(b) (4)

The applicant intends to address these findings by re-evaluating all potential mutagenic impurities (b) (4) and developing analytical methodology to assess the level of these compounds in the crisaborole drug substance. The applicant proposed to submit the data package before November 1, 2016. The content of the submission may impact the review timeline and approvability of the product

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

To support approval of the original NDA, the applicant submitted data from an extensive non-clinical program. The key findings which impacted the clinical development of EUCRISA (crisaborole) ointment, 2%, related to safety pharmacology, carcinogenicity and reproductive toxicology studies. Refer to the review by Kumar D. Mainigi, PhD dated 8/15/2016 for a detailed discussion of these results.

The applicant evaluated the potential of crisaborole (AN2728) to induce the human Ether-à-go-go-Related Gene (hERG) channel inhibition and conducted safety pharmacology studies in rats, mice, dogs and minipigs to evaluate the cardiovascular effects of crisaborole. Although crisaborole was identified as a low-potency hERG-channel blocker by in vitro assays, the results of safety pharmacology studies in animals did not demonstrate effects on cardiovascular functioning in rats and mice at an oral dose of 1000mg/kg (40 and 81 maximum recommended human dose (MRHD)) or in male dogs at oral doses of 30 and 100 mg/kg (27 MRHD). One dog in the high-dose group (300 mg/kg) died from hypertensive shock; however, at the same dose level, ECG parameters including QTc intervals, and locomotor activity were not affected. Minipigs treated with crisaborole, 5% ointment for 3 months and crisaborole, 7% ointment twice daily for 9 months had no ECG changes during treatment or recovery.

Because crisaborole was classified as a low-potency hERG-channel blocker and topical application of the proposed product resulted in significant systemic exposure (> 50 ng/mL), the applicant conducted a thorough QT study (TQT). See Sections 4.5.2 and 8.4.9 for the discussion of the data regarding the cardiovascular safety evaluation.

The evaluation of topical drug products also includes an assessment of the potential for irritation and sensitization. There was no skin sensitization in the mouse local lymph node assay at concentrations of 1, 5, and 10% (w/v) of crisaborole. In primary ocular and skin irritation assays in rabbits, 2% crisaborole ointment was identified as a mild to moderate irritant.

The potential for drug-drug interactions was assessed with a set of in vitro assays using freshly isolated human hepatocytes from three healthy volunteers. Crisaborole did not induce any critical CYP enzymes including CYP3A4, which is induced by a broad spectrum of drugs in humans.

In addition, the applicant conducted an oral rat carcinogenicity study and a dermal mouse carcinogenicity study. The Executive Carcinogenicity Assessment Committee (CAC) agreed with the study designs and proposed dose selection and discussed the final study reports during a meeting on 6/21/ 2016. (Executive CAC Meeting Minutes dated 6/ 23/2016, Barbara Hill, PhD). The following were the Executive CAC Recommendations and Conclusions:

<u>Oral Rat Carcinogenicity Study</u>

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that there was a drug related increased incidence of granular cell tumors in the uterus, with cervix or vagina (combined) in high dose female rats.

<u>Dermal Mouse Carcinogenicity Study</u> (doses up to 7% crisaborole ointment)

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that the study was negative for drug related neoplasms

The clinical significance of the increased incidence of granular cell tumors in female rats is not known.

The applicant also conducted genetic toxicology and reproductive and developmental toxicology studies to support the safety of their product. Crisaborole was non-mutagenic in Ames assays conducted using four *Salmonella* and one *E. coli* strains. There were no structural/numerical chromosomal aberrations in activated/nonactivated human peripheral blood lymphocytes. In the rat micronucleus assay, crisaborole did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes at doses up to 2,000 mg/kg.

No drug related fetal malformations were noted in the rat or rabbit embyrofetal development studies which were conducted with crisaborole. Oral doses up to 300 mg/kg/day crisaborole were administered to pregnant rats during the period of organogenesis and oral doses up to 100 mg/kg/day crisaborole were administered to pregnant rabbits during the period of organogenesis.

No drug related effects on fetal development were noted in the rat prenatal/postnatal development study conducted at oral doses up to 600 mg/kg/day crisaborole administered to pregnant rats during gestation and lactation. No drug related effects on fertility were noted in male or female rats administered oral doses up to 600 mg/kg/day crisaborole prior to and during early pregnancy.

The Pharmacology/Toxicology Reviewer, Kumar D. Mainigi, PhD, concluded the following:

> "A comprehensive nonclinical safety profile for EUCRISA (crisaborole), Ointment, 2% supports the safety of the proposed clinical dosing regimen for the topical treatment of mild to moderate atopic dermatitis. This NDA is approvable from a Pharmacology /Toxicology perspective."

Labeling

The Division and Pharmacology/Toxicology team recommended the following language for Section 13 Nonclinical Toxicology. The **bold and underlined** text indicates a recommended insertion and ~~strikethrough~~ text indicates a recommended deletion.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 30, 100, and 300 mg/kg/day crisaborole were administered to rats once daily. A drug- related increased incidence of granular cell tumors in the uterus with cervisx or vagina (combined) was noted in 300 mg/kg/day crisaborole treated female rats (2 times the MRHD on an AUC comparison basis). The clinical ~~R~~relevance of this finding (b) (4) is unknown.

In a dermal carcinogenicity study in CD-1 mice, topical doses of 2%, 5% and 7% crisaborole ointment were administered once daily. No drug-related neoplastic findings were noted at topical doses up to 7% crisaborole ointment (2 times the MRHD on an AUC comparison basis).

Crisaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

(b) (4) **No effects on** (b) (4) fertility **were observed** in male or female rats (b) (4) **that were administered oral doses up to** 600 mg/kg/day **crisaborole (18** (b) (4) times the MRHD **on an AUC comparison basis) prior to and during early pregnancy**.

4.5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Chinmay Shukla, Ph.D. provided a comprehensive discussion of the clinical pharmacology findings that were pertinent to the evaluation of the clinical trials (Review dated 8/30/2016). The Clinical Pharmacology program included the following trials and studies:

- Maximal use pharmacokinetic (PK) trial in subjects with AD (AN2728-AD-102)
- Adolescent PK trial in subjects with AD (AN2728-AD-203)
- Thorough QTc trial in healthy subjects (AN2728-TQT-108)
- In-vitro drug interaction studies
- In-vivo drug interaction study in healthy subjects (AN2728-PK-101)
- Drug metabolism study (AN2728-PSR-105)

- In-vitro plasma protein binding study

In general, trials incorporating bilateral designs or other formulations of the proposed product were not discussed in the Clinical Pharmacology review. The results of the pharmacokinetic (PK) Trial AN2728-AD-203 which was conducted in pediatric subjects age 12 to 17 years was considered to be supportive because it was not conducted under maximal use conditions. The Clinical Pharmacology Reviewer summarized the key findings from the Clinical Pharmacology program as follows:

Pharmacokinetics (PK)

The applicant conducted a maximal -use PK trial (AN2728-AD-102) to assess the PK of crisaborole (AN2728), its major metabolite AN7602 and the downstream metabolite of AN7602 (AN8323). A total of 33 male and female subjects age 2 to 17 years with mild to moderate AD applied 3 mg/cm^2 of crisaborole ointment, 2% twice daily to a mean body surface area (BSA) of involvement of 49 ± (SD) 20%. Systemic concentrations of crisaborole and its metabolites were quantifiable in all subjects and steady state was reached by Day 8. The mean maximum plasma concentration (C_{max}) of crisaborole on Day 8 was 127 ± 196 ng/mL and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) was 949 ± 1240 ng*h/mL.

These results are compared with data from trials conducted in other study populations (healthy subjects and subjects with psoriasis) in Table 4.

Table 4: Comparison of PK Parameters from Trials PSR-104, PSR-106, AD-102 and AD-203

	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0-12)}$ (ng*h/mL)	$t_{1/2}$ (h)
PSR-104 healthy subjects, n=6 BSA=35%, dose=33.1 g. Day 7	93.3 (34.4)	2.0 (0.0)	476.8 (111.2)	15.3 (3.5)
PSR-106 psoriasis patients, n=33 mean BSA=37.9%, mean dose=24.25 g. Day 8	109 (73.7)	2	748 (455)	9.77 (2.68)
AD-203 AD adolescent patients, n=23 BSA=10-35%. Day 8	94.6 (189)	2.17	462 (506)	11.9 (8.28)
AD-102 AD pediatric patients 2-17 years, n=34. BSA ≥35% (ages 2-11 years) or ≥25% (ages 12-17 years). Day 8.	127 (196)	3.00	949 (1240)	

Source: Review by An-Chi Lu, M.S., Pharm.D., IND 77537 dated 2/28/2014
Trial AN2728-AD-203 was not conducted under maximal use conditions

Drug interaction assessment:

The applicant conducted an in-vitro drug interaction assessment to evaluate the potential of crisaborole and its metabolites (AN7602 and AN8323) to induce and inhibit cytochrome P450 enzymes. In-vitro studies in human liver microsomes indicated that under the conditions of clinical use, crisaborole and AN7602 were not expected to inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4. The downstream metabolite AN8323 was a weak direct inhibitor of CYP1A2 and 2B6 and a moderate direct inhibitor of CYP2C8 and 2C9. The most sensitive enzyme, CYP2C9, was further investigated for drug interaction potential in a clinical trial (AN2728-PK-101) using 25 mg oral dose of warfarin as a CYP2C9 substrate. The results of this clinical trial showed there was no drug interaction potential and further investigation of other enzymes was not warranted. Overall, the data indicated that AN8323 is not expected to inhibit any CYP enzymes under the conditions of clinical use.

TQT assessment

The applicant evaluated the effects of EUCRISA (crisaborole) ointment, 2% on the QT interval compared to vehicle and moxifloxacin positive control in healthy subjects (AN2728-TQT-108). The protocol- specified definition of "therapeutic dose" was the application of crisaborole to 30% body surface area (BSA) and the definition of "supra-therapeutic dose "was the application of crisaborole to 60% BSA.

Because the study population included healthy adult volunteers rather than subjects with atopic dermatitis, the systemic concentrations of crisaborole following the supra-therapeutic dose were approximately 30% lower than those achieved in the maximal use PK trial in pediatric subjects with AD (AN2728-AD-102). Regression analysis showed no positive relationship in the plot of vehicle-corrected change from time-matched baseline in QTcF (ΔΔQTcF) versus concentration of crisaborole. Based on the totality of data, there was no evidence that crisaborole has a clinically meaningful effect on the QTc interval.

Absorption Distribution Metabolism and Excretion (ADME) Trial (not conducted with the to-be-marketed formulation)

The applicant conducted an Absorption Distribution Metabolism and Excretion (ADME) trial in 6 healthy male subjects following a single topical dose of [14C]-AN2728 ointment E, 2%. Following a single topical administration, radioactivity readily appeared with median T_{max} values of 8 hours and $t_{1/2}$ values of 20.0 hours in plasma. Approximately 25% of the applied dose was absorbed percutaneously. The results indicated that approximately 81% of the absorbed radioactivity was recovered in the urine within 16 hours post-dose, and approximately 1% of the absorbed radioactivity was recovered in feces. By 168 hours post-dose, the absorbed

radioactivity was almost completely recovered. Renal excretion was the major route of elimination in humans after a topical dose.

Other effects
The applicant did not explore the impact of intrinsic factors such as gender and age on the pharmacokinetics of crisaborole. Although Trial AN2728-AD-102 enrolled male and female subjects age 2 to 17 years, confounding factors and limited numbers of subjects in each age group prevented subgroup analyses. However, the effect of % BSA on the exposure of crisaborole was evaluated by the Clinical Pharmacology Reviewer. The analysis indicated that after topical application of crisaborole, the values of C_{max} and AUC_{0-12} on Day 8 appeared to increase with increasing BSA.

The Division and Clinical Pharmacology team recommended the following language for Section 12 Clinical Pharmacology of labeling. The **bold and underlined** text indicates a recommended insertion and ~~strikethrough~~ text indicates a recommended deletion.

4.5.1. Mechanism of Action

Crisaborole is a (b) (4) *phosphodiesterase 4 (PDE-4) inhibitor* (b) (4) *- PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels.* (b) (4) *The specific mechanism(s) by which crisaborole exerts its therapeutic action for the treatment of atopic dermatitis is not ~~well defined~~* (b) (4)

Reviewer Comment:

Although PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels, the precise mechanism of action in the treatment of AD is unknown. Thus, the Division removed the (b) (4) *in Section 12.1 regarding* (b) (4) *since the mechanism of action is not well characterized.*

4.5.2. Pharmacodynamics

The applicant evaluated crisaborole (1 µM) for hERG channel inhibition. Although testing indicated that Crisaborole was a low-potency hERG-channel blocker, safety pharmacology studies revealed no significant signals for adverse cardiovascular or CNS effects. In view of the non-clinical findings and systemic exposure data, the applicant conducted a thorough QT Trial (TQT) AN2728-TQT -108.

After reviewing the summary Clinical Pharmacology data, clinical safety data, cardiovascular safety report and previous reviews of the TQT data from Trial AN2728-TQT -108 (Review dated 5/20/2014 under IND 77537), the QT Interdisciplinary Review Team (QT-IRT) recommended the following language for Section 12.2 (Memorandum dated 7/22/2016):

12.2 Pharmacodynamics

"Cardiac Electrophysiology

In the thorough QT study in subjects who had treatment areas up to 60% body surface area, TRADENAME has not led to clinically significant effects on heart rate (HR), PR, and QRS interval durations or electrocardiogram (ECG) morphology, including prolongation of QTc.

In the Phase 3 studies in pediatrics and adults, no subject had QTcF > 480 ms or change of QTcF from baseline > 30 ms.

Reviewer Comment:

The Clinical Pharmacology team leader, Doanh Tran, PhD, stated that to compare the results of the TQT trial which was conducted in healthy adult subjects to the anticipated exposure in adult and pediatric subjects with atopic dermatitis would require a longer text than proposed by QT-IRT team. Even when applied to lower %BSA of involved skin, the systemic exposure in the TQT trial was lower than observed under maximal use conditions. Thus, presenting the trial results without explanation may be misleading. He stated the following

" The overall conclusion was derived from looking at the exposure response relationship and overall lack of QT safety signals across all trials."(Email communication dated 8/24/2016)

Thus, the Division and Clinical Pharmacology team recommended the following labeling for Section 12.2:
(The **bold and underlined** text indicates a recommended insertion and ~~strikethrough~~ text indicates a recommended deletion).

12.2 Pharmacodynamics

At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent. (b) (4)

4.5.3. Pharmacokinetics

The Division and Clinical Pharmacology team recommended the following labeling for Section 12.3:
(The **bold and underlined** text indicates a recommended insertion and ~~strikethrough~~ text indicates a recommended deletion).

Absorption
The pharmacokinetics (PK) of EUCRISA were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis (a mean ± SD body surface area involvement of 49 ± 20% [range 27% to 92%]). In this study, subjects applied approximately 3 mg/cm^2 of EUCRISA ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days.

Plasma concentrations were quantifiable in all the subjects. The mean ± SD maximum plasma concentration (C_{max}) and area under the concentration time curve from 0 to 12 hours post dose (AUC_{0-12}) for crisaborole on Day 8 were 127 ± 196 ng/mL and 949 ± 1240 ng*h/mL, respectively. Systemic concentrations of crisaborole were at steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean

accumulation factors for crisaborole was 1.9.

Distribution
Based on in vitro study, crisaborole is 97% bound to human plasma proteins.

Elimination
Metabolism

Crisaborole is substantially metabolized into inactive metabolites. The major metabolite was 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol (metabolite 1) formed via hydrolysis; this metabolite was further metabolized into downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (metabolite 2), formed via oxidation, was considered a major metabolite.

PK of metabolites 1 and 2 were assessed in the PK study described above and the systemic concentrations were at or near steady state by Day 8. Based on the ratios of AUC_{0-12} between Day 8 and Day 1, the mean accumulation factors for metabolites 1 and 2 were 1.7 and 6.3, respectively.

Excretion
Renal excretion is the major route of elimination.

Drug Interactions Studies

In vitro studies using human liver microsomes indicated that under the conditions of clinical use, crisaborole and metabolite 1 are not expected to inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

In vitro human liver microsomes studies for metabolite 2 showed that it did not inhibit activities of CYP2C19, 2D6, and 3A4; was a weak inhibitor of CYP1A2 and 2B6; and a moderate inhibitor of CYP2C8 and 2C9. The most sensitive enzyme, CYP2C9, was further investigated in a clinical trial warfarin as a CYP2C9 substrate. The results of this study showed no drug interaction potential.

In vitro studies in human hepatocytes showed that under the conditions of clinical use crisaborole and metabolites 1 and 2 are not expected to induce CYP enzymes.

Other recommendations provided by the Clinical Pharmacology team included removing Section 7 of labeling. Chinmay Shukla, PhD provided the following rationale: "CDER good labeling practices state that section 7 should Include clinically significant DI information

(also generally actionable) and DI findings with negative results (i.e., no interaction was found) should generally not appear in this section unless this information is clinically relevant for the prescriber (e.g., if two drugs are commonly used together or if a drug does not have the same interaction as other drugs in the same class). Also according to CFR 201.56(d)(4), any section, subsection, or subsection information may be omitted from the labeling if clearly inapplicable (i.e., if the negative information is removed and section 7 is empty it can be removed. (b) (4) mail communication dated 8/29/2016)

(b) (4)

Clinical Pharmacology Recommendation and Conclusion
Clinical Pharmacology reviewer indicated this application was acceptable provided the labeling comments were adequately addressed by the applicant. (Clinical Pharmacology Review dated 8/30/2016)

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The applicant conducted 23 clinical trials to evaluate the proposed product: 7 trials in healthy volunteers, 7 trials in subjects with AD and 9 trials in subjects with psoriasis. Eleven trials included the to-be-marketed formulation. Table 5 provides a summary of all trials pertinent to the evaluation of the efficacy and safety of EUCRISA (crisaborole) ointment, 2% for the treatment of

mild to moderate atopic dermatitis. (b) (4) this submitted safety data was considered supportive and was briefly discussed in Section 8. For a discussion of the pharmacokinetic trials (including drug-drug interaction studies) the reader should refer to the Clinical Pharmacology Review Chinmay Shukla, Ph.D. dated 8/30/2016)

Table 5: Listing of Clinical Trials Relevant to this NDA 207695

Trial Identity	Trial Design	Regimen/ schedule/ route§	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
AN2728-AD-301	Phase 3 multicenter, randomized, double-blind Vehicle-controlled trial	Crisaborole Ointment, 2%, BID or Vehicle Ointment, BID topical application	Proportion of subjects with ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline/ Day 1	Study product applied twice daily for 28 days	ITT: 759 332 M 427 F Age (yrs) 2-11:468 12-17:188 ≥ 18: 103 Safety: 754 328 M 426 F	Male and female subjects age ≥2 years with mild to moderate AD (ISGA score of mild (2) or moderate (3) and ≥5% treatable BSA (excluding scalp))	48 investigational sites in the United States.
AN2728-AD-302	Phase 3 multicenter, randomized, double-blind Vehicle-controlled trial	Crisaborole Ointment, 2%, BID or Vehicle Ointment, BID topical application	Proportion of subjects with ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline/ Day 1	Study product applied twice daily for 28 days	ITT: 763 332 M 427 F Age (yrs) 2-11:474 12-17:183 ≥ 18: 106 Safety: 757 340 M	Male and female subjects age ≥2 years with mild to moderate AD (ISGA score of mild (2) or moderate (3) and ≥5% treatable BSA (excluding scalp))	42 investigational sites in the United States.

					417 F		
Studies to Support Safety							
AN2728-AD-303	Phase 3 multicenter, open label long term safety trial	Crisaborole Ointment, 2%, BID as needed	Safety endpoints: AEs, SAEs, TEAE, local tolerability, clinical laboratory results, vital signs, and physical examinations	28-day cycles for up to 48 weeks	517 subjects Age (yrs) 2-11:308 12-17:146 ≥ 18: 63	Subjects age 2 to 72 years with mild to moderate atopic dermatitis	41 investigational sites in the United States
AN2728-TQT-108	Phase 1, single-center, randomized, 3-cohort parallel study, with a nested crossover design to assess the effects of Crisaborole Ointment, 2% on QT/QTc intervals compared to vehicle and moxifloxacin positive control	Crisaborole Ointment, 2% Or Vehicle QD Days 1, 2, and 9 and BID Days 3–8; Moxifloxacin tablets or placebo tablets Day 2, 10	Safety endpoints: TEAEs, including SAEs, changes in selected laboratory parameters, VS, and/or ECGs	10 days	180 adult subjects	Healthy subjects age 18 to 45	1 investigational sites in the United States
AN2728-RIPT-101	Phase 1, randomized, controlled trial to evaluate the sensitizing potential and cumulative irritation potential of Crisaborole Ointment, 2% in healthy volunteers using a Repeat Insult Patch Test and	Cohort 1: 9 applications during the Induction Period and 1 application at Challenge	<u>Safety:</u> Signs of irritation and sensitization, AEs	Cohort 1: 21 induction period, 10-14 day rest period and then 2 days rechallenge	278 adult subjects Cohort 1: 238 Cohort 2: 40 subjects	Healthy male and female subjects age 18-75 years, any skin type or race with pigmentation allowing the discernment of	1 investigational sites in the United States

	Cumulative Irritation Design	Cohort 2: 21 applications		Cohort 2: 21 days of treatment for assessment of cumulative irritation		erythema	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
AN2728-AD-102	Phase 1b, multicenter, open-label, maximal use trial to assess safety and PK.*	Crisaborole Ointment, 2%, PK Phase: QD (Days 1 and 8) BID (Days 2–7) Non-PK Phase: BID (Days 9–28)	PK profile Safety endpoints: AEs, SAEs, TEAE, VS and laboratory results. Secondary endpoint: treatment success defined as a score of ≤1 (clear or almost clear) with ≥2-grade improvement from Baseline, based on the ISGA	Study product applied for 28 days	34 pediatric subjects	Male and female subjects age 2 to 17 years with mild to moderate AD subjects 12-17 years: AD involving ≥25% treatable BSA, excluding the scalp/ venous access areas subjects 2-11 years: AD involving ≥35% Treatable BSA,	12 investigational sites in the United States (3 sites enrolled no subjects)
AN2898-AD-202	Phase 2a, multicenter, randomized, double-blind,	Crisaborole Ointment, 2%	Safety: AEs, SAEs, TEAE,	6 weeks	46 adult subjects	Male and female subjects age 19-73	14 investigational

	vehicle controlled bilateral lesion comparison to evaluate safety, tolerability and efficacy **	AN2898 Ointment, 1% Ointment, Vehicle BID for 6 weeks	VS and laboratory results. Efficacy: The primary endpoint for this study was the change from Baseline in ADSI score		with mild to moderate AD	years with mild to moderate AD	sites in Australia
AN2898-AD-203	Phase 2a, multicenter, open-label, safety/ tolerability, and PK trial*	Crisaborole Ointment, 2% PK Phase: QD (Days 1 and 8); BID (Days 2–7) Non-PK Phase: BID (Days 9–28)	PK profile Safety: local tolerability (burning/ stinging), AEs, SAEs, TEAE, VS and laboratory results. Efficacy: treatment success defined as an ISGA score of ≤1 (clear or almost clear) with a minimum 2-grade improvement from	28 days	23 pediatric subjects with mild to moderate AD	Male and female subjects age 12-17 years with mild to moderate AD	8 investigational sites in in the United States

			Baseline.				
AN2898-AD-204	Phase 2, multicenter, randomized, double-blind, vehicle controlled bilateral lesion comparison to evaluate safety and efficacy **	Crisaborole Ointment, 2% or AN2898 Ointment, 0.5% applied QD or BID for 29 days	Safety: AEs, SAEs, TEAE, VS and laboratory results. Efficacy: The primary endpoint for this study was the change from Baseline in ADSI score	29 days	86 pediatric subjects with mild to moderate AD	Male and female subjects age 12-17 years with mild to moderate AD involving ≤35% BSA, with 2 target lesions 10–500 cm^2 of similar severity located on the trunk or UE/LE, ≥10 cm apart with an ADSI score ≥6 and ≤12 and an erythema subscore ≥2	18 investigational sites: 10 sites in the United States and 8 in Australia

§=the route of administration of all study products is topical except moxifloxicin/placebo which is administered orally
AD=atopic dermatitis
ADSI=atopic dermatitis severity index. ADSI score represents the sum of the subscores for erythema, excoriation, exudation, lichenification, and pruritus.
BID=twice daily
BSA=body surface area
ISGA=Investigator's Static Global Assessment scale
LE=lower extremity
PK=pharmacokinetics
QD=once daily
SAEs= serious adverse events
TEAEs =treatment-emergent adverse events
UE=upper extremity
VS=vital signs
§ See Table 12 for the distribution of subjects within the pediatric population
* These open –label safety trials were designed to provide data regarding systemic exposure. The reader should refer to the Clinical Pharmacology Review for detailed information regarding the pharmacokinetics of Crisaborole Ointment in the pediatric and adult populations. Local safety findings will be addressed in this review
** These trials were not reviewed in depth because the trial design which included bilateral, within subject comparisons was inadequate to support systemic safety or efficacy. The evaluation of efficacy in trials AN2898-AD-202 and AN2898-AD-204 was based on ADSI and not ISGA.

5.2. Review Strategy

The primary analysis of safety and efficacy to support labeling was based on data from 2 adequate and well-controlled Phase 3 trials, AN2728- AD-301 and AN2728- AD-302. These two identical, randomized, vehicle-controlled, parallel group Phase 3 trials enrolled 1511 subjects with mild to moderate atopic dermatitis (AD) who applied Crisaborole Ointment, 2% twice daily for 29 days. The study population included male and female subjects aged 2 years and older with clinical diagnosis of AD according to the criteria of Hanifin and Rajka , involvement of ≥ 5% treatable percent body surface area (% BSA excluding the scalp) and an Investigator Static Global Assessment (ISGA) score of Mild (2) or Moderate (3) on a 5- point scale. The primary source of data for the evaluation of long term safety was Trial AN2728- AD-303. Eligible subjects included males and females aged 2 years and older who completed study AN2728-AD-301 or AN2728-AD-302 without study drug-related safety issues that precluded further treatment with Crisaborole Ointment.

This review includes relevant analyses performed by the applicant, the statistical reviewer and this reviewer. Analytical tools utilized by Agency reviewers include JMP, MAED and JReview.

Based on the differences in study design (e.g. bilateral comparisons of target lesions, open-label trials, microplaque assessments etc.), study populations, and indications (e.g. psoriasis versus atopic dermatitis), the data from the remaining trials was considered supportive and was not reviewed in detail.]

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial AN2728-AD-301

"A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis"

6.1.1. Study Design

Overview and Objective

Trial AN2728-AD-301 was entitled "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis." This was a Phase 3 efficacy and safety trial with the primary objective of evaluating whether EUCRISA (crisaborole)

ointment, 2% (AN2728 ointment) was superior to vehicle ointment in subjects with mild to moderate atopic dermatitis at Day 29 based on Investigator's Static Global Assessment (ISGA) scale. The secondary objective was to evaluate the safety and tolerability of crisaborole ointment at Day 29 compared to vehicle ointment in this population.

Trial Design

Trial AN2728-AD-301 was a multi-center, randomized, double-blind, vehicle-controlled trial enrolling subjects age 2 years and older with mild to moderate atopic dermatitis. The trial was conducted in 48 investigational sites which were located throughout the United States (1 investigational site did not enroll any subjects).

Reviewer's comment

- *As proposed in the End- of- Phase 2 Meeting package, the Division agreed that the trial designs were adequate to support the efficacy of the proposed product (21 U.S Code of Federal Regulations (CFR) 314.126). However, estimates of treatment effect used for powering the Phase 3 trials were not based on Phase 2 trials which included the same study population, the same measure and the same definition of 'success/failure' that were used in the Phase 3 trials. The Phase 2 trials employed intra-subject comparisons, different endpoints and different scales (EASI score).*
- *The locations of the study centers in more than 20 different states provided a geographically diverse study population. Subjects living in urban areas who tend to be at increased risk for the development of severe disease were adequately represented.*

Study population
The trial enrolled 759 male and female subjects with mild-to-moderate AD with at least 20% of the subjects between the ages of 2 and 6 years and up to 15% $\geq$ 18 years.

The key inclusion criteria were:

- Is male or female and 2 years of age and older at Baseline/Day 1
- Has a clinical diagnosis of AD according to the criteria of Hanifin and Rajka
- Has AD involvement ≥ 5% Treatable % body surface area (BSA) (excluding the scalp)
- Has an ISGA score of Mild (2) or Moderate (3) at Baseline/Day 1

The key exclusion criteria were:

- Has any clinically significant medical disorder, condition, or disease or clinically significant physical examination finding at Screening that may interfere with study objectives/safety of participants
- Has unstable AD or any consistent requirement for high-potency topical corticosteroids to manage AD signs and symptoms

- Has a significant active systemic or localized infection, including known actively infected AD
- Has a history of use of biologic therapy including intravenous immunoglobulin at any time prior to study
- Has recent or anticipated concomitant use of systemic or topical therapies that might alter the course of AD
- Has undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only)

Reviewer's comment

- *The entry criteria adequately define the disease of interest and specify a study population which reflects the target population in the United States.*

Trial procedures

Trial AN2728-AD-301 was comprised of the following 3 periods:

- Screening Period: maximum duration of 35 days (If no drug washout was needed, the Screening Visit was combined with Baseline/Day 1 of the Study Drug Application Period.)
- Study Drug Application Period: 29 days (treatment Days 1–28 and End-of-Treatment Visit at Day 29)
- Post-treatment Follow-up Period: 7 days

After the screening period, eligible subjects were randomized using an Interactive Web Response System (IWRS) based randomization system using blocks with stratification by study center. Subjects were randomized to the following treatment groups in the ratio of 2:1:

1) Crisaborole ointment, 2% applied BID for 28 days
2) Vehicle applied BID for 28 days

After completing the treatment period, subjects scheduled a final safety evaluation for assessment of vital signs, adverse events and local tolerability.

Dosing instructions

After the study staff identified and documented the treatment area, they applied a thin layer of the study product to all treatable lesions of atopic dermatitis (excluding the scalp) while wearing gloves. The staff instructed subjects to administer the remaining doses twice daily at home for 28 days. Subjects were instructed to avoid removing or occluding the study product by wearing loose-fitting clothing, not wiping their skin, and refraining from swimming or bathing/washing the treated areas within 4 hours after application. Subjects continued to treat

all areas which were identified on Day 1 "regardless of whether they become clinically clear prior to Day 29". Subjects documented all applications in the Dosing Diary and applied any missed doses as soon as possible.

Investigator reevaluated safety and efficacy parameters on Days 8, 15, 29. Safety assessments included physical examinations, vital sign measurements, AE reports, clinical laboratory testing (hematology, serum chemistry, and urinalysis), evaluation of concomitant medications, and assessment of local tolerability. Efficacy assessments included an evaluation of global severity of AD on 5- point ISGA scale, severity of pruritus on a 4-point scale and severity of signs of AD (erythema, induration/papulation, exudation, excoriation, and lichenification) on a 4-point scale.

To assess compliance, investigators weighed the tubes of study product when dispensed and returned and recorded all missed doses.

Reviewer comment

- *The applicant used an intra-subject study design to evaluate various doses (0.5% to 2%) and dosing regimens (QD to BID) during the Phase 2 development program (Trials AN2728-203 and AN2728-204). The dose and dosing regimen selected for Phase 3 appeared to consider the benefits and risks of exposure to the proposed product.*
- *Treatment of areas of AD which have cleared with the application of the study product presented an ethical dilemma especially in the youngest pediatric age group. The Division agreed to continue dosing because the duration of treatment was short and adverse event profile was favorable.*

<u>Early Discontinuation of Study Drug (Stopping Rules)</u>

- Subjects were permitted to withdraw from the trial at any time for any reason. The reasons were captured in one of the following categories:
  - AE
  - Withdrawal by subject
  - Withdrawal by parent/guardian
  - Lost to follow-up
  - Death
  - Other

- Subjects were required to discontinue the study drug under the following circumstances:
  - Persistent 2-grade worsening of any specific sign of AD assessed in two consecutive visits
  - Development of an intercurrent illness that would jeopardize the safety, or significantly affect assessments of clinical status of a subject
  - Development of any study drug-related SAE
  - Suspected or laboratory-confirmed pregnancy

The investigator and medical monitor were responsible for the decisions to retain or discontinue subjects who experienced adverse events or clinically significant laboratory abnormalities.

Prohibited Medications

Systemic Medications Prohibited Throughout the Trial

- Use of systemic (oral, parenteral) corticosteroids, within 28 days prior to Baseline and during the trial
- Use of systemic immunosuppressive agents (e.g. methotrexate, cyclosporine, azathioprine, hydroxychloroquine, and mycophenolate mofetil (MMF)) within 28 days prior to Baseline)
- Escalating, decreasing, or as-needed (PRN) use of topical retinoids or benzoyl peroxide (BPO) on treatable AD lesions, within 28 days prior to Baseline/Day 1
- Use of systemic antihistamines in a non-stable regimen

Topical Medications Prohibited On the Body Throughout the Trial

- Use of topical corticosteroids (TCS), or calcineurin inhibitors anywhere on the body
- Use of sunbathing, tanning bed use, or light therapy anywhere on the body, within 14 days prior to Baseline
- Escalating, decreasing, or PRN use of topical retinoids or benzoyl peroxide products (BPO) on treatable AD lesions (Subjects on a stable topical retinoid and/or BPO regimen with ≥14 days of consistent use prior to Baseline may continue)
- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body
- Use of topical antihistamines or topical hydrocortisone 1% anywhere on the body
- Bland emollients on treatable lesions of AD

Medications Permitted During the Trial

- Stable doses of: systemic antihistamines, inhaled or intranasal corticosteroids and topical retinoids and/or benzoyl peroxide products (BPO)
- Short courses (≤ 14 days) systemic antibiotics
- Acceptable bland emollient(s) adjacent to/not overlapping treatment area
- Nonsteroidal anti-inflammatory drugs
- Routine preventative immunizations are permitted (but not recommended)
- For female subjects of childbearing potential: Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception
- Concomitant medications for other chronic medical conditions (unless specifically prohibited in the protocol)

Reviewer Comment:

With regard to the choice of concomitant medications, the applicant states "Concomitant medications and therapies permitted by the protocol ….were intended to allow for reasonable and medically necessary use of these agents as related to an AE or to the subject's medical history while minimizing the impact on efficacy and safety assessments." Subjects used bland emollients as needed on xerotic skin which was not actively involved with atopic dermatitis.

Assessments: Refer to the Schedule of Events below.

Efficacy

- Total body surface area (BSA): at Baseline using the Mosteller formula
- Calculation of Treatable % BSA (% total BSA that is AD-involved, excluding the scalp): at Screening, Baseline and Day 29. Completed by one of 2 methods
  - "*Handprint Method*": the area represented by the palm with all five digits adducted together is approximately 1% of the subject's BSA
  - "*Rule of Nines*": method used for calculating body surface area whereby values of 9% or 18% of surface area are assigned to specific regions in the adult
- Investigator's Static Global Assessment (ISGA): all visits through Day 29.
- Signs of atopic dermatitis: all visits from Baseline through Day 29
- Severity of pruritus: all visits from Baseline through Day 29
- Quality of life questionnaires: BID using eDiary from Baseline through Day 29

Safety

- Vital signs (temperature, respiratory rate, pulse rate, BP): all study visits
- Height and weight: Screening and Baseline/Day 1 Visits
- Complete physical examination will be performed at the Screening Visit
- Disease-focused physical examination of all AD-involved areas: Baseline and the Day 29
- Concomitant medications: all visits
- AEs and SAEs: all visits
- Clinical laboratory tests: Baseline and the Day 29 (hematology, serum chemistry, pregnancy testing). See Table 34.
- Local tolerability (burning and stinging) at every clinical visit through Day 36. Also refer to Table 65.

Figure 1: Trial Flow Diagram- Trial AN2728-AD-301

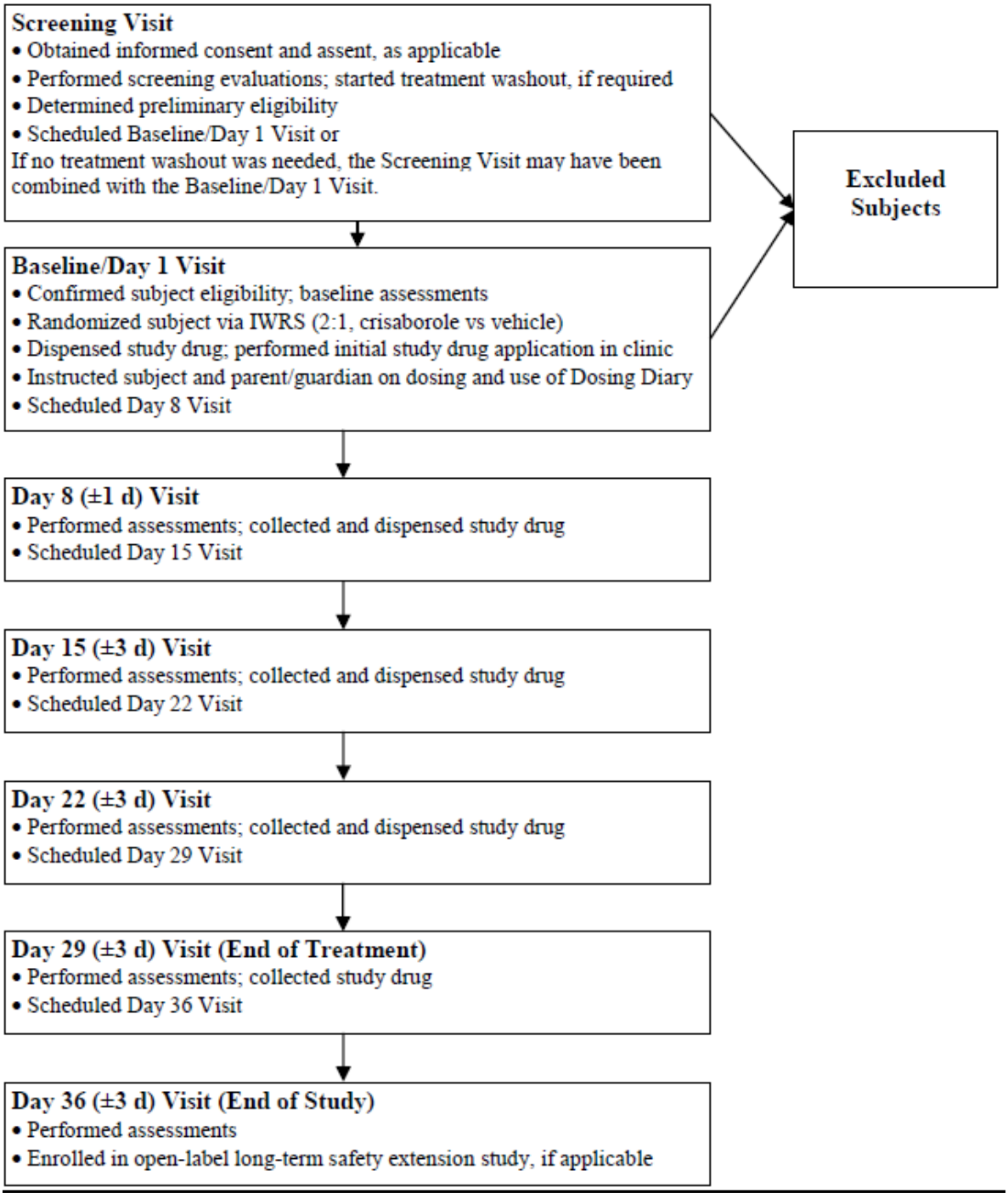


Table 6: Schedule of Events- Trial AN2728-AD-301

Day	–35 to 1	1	8 (±1 d)	15 (±3 d)	22 (±3 d)	29 (±3 d)	36 (±3 d)		
Visit	Screening [a]	Baseline [a]				End of Treatment	End of Study	Unsch Visit [b]	Early Discon
Informed consent, including assent	x								
Demographics	x								
Review of Inclusion and Exclusion Criteria	x	x							
Significant/relevant medical history and height and weight	x	x							
Prior and concomitant medications	x [c]	x	x	x	x	x	x	x	x
Electrocardiogram [d]		x	x						
Vital signs [e]	x	x	x	x	x	x	x	x	x
Physical examination	x [f]	x [g]				x [f]			x [f]
Photography of representative AD lesion (selected study sites only)		x	x	x	x	x			x
Calculate Treatable %BSA	x	x				x			x
Assess for AEs and SAEs	x	x [h]	x	x	x	x	x	x	x
Grading of local tolerability		x	x	x	x	x	x		x
ISGA [i]	x	x	x	x	x	x			x
Signs of AD [i]		x	x	x	x	x			x
Severity of Pruritus Scale		To be captured via electronic diary, BID (morning and evening)							x
Quality-of-life questionnaires: CDLQI, DLQI, and DFI [j]		x				x			x
Serum chemistry and hematology		x [k]				x			x
Urine pregnancy (female subjects of childbearing potential only) [l]	x	x				x			x
Contact IWRS	x	x	x	x	x	x	x	x	x
Randomization		x							
In-clinic dosing instruction		x	x	x	x			x	
In-clinic dose application by study staff (1st dose [AM])		x							
At-home dosing, applied by parent/guardian (or subject, if applicable) [m]		2nd dose (PM) on Day 1, then BID through Day 28						x	
Dispense/review Dosing Diary		x	x	x	x	x		x	x
Obtain Dosing Diary data and assess compliance [n]			x	x	x	x		x	x
Weigh study drug tube(s) and dispense for at-home dosing		x	x	x	x			x	

Day	–35 to 1	1	8 (±1 d)	15 (±3 d)	22 (±3 d)	29 (±3 d)	36 (±3 d)		
Visit	Screening [a]	Baseline [a]				End of Treatment	End of Study	Unsch Visit [b]	Early Discon
Collect and weigh returned study drug			x	x	x	x		x	x
Collect Dosing Diary						x			x
Schedule/reconfirm next study visit	x	x	x	x	x	x		x	

Source: Protocol AN2728-AD-301 page 122

[a] If no treatment washout was needed (see Section 8.4.7), the Screening and Baseline/Day 1 Visits could have been combined.

[b] Depending on the reason for the visit, some procedures may not have applied.

[c] Recorded all treatments (including medications and non-medication therapies) used for AD within 90 days prior to Screening and all other medications (including bland [non-medicated] emollients, over-the-counter drugs, vitamins, and antacids) used within 28 days prior to Screening.

[d] Subjects must have been in a supine position for at least 5 minutes before obtaining the electrocardiogram. Electrocardiograms should have preceded measurement of vital signs and blood draw for clinical laboratory tests.

[e] Temperature, respiratory rate, pulse rate, and blood pressure were taken in the seated or supine position, after the subject had been calmly sitting or lying face up for a minimum of 5 minutes. At Baseline/Day 1 and Day 29, assessment of vital signs should have preceded blood draw for clinical laboratory tests.

[f] Complete physical examination. If Screening and Baseline/Day 1 were combined, a complete physical examination was performed at the Screening/Baseline Visit.

[g] Disease-focused physical examination of all AD-involved skin (in treatable and non-treatable areas) and evaluation of any current or reported symptoms for clinically significant changes.

[h] Assessed for AEs and SAEs before and after the in-clinic study drug application on Baseline/Day 1.

[i] The ISGA must have been completed prior to the AD signs assessment.
[j] The CDLQI was completed by all subjects aged 2–15 years, based on the age at Baseline/Day 1. The DLQI was completed by all subjects aged 16 years and older, based on the age at Baseline/Day 1. The DFI was completed by all parents/guardians of subjects aged 2–17 years, based on the age at Baseline/Day 1.
[k] Blood draw for clinical laboratory tests (serum chemistry and hematology) must have been performed before the in-clinic study drug application.
[l] Women who became of childbearing potential during the study who were previously considered of non-childbearing potential (ie, menses began) must have had a urine pregnancy test performed at the next study visit.
[m] In the event the scheduled Day 29 (End-of-Treatment) Visit did not occur on Day 29, e.g., due to an unavoidable scheduling conflict, the parent/guardian and/or subject were instructed to continue study drug application BID through the evening before the day that the rescheduled End-of-Treatment Visit was to occur.
[n] During study visits at Days 8, 15, 22, and 29, parent/guardian and/or subject were re-educated if any study drug doses were missed during the interval since the previous study visit.

Study Endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the proportion of subjects achieving success on Investigator's Static Global Assessment (ISGA) at Day 29. Success on ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The ISGA (Table 7) was a five-point global static assessment of AD severity.

Table 7: Investigator's Static Global Assessment (ISGA)

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

Source: Protocol AN2728-AD-301 *v3*, Table 8, page 81

Reviewer Comment:

The Agency agreed with the proposed primary efficacy endpoint. (End-of-Phase 2 Meeting Minutes dated 3/6/2014.)

Secondary efficacy endpoints

The two secondary efficacy endpoints were the following:

- Proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29

- Time to success in ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

The statistical analysis method for the primary efficacy endpoint of success on ISGA at Day 29 and the first secondary endpoint of the proportion of subjects with an ISGA score of 0 or 1 at Day 29 was logistic regression with factors of treatment group and analysis center. The secondary endpoint of time to success in ISGA was analyzed using Kaplan-Meier methods and the log-rank test. Hypothesis testing for the secondary endpoints was conducted in a sequential manner. Time to Success in ISGA was only tested because ISGA of Clear or Almost Clear at Day 29 was statistically significant.

Exploratory efficacy endpoints

The two exploratory efficacy endpoints were the following:

- Time to improvement in pruritus (defined as a pruritus score of None [0] or Mild [1] with at least a 1-grade improvement from Baseline)
- Signs of atopic dermatitis (erythema, induration/papulation, exudation, excoriation and lichenification) evaluated globally on a 4-point scale and not by body region

Reviewer Comment:

At End-of-Phase 2 Meeting 2/26/2014, the Division stated the following:

"The secondary endpoints that the Division recommends include an evaluation of the signs and symptoms of atopic dermatitis (e.g. erythema, induration/papulation, scaling and oozing/crusting) which should be dichotomized to success/failure a priori in the protocol. These signs should be evaluated globally on a 4-5 point scale and not by body region (as in the EASI score.)"

"You propose to evaluate the time to improvement in pruritus, defined as a pruritus score of None (0) or Mild (1), as a secondary endpoint. However, you do not clearly identify the population that you intend to enroll with regard to baseline pruritus score. In addition, you do not provide supporting data (e.g., PRO dossier) that the instrument used to assess pruritus is reliable, valid, and able to detect clinically meaningful changes. Because of these deficiencies, the assessment of pruritus in this trial has limited regulatory utility."

In response to Agency comments, "Time to improvement in pruritus" and "evaluation of the signs and symptoms of atopic dermatitis" were categorized as exploratory efficacy endpoints which were not intended for labeling.

The applicant used the following scale to assess the severity of pruritus:

Table 8: Severity of Pruritus

Score	Grade	Definition
0	None	No itching
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching which is not disturbing sleep
3	Severe	Bothersome itching/scratching which is disturbing sleep

Source: Protocol AN2728-AD-301, Table 11 page 85
The signs of AD were assessed on the following 4-point scales (Table 9):

Table 9: Signs of Atopic Dermatitis

Erythema (Redness)		
Score	**Grade**	**Description**
0	None	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
Score	**Grade**	**Description**
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Exudation (Oozing or Crusting)		
Score	**Grade**	**Description**
0	None	No oozing or crusting
1	Mild	Minor or faint signs of oozing
2	Moderate	Definite oozing or crusting present
3	Severe	Marked and extensive oozing or crusting present

Excoriation (Evidence of Scratching)		
Score	**Grade**	**Description**
0	None	No evidence of excoriation
1	Mild	Mild excoriation present
2	Moderate	Definite excoriation present
3	Severe	Marked, deep, or extensive excoriation present

Lichenification (Epidermal Thickening)		
Score	**Grade**	**Description**
0	None	No epidermal thickening
1	Mild	Minor epidermal thickening
2	Moderate	Moderate epidermal thickening; accentuated skin lines
3	Severe	Severe epidermal thickening; deeply accentuated skin lines

Source: Protocol AN2728-AD-301, Table 9 page 83

Reviewer comment

The Agency agreed with the specified primary efficacy endpoint and general approach to the analysis (EOP2 Meeting conducted 2/26/2016).

Statistical Analysis Plan

Study Populations

The applicant performed the primary efficacy analysis on the Intent-to-Treat (ITT) Population defined as all subjects who are randomized and dispensed study drug. The Per Protocol (PP) Population was defined as all subjects in the ITT Population who completed the Day 29 evaluation without any major protocol deviations as follows:

- Met all of the Inclusion Criteria and none of the Exclusion Criteria
- Have not taken any interfering concomitant medications or therapies during the 29-day study period
- Completed the Day 29 Visit, including the Day 29 efficacy evaluation
- Have applied 80%–120% of the total number of expected doses during the Study Drug Application Period
- Have not missed 6 or more consecutive doses during the Study Drug Application Period

- Were in the visit window (±3 days) for the Day 29 Visit

The safety population included all subjects who were randomized and received at least one confirmed dose of the study drug and received at least one post baseline assessment.

Pooling
The applicant specified that centers that did not enroll at least 12 subjects would be pooled. These combined groups will be referred to as "analysis centers" in the statistical analyses based on logistic regression testing. Prior to pooling, analysis of center-to-center variability using main factor analysis and interaction analysis would be conducted.

Background and Demographic Characteristics
The applicant summarized the subject demographic and baseline characteristics by treatment group.

Efficacy
The primary method of handling missing efficacy data was based on Markov Chain Monte Carlo (MCMC) imputation.

Safety
The applicant summarized data for the safety population without imputation for missing data. Subgroup analyses were performed based on age (2-11 years, ages 12-17 years, and ages 18 years and older). Verbatim terms of adverse events on the electronic case report forms (eCRF) were classified using Medical Dictionary for Regulatory Activities (MedDRA 16.1). The number of subjects reporting adverse events was summarized by system organ class, preferred term, severity and relationship to study medication and compared between treatment groups.

Using descriptive statistics, the applicant summarized local tolerability grades and changes from baseline in vital signs and laboratory parameters. Changes in laboratory values were summarized using shift tables.

For detailed information regarding the statistical methodology and findings refer to the Statistical Review and Evaluation by Matthew Guerra, Ph.D. dated 8/19/2016.

Protocol Amendments

The applicant provided 2 amended versions of Phase 3 Protocol AN2728-AD-301. Version 3 incorporated changes in the study population, safety monitoring and efficacy assessments compared with the initial submission. The majority of these modifications were added in response to Agency comments. Changes in the study population to specify enrollment of up to

15 % of subjects ≥ 18 years old and 20% of subjects age 2 to 6 years were implemented to reflect the prevalence of AD in the United States population. Modifications to the safety monitoring included the addition of an assessment of local tolerability at every visit, ECGs performed at baseline and steady state (Day 8) at selected sites and a full physical examination at the end of treatment (per Advice Letter 6/16/2014).In addition, the applicant redefined the subject stopping rules with greater specificity (e.g. early discontinuation due to “Persistent 2-grade worsening of any specific sign of AD assessed in two consecutive visits" or "Development of any study drug-related SAE”) to reduce the variability in investigator decisions regarding the withdrawal of subjects from the trial. Lastly, because there was no concern regarding reproductive toxicity, the applicant removed the protocol specified requirement for male subjects with female partners of childbearing potential to use an acceptable form of contraception.

The applicant included a number of revisions to the evaluation of treatment effect and statistical analysis plan. First, the applicant revised the ISGA scale to ensure that the category of “clear” indicated the true absence of disease. Second, the EASI assessment was replaced by the AD sign assessment which represents an evaluation of the global severity of individual signs rather than the local severity by body region. Third, the applicant included Quality of Life instruments in the protocol which were targeted to the relevant age group (DLQI for subjects 16 years and older and CDLQI for subjects age 2-15 years.) Fourth, based on comments regarding the regulatory utility of “time to improvement in pruritus,” this endpoint was changed to an exploratory efficacy analysis rather than a secondary analysis. Fifth, the applicant proposed to conduct a one-way logistic regression with a factor of site prior to pooling as recommended by the statistical reviewer. Lastly, to test for consistency of treatment response the factors of analysis center, treatment, and analysis center by treatment interaction were specified.

The implementation of the recommended revisions permitted conclusions regarding the safety and efficacy of this new molecular entity to be based on adequate data.

Data Quality and Integrity: Sponsor’s Assurance

The applicant required that participating investigators agree to conduct the trials in compliance with the protocol approved by the appropriate institutional review board (IRB), according to International Conference on Harmonization (ICH) and local good clinical practices (GCP) standards, and in accordance with the ethical principles that have their origin in the Declaration of Helsink**i.** The applicant required trained authorized site personnel to enter all the information collected during the trial to electronic case report forms (eCRF) and save the information to the clinical trial database. The applicant also required the site personnel to provide an explanation for all missing data.

The applicant or authorized representative carefully monitored all aspects of the study to ensure the integrity of the data and compliance with applicable local government regulations. The applicant stated that the following procedures were performed at regular intervals:

- Conducted training sessions and provide instruction manuals
- Audited all records and verify the entries in the eCRF for adherence to the protocol, completeness, accuracy, and consistency of data.
- Monitored PIs and sub-investigators and staff by designated personnel
- Reviewed the progress of the study with the principal investigator (PI).
- Inspected site facilities (i.e., subject areas, drug storage areas, record storage areas, etc.)

The applicant conducted an ongoing clinical data management review on accumulating subject data. Reviewers evaluated the data for inconsistencies, omissions, discrepancies, adherence to the protocol and GCP. Data must be able to be verified with the source documents.

Reviewer's comment
These measures appear to be adequate to ensure compliance with ICH guidelines and good clinical practice (GCP) to protect human subjects.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant confirmed that participating investigators conducted the trials in compliance with the protocol approved by the appropriate institutional review board (IRB). The applicant appears to have implemented the proposed monitoring to ensure the integrity of the data and compliance with applicable local government regulations with respect to current good clinical practice (GCP). There were no issues related to unblinding, adherence to protocol, subject retention, protocol amendments or post hoc data analysis that impacted the collection of the data or the results. However, as reported by the applicant, there was a single site where both investigators procured significant equity interests in Anacor Stock during the Phase 3 trials (described below).

Financial Disclosure

The applicant disclosed financial interests and arrangements with clinical investigators participating in "covered clinical studies" as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. The applicant indicated that 2 investigators, participating in Trial AN2728-AD-301 at the same site ((b) (6)), reported significant equity

interests in Anacor Stock (ANAC) above $50,000. The applicant provided Form FDA 3455 for investigator, (b) (6), and sub-investigator, (b) (6).
The applicant addressed this conflict of interest and stated that their study design and conduct minimized the potential for bias in this case due to the following:

1. Trial AN2728-AD-301 was a randomized, double-blind, vehicle-controlled, multi-center, parallel-group trial.
2. Randomization was accomplished with an Interactive Web Response System (IWRS). Monitoring and audits indicated no evidence that data was unblinded for this site.
3. The Contract Research Organization, (b) (4) conducted seven interim monitoring visits and a close-out visit at the site. There were no significant protocol deviations or compliance issues identified at these monitoring visits.

(b) (6) had an enrollment of (b) (6) subjects with a moderate treatment effect in the Eucrisa arm (36.4%) and no treatment effect in the vehicle arm (0.0%) with no missing data. Refer to Appendix 13.2 for the Financial Disclosure template containing additional information.

Reviewer's comment
The applicant adequately disclosed financial interests involving clinical investigators. The strategies employed by the applicant to minimize potential bias arising from investigator behavior appear reasonable. Statistical reviewer, Matthew Guerra, PhD conducted a sensitivity analysis excluding data from this site. He indicated that there was only a very slight change in the response rates with the removal of this center. (Statistical Review by Matthew Guerra, Ph.D. dated 8/19/2016.) Therefore, this disclosure of the acquisition of Anacor stock by two investigators at a single site did not impact the integrity of the data as a whole.

Subject Disposition

The majority of the subjects completed Trial AN2728-AD-301. A greater proportion of subjects discontinued from the vehicle group (12.1%) than the EUCRISA (crisaborole) ointment, 2% group (5.9%). However, the same percentage of subjects in each group withdrew due to the occurrence of adverse events.

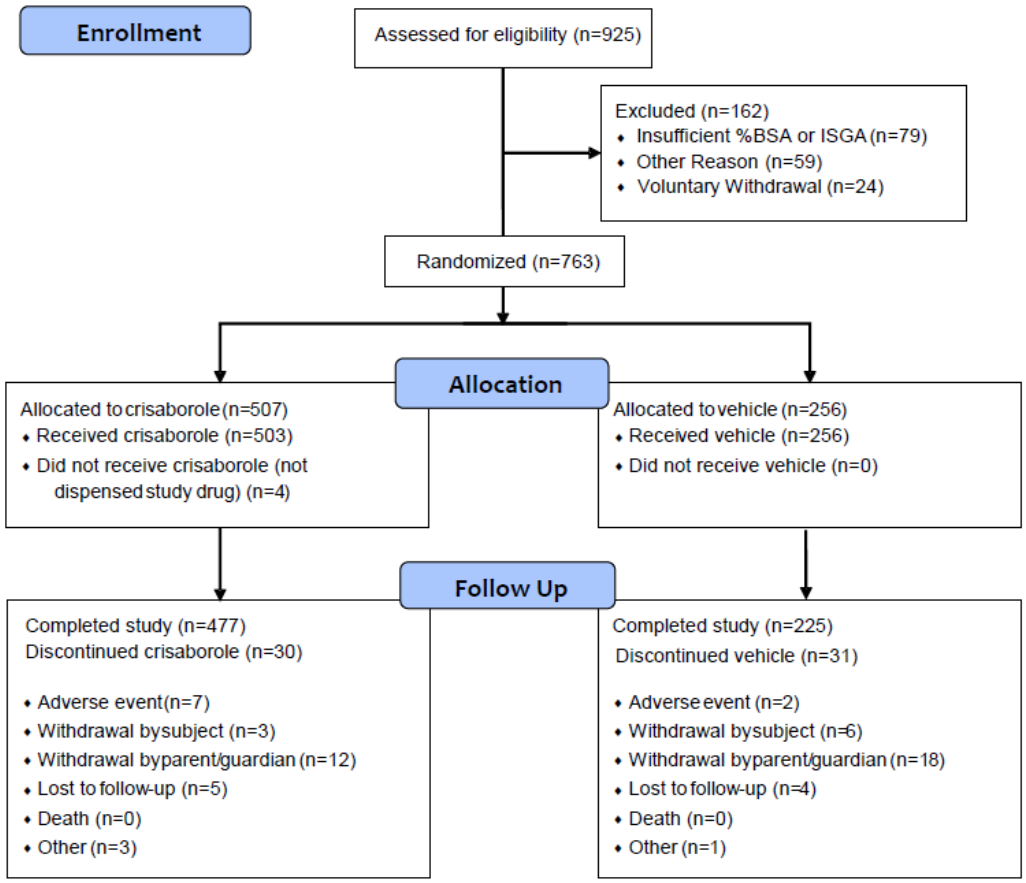
Table 10: Subject Disposition in Trial AN2728-AD-301 and Trial AN2728-AD-302

	Trial AN2728-AD-301		Trial AN2728-AD-302	
	Crisaborole ointment, 2% (N=507)	Vehicle ointment (N=256)	Crisaborole ointment, 2% (N=513)	Vehicle ointment (N=250)
Completed	477 (94.1%)	225 (87.9%)	483 (94.0%)	213 (85.2%)
Discontinued	30 (5.9%)	31 (12.1%)	31 (6.0%)	37 (14.8%)
Adverse Event	7 (1%)	2 (1%)	5 (1%)	4 (2%)
Lost to Follow-Up	5 (1%)	4 (2%)	4 (1%)	4 (2%)
Other	3 (1%)	1 (<1%)	2 (<1%)	6 (2%)
Withdrawal by Parent/Guardian	12 (2%)	18 (7%)	14 (3%)	20 (8%)
Withdrawal by Subject	3 (1%)	6 (2%)	6 (1%)	3 (1%)

Source: Table 22 Summary of Clinical Safety (confirmed by Statistical Reviewer).
N=number randomized

Refer to Section 8.4.3 for a tabulation of the specific adverse events which lead to discontinuation from Trial AN2728-AD-301.

Figure 2: Subject Disposition- Trial AN2728-AD-301



Source: Clinical Study Report for AN2728-AD-301, Figure 2

Reviewer Comment:

Retention of subjects who are randomized to the vehicle/placebo group is frequently difficult due to lack of treatment effect. The small imbalance in the proportions of subjects who were withdrawn by their parents is not sufficient to affect the trial results.

Protocol Violations/Deviations

The protocol deviations occurring with the greatest frequency and resulting in exclusion from the Per Protocol (PP) population analysis in Trial AN2728-AD-301 were the following:

Table 11: Primary Protocol Deviations

	Crisaborole group (N)	Vehicle group (N)
Out-of-window for the Day 29 Visit	51	39
Did not apply 80% - 120% of the expected doses	42	33
Did not complete the Day 29 Visit	29	28
Used prohibited medication during treatment period	25	15
Did not meet all the Inclusion /Exclusion criteria	14	10

Source: Reviewer's Table

Among the protocol deviations which did not result in exclusion from the PP analysis set, the most frequent was the failure of subjects to complete the pruritus assessment.

Reviewer Comment:

More subjects in the crisaborole group had protocol deviations than the vehicle group in all categories. However, the proportion of subjects with protocol deviations is greater in the vehicle group and this slight imbalance is unlikely to impact the efficacy results.

Table of Demographic Characteristics

The demographic characteristics of subjects enrolled in each treatment group in Trial AN2728-AD-301 were comparable. The majority of subjects in both groups were White, female and not Hispanic/Latino. The mean age of subjects in the vehicle group (12.4 years) was slightly higher than the mean age of subjects in the crisaborole group (12.0 years) and approximately 60% of subjects in both groups were in the 2 to 11 year old age group.

Table 12: Demographic Characteristics and Other Baseline Data (Intent-to-Treat Population)

	Trial AN2728-301		Trial AN2728-302	
	Crisaborole	Vehicle	Crisaborole	Vehicle
Age				
Mean (SD)	12.0 (11.6)	12.4 (10.7)	12.6 (12.7)	11.8 (12.6)
Median	9.0	10.0	9.0	8.5
Range	2 – 65	2 – 63	2 – 79	2 – 79
Categories				
2-11	317 (63%)	151 (59%)	310 (60%)	164 (66%)
2-6 years	162 (32.2%)	162 (32.2%)	173 (33.7%)	93 (37.2%)
7-11 years	155 (30.8%)	155 (30.8%)	137 (26.7%)	71 (28.4%)
12-17	121 (24%)	67 (26%)	126 (25%)	57 (23%)
18+	65 (13%)	38 (15%)	77 (15%)	29 (12%)
Gender				

Male	219 (44%)	113 (44%)	231 (45%)	112 (45%)
Female	284 (56%)	143 (56%)	282 (55%)	138 (55%)
Race				
White	308 (61%)	162 (63%)	309 (60%)	144 (58%)
Black	138 (27%)	61 (24%)	147 (29%)	78 (31%)
Asian	26 (5%)	17 (7%)	26 (5%)	10 (4%)
Am Indian Alaska Native	8 (2%)	3 (1%)	3 (1%)	2 (1%)
Hawaiian/Pacific slander	0	4 (2%)	7 (1%)	4 (2%)
Other	23 (5%)	9 (4%)	21 (4%)	12 (5%)
Ethnicity				
Hispanic/Latino	126 (25.0%)	66 (25.8%)	74 (14.4%)	35 (14.0%)
Not Hispanic/Latino	377 (75.0%)	190 (74.2%)	439 (85.6%)	215 (86.0%)

Source: NDA 207695, Clinical Study Report for AN2728-AD-301, Table 15. Clinical Study Report for AN2728-AD-302, Table

Reviewer Comment:

The applicant met the enrollment targets discussed at the End- of- Phase 2 Meeting (e.g. up to 15% of subjects ≥ 18 years of age and at least 20% age 2 to 6).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The treatment groups were comparable with regard to other baseline characteristics such as global severity, severity of pruritus and percent of body surface area affected by atopic dermatitis. The majority of subjects had AD of moderate severity with moderate to severe pruritus. The mean Treatable Percent Body Surface Area was 19% for both the crisaborole and vehicle groups.

Table 13: Other Baseline Characteristics (Intent-to-Treat Population)

	Trial AN2728-301		Trial AN2728-302	
	Crisaborole N=503	Vehicle N=256	Crisaborole N=513	Vehicle N=250
ISGA				
N	503	256		
2 – Mild	196 (39%)	93 (36%)	197 (38%)	100 (40%)
3 - Moderate	307 (61%)	163 (64%)	316 (62%)	150 (60%)

Severity of Pruritus				
N	446	223	457	218
0 – None	17 (3.8%)	13 (5.8%)	18 (3.9%)	6 (2.8%)
1 – Mild	115 (25.8%)	64 (28.7%)	114 (24.9%)	55 (25.2%)
2 – Moderate	158 (35.4%)	75 (33.6%)	173 (37.9%)	92 (42.2%)
3 – Severe	156 (35.0%)	71 (31.8%)	152 (33.3%)	65 (29.8%)
Treatable Percent Body Surface Area				
N	503	256	513	250
Mean (SD)	18.8 (18.55)	18.6 (18.87)	17.9 (17.49)	17.7 (15.61)
Median	12.0	12.0	10.0	12.0
Minimum to maximum	5 to 95	5 to 95	5 to 95	5 to 90

Source: NDA 207695, Clinical Study Report for AN2728-AD-301, Table 16; Clinical Study Report for AN2728-AD-302, Table 16

In addition, subjects included in the crisaborole group reported that AD had less impact on their quality of life than subjects in the vehicle group at baseline as indicated by the patient reported outcome measures in AN2728-AD-301.

Table 14: Baseline Patient Reported Outcomes (Intent-to-Treat Population)

	Trial AN2728-301		Trial AN2728-302	
	Crisaborole N=503	Vehicle N=256	Crisaborole N=513	Vehicle N=250
Dermatology Life Quality Index				
N	95	52	97	40
Mean (SD)	9.6 (6.37)	9.5 (6.52)	9.7 (6.24)	9.1 (6.67)
Median	9.0	8.0	8.0	8.0
Minimum to Maximum	1 to 27	0 to 27	0 to 26	0 to 25
Children's Dermatology Life Quality Index				
N	393	199	404	204
Mean (SD)	9.7 (6.19)	9.1 (6.54)	9.0 (5.77)	8.9 (5.48)
Median	9.0	7.0	8.0	8.0
Minimum to Maximum	0 to 28	0 to 30	0 to 28	0 to 27
Dermatitis Family Impact Questionnaire				
N	431	214	431	217

Mean (SD)	8.5 (6.63)	7.5 (6.66)	7.7 (6.57)	8.0 (5.65)
Median	7.0	6.0	6.0	7.0
Minimum to Maximum	0 to 30	0 to 30	0 to 30	0 to 24

Source: NDA 207695, Clinical Study Report for AN2728-AD-301, Table 16

Reviewer Comment:

The differences in baseline characteristics including patient reported outcome assessments between the 2 groups is small; the imbalances are insufficient to impact the efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

Compliance with treatment was similar across treatment groups. The applicant evaluated compliance with the treatment regimen by analyzing the number of doses applied, the number of dosing days and the amount of study product used by each subject. The investigational staff weighed the tubes of study product when dispensed and returned to calculate the amount of study drug that was used by each subject. In addition, subjects recorded each application of study product in the dosing diary. The applicant considered a subject "compliant" with the dosing regimen if the subject applied at least 80% but no more than 120% of the expected applications during the Study Drug Application Period and had not missed six or more consecutive doses. Subjects who discontinued the trial were considered noncompliant. The applicant excluded subjects from analysis who had missing weights of dispensed or returned tubes. Subjects who applied crisaborole were more compliant than subjects who applied vehicle.

Table 15: Dosing Compliance- AN2728-AD-301 (Intent-to-Treat Population)

	No. of Applications	No. of Dosing Days	Amount of Drug Used (g)	Compliant	
Crisaborole N=503					
No. of subjects	503	503	478	Yes	459 (91.3%)
Mean (SD)	55.2 (8.79)	28.2 (4.33)	171.6 (194.22)		
Median	56.0	29.0	109.0	No	44 (8.7%)
Min to Max	1 to 101	1 to 52	2 to 1602		
Vehicle N=256					
No. of subjects	256	256	240	Yes	221 (86.3%)
Mean (SD)	52.4 (13.35)	26.8 (6.66)	167.1 (187.90)		
Median	56.0	28.0	106.4	No	35 (13.7%)
Min to Max	1 to 88	1 to 46	1 to 1356		

Source: Modified from Clinical Study Report for AN2728-AD-301 Table 15, Clinical Study Report for AN2728-AD-302, Table 20

Reviewer Comment:

The slight imbalance in favor of superior compliance in the group applying crisaborole may be expected based on the greater treatment effect.

Concomitant Medications

The types of concomitant medications and distribution among subjects were similar across treatment groups. The majority of concomitant medications reported by subjects in Trial AN2728-AD-301 were used to treat disorders associated with atopic dermatitis such as xerosis, allergic rhinitis, asthma and skin infections. Prior and concomitant medications were coded using the World Health Organization Drug Dictionary (WHO-DD) Enhanced.[10] Page 78

Table 16: Concomitant Medications in 2% or Greater Subjects Enrolled in Trial AN2728-AD-302 (ITT Population)

Medication	Crisaborole	Vehicle	Subjects
TRIAMCINOLONE	68 (13.52%)	32 (12.50%)	100 (13.11%)
SALBUTAMOL	57 (11.33%)	32 (12.50%)	89 (11.66%)
HYDROCORTISONE	62 (12.33%)	27 (10.55%)	89 (11.66%)
OTHER EMOLLIENTS AND PROTECTIVES	45 (8.95%)	27 (10.55%)	72 (9.44%)
LIDOCAINE	40 (7.95%)	21 (8.20%)	61 (7.99%)
IBUPROFEN	41 (8.15%)	17 (6.64%)	58 (7.60%)
CETIRIZINE HYDROCHLORIDE	41 (8.15%)	13 (5.08%)	54 (7.08%)
AQUAPHOR	30 (5.96%)	21 (8.20%)	51 (6.68%)
DIPHENHYDRAMINE HYDROCHLORIDE	33 (6.56%)	15 (5.86%)	48 (6.29%)
EMLA	29 (5.77%)	18 (7.03%)	47 (6.16%)
LORATADINE	25 (4.97%)	18 (7.03%)	43 (5.64%)
FLUTICASONE PROPIONATE	28 (5.57%)	13 (5.08%)	41 (5.37%)
PARAFFIN	30 (5.96%)	9 (3.52%)	39 (5.11%)
CETIRIZINE	24 (4.77%)	15 (5.86%)	39 (5.11%)
PARACETAMOL	27 (5.37%)	11 (4.30%)	38 (4.98%)

[10] The WHO Drug Dictionary (WHO-DD)" contains a listing of those drugs previously recorded in adverse reaction reports, whether suspected of having caused the reaction or not. WHO- DD also includes drugs from clinical trials. Data is obtained from the WHO Adverse Reactions Database, official drug regulatory or other dependable sources, national drug compendia, and notifications from the pharmaceutical industry... Anatomical Therapeutic Chemical (ATC) classification is an integral part of the WHO-DD. The A TC classification is a hierarchical classification used to facilitate browsing in the dictionary and, more importantly, aggregation of statistical data for improved analysis. All drugs in the WHO-DD are assigned group/level codes according to the ATC classification. "WHO Drug Information Vol 17, No. 1, 200.

Medication	Crisaborole	Vehicle	Subjects
MULTIVITAMINS	27 (5.37%)	11 (4.30%)	38 (4.98%)
MONTELUKAST SODIUM	26 (5.17%)	10 (3.91%)	36 (4.72%)
TRIAMCINOLONE ACETONIDE	16 (3.18%)	19 (7.42%)	35 (4.59%)
HYDROXYZINE	21 (4.17%)	14 (5.47%)	35 (4.59%)
OMEGA-6 FATTY ACIDS	22 (4.37%)	12 (4.69%)	34 (4.46%)
SALBUTAMOL SULFATE	23 (4.57%)	9 (3.52%)	32 (4.19%)
CETAPHIL	17 (3.38%)	11 (4.30%)	28 (3.67%)
DESONIDE	13 (2.58%)	13 (5.08%)	26 (3.41%)
EPINEPHRINE	16 (3.18%)	9 (3.52%)	25 (3.28%)
MOMETASONE FUROATE	18 (3.58%)	5 (1.95%)	23 (3.01%)
ANESTHETICS FOR TOPICAL USE	12 (2.39%)	10 (3.91%)	22 (2.88%)
EMOLLIENTS AND PROTECTIVES	12 (2.39%)	9 (3.52%)	21 (2.75%)
MUPIROCIN	13 (2.58%)	7 (2.73%)	20 (2.62%)
FLUOCINOLONE ACETONIDE	15 (2.98%)	4 (1.56%)	19 (2.49%)
AVENA SATIVA FLUID EXTRACT	13 (2.58%)	6 (2.34%)	19 (2.49%)
AMOXICILLIN	14 (2.78%)	5 (1.95%)	19 (2.49%)
BECLOMETASONE DIPROPIONATE	11 (2.19%)	7 (2.73%)	18 (2.36%)
FLUOCINONIDE	12 (2.39%)	5 (1.95%)	17 (2.23%)
DIPHENHYDRAMINE	13 (2.58%)	4 (1.56%)	17 (2.23%)
CEFALEXIN	9 (1.79%)	8 (3.13%)	17 (2.23%)

Source: Reviewer's Table

Rescue Medication Use

According to the protocol, if subjects experienced a persistent 2-grade worsening of any specific sign of AD assessed in two consecutive visits, then investigators discontinued the study product and determined whether the subject should be withdrawn from the trial. Refer to Section 7 for a discussion regarding the use of rescue medication.

Efficacy Results – Primary and Secondary Endpoints

The results of Trial AN2728-AD-301 indicate that crisaborole was statistically superior to vehicle at Day 29 on the primary and secondary efficacy endpoints as presented in Table 17.

The primary efficacy endpoint was the proportion of subjects achieving success on the Investigator's Static Global Assessment (ISGA) at Day 29. Success on ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

The two secondary efficacy endpoints specified in the protocol were:

- Proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29
- Time to success in ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

Refer to **Table 7** for the ISGA.

Table 17: Efficacy Results at Day 29 (ITT population)

	Trial AN2728-AD-301			Trial AN2728-AD-302		
Endpoints	**EUCRISA (N=503)**	**Vehicle (N=256)**	**P-Value**	**EUCRISA (N=513)**	**Vehicle (N=250)**	**P-Value**
Primary:						
Success in ISGA[2]	32.8%	25.4%	0.038[3]	31.4%	18.0%	<0.001[3]
Secondary:						
ISGA score of Clear or Almost Clear	51.7%	40.6%	0.005[3]	48.5%	29.7%	<0.001[3]
Time to Success in ISGA[2]	NC[4]	NC	<0.001[5]	NC	NC	<0.001[5]

Source: Clinical Study Report for AN2728-AD-301, Table 17 and 18.Statistical Reviewer's Analysis (Verified Applicant's Analysis)
(1) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 140 imputed datasets for Trial 301 and the 135 datasets for Trial 302.
(2) Success is defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
(3) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.
(4) Median time to success in ISGA could not be calculated because fewer than 50% of subjects reached success in ISGA.
(5) P-value based on a log-rank test.

Table 18: Efficacy Results at Day 29 (PP population)

	Trial AN2728-AD-301			Trial AN2728-AD-302		
Endpoints	**EUCRISA (N=503)**	**Vehicle (N=256)**	**P-Value**	**EUCRISA (N=513)**	**Vehicle (N=250)**	**P-Value**
Primary:						
Success in ISGA[2]	32.4%	26.9%	0.088[a]	32.2%	18.3%	<0.001[3]
Secondary:						
ISGA score of Clear or Almost Clear	51.7%	43.8%	0.032[c]	50.0%	29.8%	<0.001[3]
Time to Success in ISGA[b]	NC[4]	NC	0.003[5]	NC	NC	<0.001[5]

Source: Trial AN2728-AD-301, Table 14.2.5.3.1, Table 14.2.5.3.2; Trial AN2728-AD-302, Table 14.2.5.3.2
a P-value from a logistic regression (with Firth option) test with factors of treatment group and analysis center. Estimates from logistic regression are 46.2% and 25.9% for AN2728 Topical Ointment, 2% and AN2728 Topical Ointment, Vehicle, respectively.

b Success in Investigator's Static Global Assessment (ISGA) defined as ISGA of Clear or Almost Clear with at least a 2-grade improvement from Baseline.
Medians computed using Kaplan-Meier methods. NC=Not calculated.
c P-value from log-rank test.
Note: Last observation carried forward used to impute missing ISGA values, for secondary endpoint of ISGA of Clear or Almost Clear at Day 29. For Time to Success in ISGA, subjects with missing values were censored at the time of the last observation. Subjects not reaching Success in ISGA by Day 29 were censored at Day 29.

Data Quality and Integrity – Reviewers' Assessment

The analysis of the data submitted by the applicant to support the efficacy of EUCRISA (crisaborole) ointment, 2% for the treatment of atopic dermatitis was verified by FDA reviewers. Although the effect size was relatively small, success was established on the primary efficacy endpoint. The results of analyses of the secondary and exploratory endpoints supported the results of the primary endpoint.

Efficacy Results –other relevant endpoints

The exploratory endpoints were based on the investigator evaluation of the signs of atopic dermatitis and the subject evaluation of the symptom of AD (pruritus) using an electronic diary. The signs were evaluated on a 4-point global assessment scale (Table 9) and the symptom was evaluated on a 4-point pruritus severity scale (Table 8). Treatment success for both endpoints was defined as None (0) or Mild (1) with at least a 1-grade improvement from baseline.

A greater proportion of subjects in the EUCRISA arm experienced improvement in all signs and symptoms of AD at Day 29 than subjects in the vehicle arm. (b) (4)

Source: Proposed labeling

The applicant included all subjects who reported at least mild pruritus at baseline. The P-values were calculated from the log-rank test.

Table 20: Analysis of Time to Improvement in Pruritus (Intent-to-Treat Population)

	AN2728-AD-301			AN2728-AD-302		
	EURISA	Vehicle	P-Value	EURISA	Vehicle	P-Value
Time to Improvement in Pruritus (days)						
N	428	210	<0.001	439	211	0.425
Median	1.32	1.87		1.41	1.54	

Note: Subjects with missing values were censored at the time of the last observation and subjects not reaching Improvement in Pruritus by Day 29 were censored at Day 29.
Source: Clinical Study Report for AN2728-AD-301, Table 14.2.5.4.1, Clinical Study Report for AN2728-AD-302, Table 14.2.5.4.1

Refer to Integrated Review of Effectiveness (Section 7 of this review) for a discussion of the results of this endpoint and the Statistical Review by Matthew Guerra, Ph.D. dated 8/19/2016.

Labeling recommendations for efficacy are discussed in detail in Section 7.2 of this review.

Reviewer Comment:

- *Success was achieved by a greater number of subjects in the active group than the vehicle group for all signs of atopic dermatitis. However, because the applicant evaluated the signs of AD as an exploratory endpoint, the results will not be included in labeling.*
- *The statistically significant results in Trial AN2728-AD-301 regarding the time to improvement in pruritus were not replicated in Trial AN2728-AD-302. The difference of 0.55 days between the active and vehicle groups does not appear to be clinically meaningful.*

Dose/Dose Response

The applicant did not design Trial AN2728-AD-301 to assess dose response.

Durability of Response

The applicant did not design Trial AN2728-AD-301 to evaluate response beyond 29 days.

Persistence of Effect

The applicant did not design Trial AN2728-AD-301 to assess treatment effect beyond 29 days.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted on the data from this trial.

6.2. Trial AN2728-AD-302

"A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis."

6.2.1. Study Design

Overview and Objective

Trial AN2728-AD-302 was entitled "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis." This was a Phase 3 efficacy and safety trial with the primary objective of evaluating whether EUCRISA (crisaborole) ointment, 2% (AN2728 ointment) was superior to vehicle ointment in subjects with mild to moderate atopic dermatitis at Day 29 based on Investigator's Static Global Assessment (ISGA) scale. The secondary objective was to evaluate the safety and tolerability of crisaborole ointment at Day 29 compared to vehicle ointment in this population.

Trial Design

Trial AN2728-AD-302 was a multi-center, randomized, double-blind, vehicle-controlled trial enrolling subjects age 2 years and older with mild to moderate atopic dermatitis. The trial was conducted in 45 investigational sites which were located throughout the United States (3 investigational sites did not enroll any subjects). The study design and procedures for Trial AN2728-AD-302 were identical to Trial AN2728-AD-301.

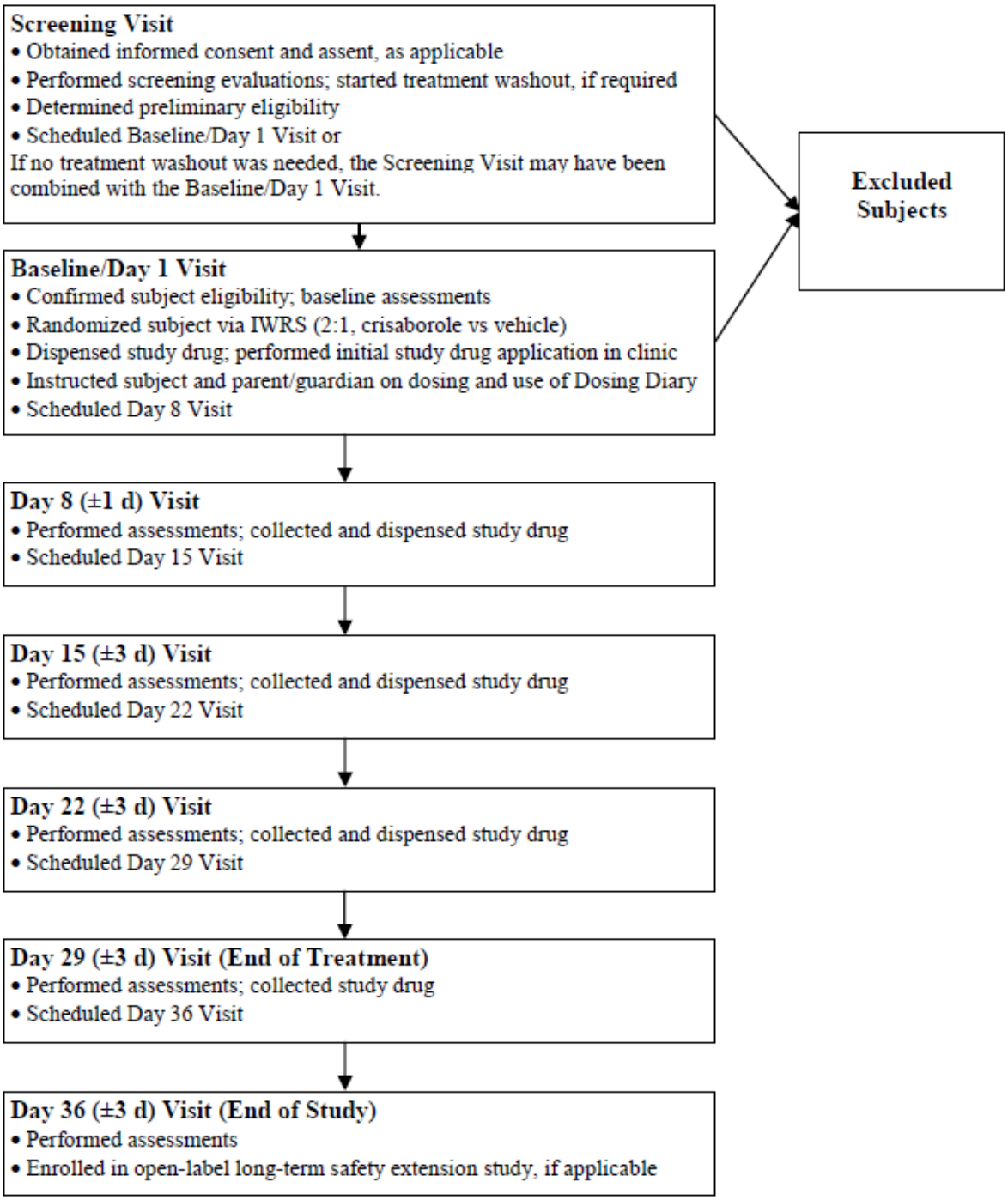
Study population
The trial enrolled 764 male and female subjects with mild-to-moderate AD with at least 20% of the subjects between the ages of 2 and 6 years and up to 15% ≥ 18 years.

The inclusion and exclusion criteria were the same as summarized above for Trial AN2728-AD-301.

Trial procedures

The trial procedures for Trial AN2728-AD-302 were identical to Trial AN2728-AD-301. Refer to Section 6.1.1.

Figure 3: Trial Flow Diagram AN2728-AD-302



Study Endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the same for Trial AN2728-AD-302 as Trial AN2728-AD-301, the proportion of subjects achieving success on Investigator's Static Global Assessment (ISGA) at Day 29. Success on ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The ISGA (Table 7) was a five-point global static assessment of AD severity.

Secondary efficacy endpoints

The two secondary efficacy endpoints were the following:

- Proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29
- Time to success in ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

Statistical Analysis Plan

The statistical analysis plan for Trial AN2728-AD-302 was identical to Trial AN2728-AD-301. Refer to Section 6.1.1.

Protocol Amendments

The applicant provided 2 amended versions of Phase 3 Protocol AN2728-AD-302 with the same modifications as Protocol AN2728-AD-301. Refer to Section 6.1.1.

Data Quality and Integrity: Sponsor's Assurance

The applicant included the same procedures in both Phase 3 protocols to ensure data quality and integrity. Refer to Section 6.1.1.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant included the following statement in the Clinical Study Reports for both pivotal trials "The Investigators agreed to conduct the study in compliance with the protocol approved by the appropriate Institutional Review Board, according to International Conference on Harmonisation *(sic)* and local good clinical practices standards, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki. There were no reports of

issues with unblinding, adherence to protocol, subject retention, protocol amendments or post hoc data analysis that impacted the collection of the data or the results. Refer to Section 6.1.1.

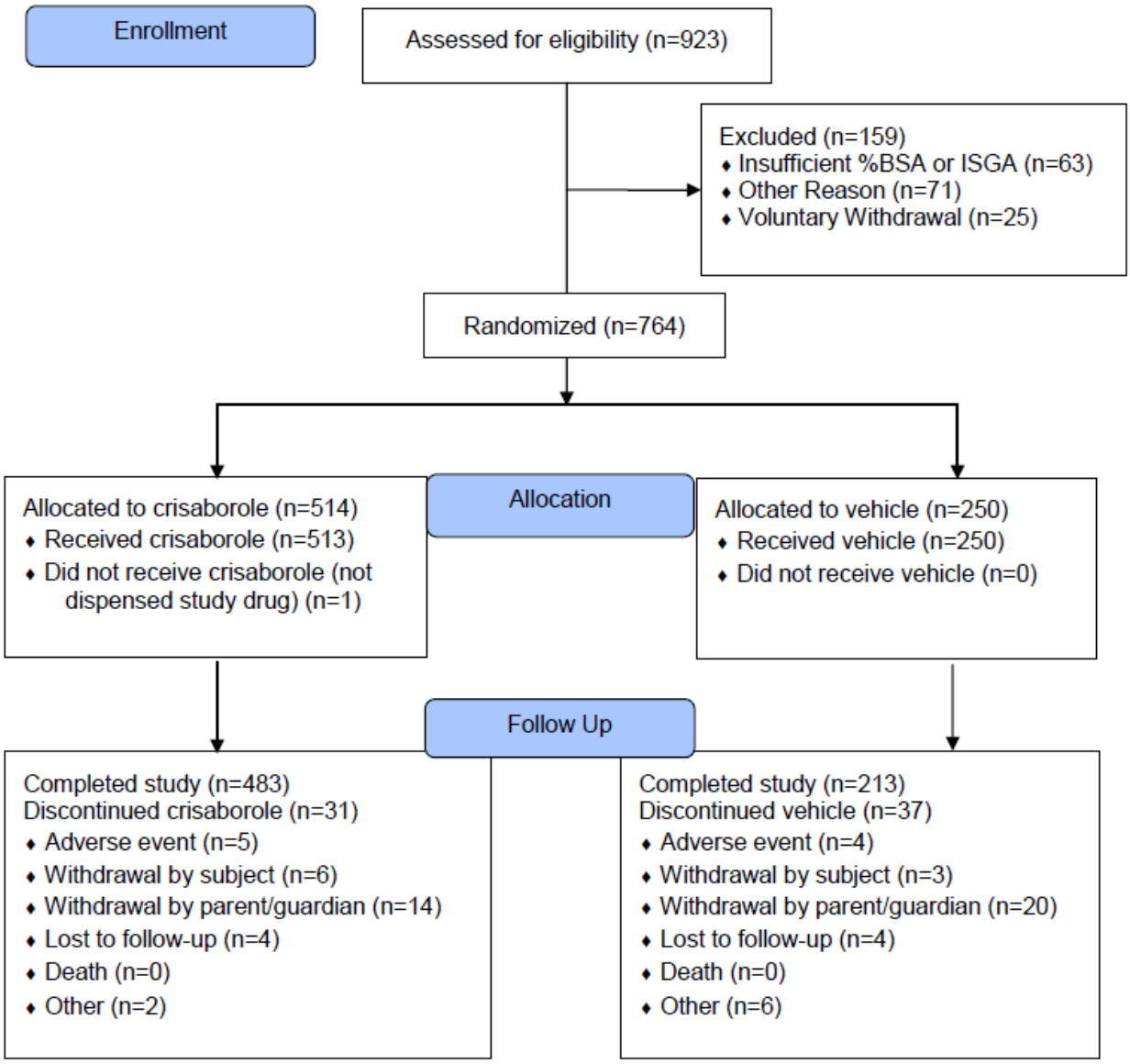
Financial Disclosure

The applicant disclosed that there were no financial interests or arrangements with clinical investigators participating in Trial AN2728-AD-302.

Subject Disposition

The great majority of the subjects completed Trial AN2728-AD-302. A greater percentage of subjects discontinued from the vehicle group (14.8%) than the Crisaborole Ointment group (6.0%). However, a slightly greater proportion of subjects withdrew from the Crisaborole Ointment group than the vehicle group due to the occurrence of adverse events.

Figure 4: Subject Disposition- Trial AN2728-AD-302



Protocol Violations/Deviations

The protocol deviations occurring with the greatest frequency and resulting in exclusion from the Per Protocol (PP) population analysis in Trial AN2728-AD-301 were the following:

Table 21: Primary Protocol Deviations- Trial AN2728-AD-302

	Crisaborole group (N)	Vehicle group (N)
Out-of-window for the Day 29 Visit	37	33
Did not apply 80% - 120% of the expected doses	31	29
Did not complete the Day 29 Visit	28	26
Used prohibited medication during treatment period	17	13
Did not meet all the Inclusion /Exclusion criteria	16	10

Source: Reviewer's Table

Reviewer Comment:

Overall, the number of protocol deviations is small and should have no impact on the efficacy results. The slight imbalance in protocol deviations is not significant.

Table of Demographic Characteristics

The demographic characteristics of subjects enrolled in each treatment group in Trial AN2728-AD-302 were comparable. The majority of subjects in both groups were White, female and not Hispanic/Latino. The mean age of subjects in the crisaborole group (12.6 years) was slightly higher than the mean age of subjects in the vehicle group (11.8 years) and approximately 60% of subjects in both groups were in the 2 to 11 year old age group.

Refer to Table 12.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The treatment groups were comparable with regard to other baseline characteristics such as global severity, severity of pruritus and percent of body surface area affected by atopic dermatitis. The majority of subjects had AD of moderate severity with moderate to severe pruritus. The mean Treatable Percent Body Surface Area was 18% for both the crisaborole and vehicle groups.

Refer to Table 13 and

Table 14.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with treatment was similar across treatment groups. The criteria for compliance were described above. The applicant considered the majority of the subjects to be "compliant" with the dosing regimen, defined as applying at least 80% but no more than 120% of the

expected applications during the Study Drug Application Period and had not missed six or more consecutive doses. Subjects who applied crisaborole were more compliant than subjects who applied vehicle.

Table 22: Dosing Compliance- AN2728-AD-302 (Intent-to-Treat Population)

	No. of Applications	No. of Dosing Days	Amount of Drug Used (g)	Compliant	
Crisaborole N=503					
No. of subjects	513	513	482	Yes	480 (93.6%)
Mean (SD)	54.3 (9.46)	27.8 (4.63)	167.0 (168.45)		
Median	56.0	28.0	120.0	No	33 (6.4%)
Min to Max	1 to 76	1 to 38	2 to 1328		
Vehicle N=256					
No. of subjects	250	250	237	Yes	219 (87.6%)
Mean (SD)	52.3 (11.21)	26.9 (5.56)	170.6 (154.71)		
Median	56.0	28.0	121.0	No	31 (12.4%)
Min to Max	1 to 73	1 to 38	1 to 991		

Source: Clinical Study Report for AN2728-AD-302 Table 20

As much as possible, the dosing regimen for concomitant medications was stabilized before Screening and remained constant during the course of the trial.

The types of concomitant medications used by subjects in each treatment group were similar. Generally, these medications were products indicated for the treatment of conditions related to atopic dermatitis such as xerosis, allergic rhinitis and asthma. The most common treatment category was antihistamines which were used by 28.2% of subjects in the crisaborole group and 32.0% of subjects in the vehicle group. The second most common treatment category was therapies indicated for obstructive airway disease such as inhaled corticosteroids and beta-agonists which were used by 24.5% of subjects in the crisaborole group and 27.9% of subjects in the vehicle group. Only 9.0% of subjects in the crisaborole and 8.9% of subjects in the vehicle group reported the concomitant use of emollients or barrier creams.

Table 23: Concomitant Medications in 2% or Greater Subjects Enrolled in Trial AN2728-AD-302 (ITT Population)

Medication Name	Crisaborole	Vehicle	Subjects
LIDOCAINE	85 (11.13%)	43 (5.63%)	128 (16.75%)
TRIAMCINOLONE	75 (9.82%)	50 (6.54%)	125 (16.36%)

Medication Name	Crisaborole	Vehicle	Subjects
SALBUTAMOL	68 (8.90%)	43 (5.63%)	111 (14.53%)
HYDROCORTISONE	67 (8.77%)	39 (5.10%)	106 (13.87%)
CETIRIZINE HYDROCHLORIDE	68 (8.90%)	28 (3.66%)	96 (12.57%)
OTHER EMOLLIENTS AND PROTECTIVES	51 (6.68%)	36 (4.71%)	87 (11.39%)
IBUPROFEN	41 (5.37%)	22 (2.88%)	63 (8.25%)
DIPHENHYDRAMINE HYDROCHLORIDE	42 (5.50%)	19 (2.49%)	61 (7.98%)
MONTELUKAST SODIUM	27 (3.53%)	28 (3.66%)	55 (7.20%)
LORATADINE	30 (3.93%)	23 (3.01%)	53 (6.94%)
PARAFFIN	35 (4.58%)	17 (2.23%)	52 (6.81%)
AQUAPHOR	33 (4.32%)	17 (2.23%)	50 (6.54%)
HYDROXYZINE	25 (3.27%)	24 (3.14%)	49 (6.41%)
OMEGA-6 FATTY ACIDS	27 (3.53%)	15 (1.96%)	42 (5.50%)
MULTIVITAMINS	35 (4.58%)	6 (0.79%)	41 (5.37%)
FLUTICASONE PROPIONATE	24 (3.14%)	16 (2.09%)	40 (5.24%)
PARACETAMOL	30 (3.93%)	10 (1.31%)	40 (5.24%)
EMLA	27 (3.53%)	12 (1.57%)	39 (5.10%)
DESONIDE	24 (3.14%)	15 (1.96%)	39 (5.10%)
CETAPHIL	29 (3.80%)	8 (1.05%)	37 (4.84%)
CETIRIZINE	23 (3.01%)	14 (1.83%)	37 (4.84%)
TRIAMCINOLONE ACETONIDE	19 (2.49%)	17 (2.23%)	36 (4.71%)
AVENA SATIVA FLUID EXTRACT	25 (3.27%)	9 (1.18%)	34 (4.45%)
EPINEPHRINE	19 (2.49%)	15 (1.96%)	34 (4.45%)
MOMETASONE FUROATE	21 (2.75%)	11 (1.44%)	32 (4.19%)
SALBUTAMOL SULFATE	26 (3.40%)	6 (0.79%)	32 (4.19%)
EMOLLIENTS AND PROTECTIVES	20 (2.62%)	11 (1.44%)	31 (4.06%)
MOMETASONE	12 (1.57%)	15 (1.96%)	27 (3.53%)
FLUOCINOLONE ACETONIDE	14 (1.83%)	8 (1.05%)	22 (2.88%)
AMOXICILLIN	13 (1.70%)	8 (1.05%)	21 (2.75%)
BECLOMETASONE DIPROPIONATE	12 (1.57%)	7 (0.92%)	19 (2.49%)
TACROLIMUS	15 (1.96%)	4 (0.52%)	19 (2.49%)

Source: Reviewer's Table

Efficacy Results - Primary and Secondary Endpoints

The results of Trial AN2728-AD-302 indicate that crisaborole was statistically superior to vehicle at Day 29 on the primary and secondary efficacy endpoints as presented in Table 16.

The primary efficacy endpoint was the proportion of subjects achieving success on the Investigator's Static Global Assessment (ISGA) at Day 29. Success on ISGA was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

The two secondary efficacy endpoints specified in the protocol were:

- Proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29
- Time to success in ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

Refer to Table 6 for the ISGA.

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population which was defined as all randomized subjects who were dispensed study drug. Refer to Section 6.1.2.

Refer to Table 17, Table 18, Table 19 and Table 20.

Data Quality and Integrity - Reviewers' Assessment

The analysis of the data submitted by the applicant to support the efficacy of crisaborole ointment for the treatment of atopic dermatitis was verified by FDA reviewers. Although the effect size was relatively small, success was established on the primary efficacy endpoint. The results of analyses of the secondary and exploratory endpoints supported the results of the primary endpoint.

Efficacy Results- other relevant endpoints

The exploratory endpoints were based on the investigator evaluation of the signs of atopic dermatitis and the subject evaluation of the symptom of AD (pruritus) using an electronic diary. The signs were evaluated on a 4-point global assessment scale (Table 9) and the symptom was evaluated on a 4-point pruritus severity scale (Table 8). Treatment success for both endpoints was defined as None (0) or Mild (1) with at least a 1-grade improvement from baseline.

A greater proportion of subjects in the EUCRISA arm experienced improvement in all signs and symptoms of AD at Day 29 than subjects in the vehicle arm. See Table 19.

Dose/Dose Response

The applicant did not design Trial AN2728-AD-301 to assess dose response.

Durability of Response

The applicant did not design Trial AN2728-AD-301 to evaluate response beyond 29 days.

Persistence of Effect

The applicant did not design Trial AN2728-AD-302 to assess treatment effect beyond 29 days.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted on the data from this trial.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The applicant submitted data from 2 adequate and well-controlled clinical trials (Trial AN2728-AD-301 and Trial AN2728-AD-302) of identical design in support of NDA 207695 for EUCRISA. The pre-specified primary efficacy endpoint for both trials was the proportion of subjects achieving success on the Investigator's Static Global Assessment (ISGA) at Day 29. Success was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The Division agreed with this proposed endpoint, the primary analysis method, (logistic regression with factors of treatment group and analysis center) and the strategy for handling missing data (multiple imputation method.) (EOP2 Meeting Minutes dated 3/6/204) The results for the ITT population are summarized in Table 24.

Table 24: Results for the Primary Efficacy Endpoint at Day 29 (ITT, MI[1])

	Trial 301			Trial 302		
Endpoint	**EUCRISA (N=503)**	**Vehicle (N=256)**	**P-Value[2]**	**EUCRISA (N=513)**	**Vehicle (N=250)**	**P-Value[2]**
Success in ISGA[3]	32.8%	25.4%	0.038	31.4%	18.0%	<0.001

Source: Statistical Review by Matthew Guerra, Ph.D. dated 8/19/2016

(1) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 140 imputed datasets for Trial 301 and the 135 datasets for Trial 302.

(2) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.

(3) Success is defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline

Refer to the Statistical Review by Matthew Guerra, Ph.D. for an analysis of the imbalance of missing data in the vehicle arm compared with the active arm and the results of multiple sensitivity analyses. The statistical reviewer concluded that the results were similar across the various methods for handling missing data.

Reviewer Comment:

This is a well-established endpoint for the evaluation of efficacy for topical products indicated for the treatment of AD. The statistical reviewer was able to replicate the trial findings with confirmation with multiple sensitivity analyses. Although the effect size is modest, it is clinically meaningful for patients seeking an alternative to chronic/intermittent treatment with topical corticosteroids.

7.1.2. Secondary and Other Endpoints

The secondary efficacy endpoints specified in the Phase 3 Protocols (AN2728-AD-301 and AN2728-AD-302) were the following:

- Proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29
- Time to success in ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

The Division agreed with the proposed approach to control for multiplicity by sequential analysis.

The results for the secondary efficacy endpoints are presented in Table 25 for the ITT population. EUCRISA was statistically superior to vehicle (p-values ≤ 0.005) on both secondary efficacy endpoints in Trial AN2728-AD-301 and AN2728-AD-302. Refer to the Statistical Review by Matthew Guerra, Ph.D. dated 8/19/2016 for the results of the supportive analysis conducted for the Per Protocol population.

Table 25: Results for the Secondary Efficacy Endpoints at Day 29 (ITT, MI [1])

	Trial 301			Trial 302		
Endpoint	**EUCRISA (N=503)**	**Vehicle (N=256)**	**P-Value**	**EUCRISA (N=513)**	**Vehicle (N=250)**	**P-Value[2]**
ISGA score of Clear or Almost Clear	51.7%	40.6%	0.005[2]	48.5%	29.7%	<0.001[2]
Time to Success in ISGA[3] Median[4]	NC	NC	<0.001[5]	NC	NC	<0.001[5]

Source: Statistical Review by Matthew Guerra, Ph.D.

(1) Missing data was imputed using multiple imputation (MI). The values displayed are the averages over the 140 imputed datasets for Trial 301 and the 135 datasets for Trial 302.

(2) P-value from a logistic regression (using Firth's Penalized Likelihood) with treatment and analysis center as factors.

(3) Success is defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.
(4) Median time to success in ISGA could not be calculated because fewer than 50% of subjects reached success in ISGA.
(5) P-value based on a log-rank test.

Reviewer Comment:

The Division indicated that the secondary endpoints should be clinically meaningful and supportive of the proposed primary efficacy endpoint but communicated no other specific comments regarding these endpoints.

Regarding the endpoint "Time to Success in ISGA", the Statistical Reviewer stated "It should be noted that the median time to success in ISGA (i.e., the time at which 50% of the subjects achieved success in ISGA) could not be calculated, as fewer than 50% of subjects achieved success in ISGA." As an alternative analysis, he presented the proportion of subjects who achieved success in ISGA over time (i.e., Days 1, 8, 15, 22 and 29) for both trials. See figures below.

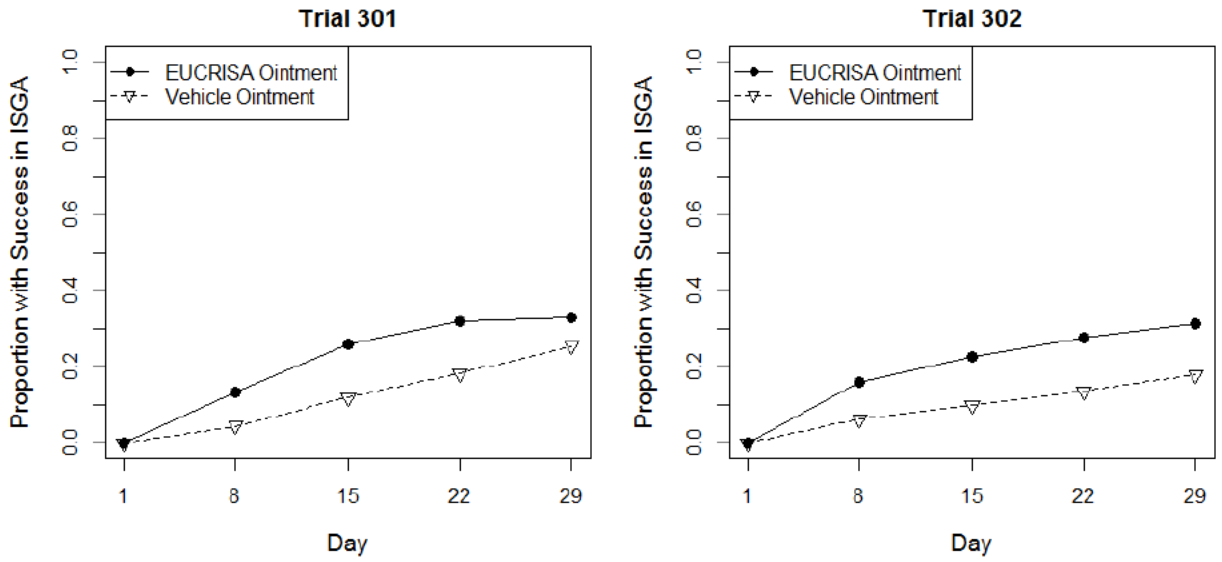


Figure 5: Success in ISGA over Time (ITT, MI)

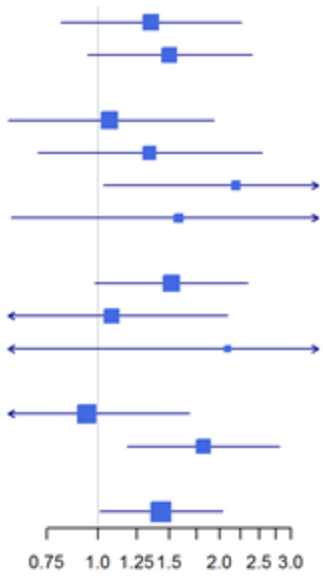
Source: Statistical Review and Analysis by Matthew Guerra, dated 8/19/2016.

7.1.3. Subpopulations

The subpopulations which were analyzed for meaningful differences in response rate to EUCRISA compared to vehicle included: gender, race, sex, age and baseline ISGA score. Analysis of the data by the Statistical Reviewer (Review dated 8/19/2016) indicated that treatment effect was greater in females than males and greater in Whites than Blacks and greater in those subjects with moderate disease at baseline in both trials. However, subjects with mild disease at baseline in Trial AN2728-AD-301 had greater treatment effect with vehicle. Treatment effect was also greater in Hispanic/Latino subjects compared with non- Hispanic/Latino subjects. Most importantly, the results for different age groups were inconsistent across the two trials as presented in Table 26 and Table 27.

Table 26: Results for the Primary Efficacy Endpoint at Day 29 by Gender, Age, Race and Baseline ISGA for Trial AN2728-AD-301 (ITT, MI)

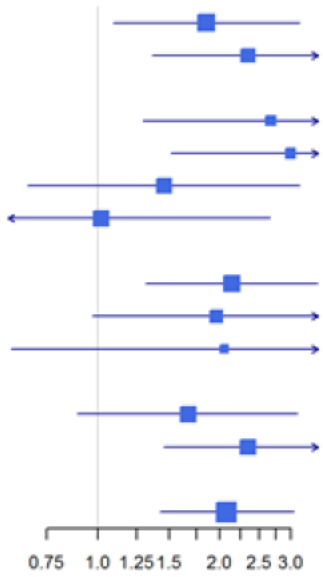
Subgroups (N[E], N[V])	EUCRISA (N=503)	Vehicle (N=256)	OR
Gender			
Males (219, 113)	33.2%	26.9%	1.35
Females (284, 143)	32.5%	24.2%	1.50
Age			
2-6 (162, 78)	33.6%	32.1%	1.07
7-11 (155, 73)	31.4%	25.4%	1.34
12-17 (121, 67)	34.2%	19.2%	2.19
18+ (65, 38)	31.6%	22.7%	1.58
Race			
White (308, 162)	33.8%	25.2%	1.52
Black (138, 61)	34.5%	32.7%	1.08
Other (57, 33)	23.2%	12.9%	2.09
Baseline ISGA			
2 - Mild (196, 93)	24.4%	25.5%	0.94
3 - Moderate (307, 163)	38.2%	25.4%	1.82
Overall	32.8%	25.4%	1.43



Source: Statistical Review by Matthew Guerra, Ph.D. dated 8/19/2016 (These results replicated applicant's data, 2.7.3 Summary of Clinical Efficacy)

Table 27: Results for the Primary Efficacy Endpoint at Day 29 by Gender, Age, Race and Baseline ISGA for Trial AN2728-AD-302 (ITT, MI)

Subgroups (N[E], N[V])	EUCRISA (N=513)	Vehicle (N=250)	OR
Gender			
Males (231, 112)	34.4%	22.1%	1.85
Females (282, 138)	29.0%	14.8%	2.35
Age			
2-6 (173, 93)	27.4%	12.4%	2.67
7-11 (137, 71)	42.9%	20.1%	2.99
12-17 (126, 57)	26.3%	19.7%	1.46
18+ (77, 29)	28.1%	27.7%	1.02
Race			
White (309, 144)	33.1%	18.8%	2.14
Black (147, 78)	29.7%	17.7%	1.96
Other (57, 28)	26.3%	14.9%	2.05
Baseline ISGA			
2 - Mild (196, 93)	25.4%	17.0%	1.67
3 - Moderate (307, 163)	35.1%	18.7%	2.35
Overall	31.4%	18.0%	2.08



Source: Statistical Review by Matthew Guerra, Ph.D. (These results replicated applicant's data, 2.7.3 Summary of Clinical Efficacy)

Statistical Reviewer's Assessment

The Statistical Reviewer, Matthew Guerra, Ph.D. provided the following conclusions regarding the data to support the efficacy of ECRUISA (Review dated 8/19/2016):

> "Efficacy findings from two pivotal Phase 3 trials (Trials 301 and 302) established the efficacy of EUCRISA ointment, 2% for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older."

7.1.4. Dose and Dose-Response

The applicant conducted a dose ranging trial during the development of EUCRISA for the treatment of AD. Trial AN2728-AD-204 was a multicenter, randomized, double-blind, 4-Week, bilateral trial evaluating 2 concentrations of crisaborole administered once or twice daily in pediatric subjects age 12-17 years with mild to moderate AD. A total of 86 subjects (34 males and 52 females) were randomized 1:1 to once daily or twice daily treatment groups.

Group 1

- Crisaborole Ointment, 2% QD for 29 Days AND
- Crisaborole Ointment, 0.5% QD for 29 Days

Group 2

- Crisaborole Ointment, 2% BID for 29 Days AND
- Crisaborole Ointment, 0.5% BID for 29 Days

Investigators identified 2 target lesions on each subject approximately 10–500 cm^2 of similar severity located on the trunk or upper or lower extremities. Target lesions were $\geq$ 10 cm apart with an Atopic Dermatitis Severity Index (ADSI) scores $\geq$ 6 and $\leq$ 12 and an erythema subscore $\geq$2 (difference in ADSI scores $\leq$ 1). Subjects in the once daily dosing group applied Crisaborole Ointment, 0.5% on one target lesion and Crisaborole Ointment, 2% on the other target lesion once daily; similarly, subjects in the twice daily dosing group applied Crisaborole Ointment, 0.5% on one target lesion and Crisaborole Ointment, 2% on the other target lesion twice daily.

Subjects applied 4 doses in the clinic under supervision during study visits on Days 1, 8, 15, and 22. Subjects applied all other doses at home. At each application, a dose of approximately 3 mg/cm2 study drug was applied to each Target Lesion.

The safety evaluation included: physical examinations, vital signs, and queries for AEs and concomitant medications at each visit. Investigators performed a laboratory evaluation at Screening, Baseline and Day 29 (Serum chemistry, hematology, and in female subjects pregnancy testing.)

The primary endpoint for this study was the change from Baseline in ADSI score (ADSI score represents the sum of the subscores for erythema, excoriation, exudation, lichenification, and pruritus). Exploratory efficacy endpoints included total clearance (ADSI =0), partial clearance (0< ADSI ≤2), total or partial clearance (ADSI ≤2), and ≥4-point improvement from baseline (Baseline minus Visit score) in ADSI at Days 8, 15, 22, and 29.

Table 28: Atopic Dermatitis Severity Index

Erythema (redness present at the target lesion)		
Score	Grade	Description
0	None	No redness
0.5		
1.0	Mild	Mildly detectable erythema; pink
1.5		
2.0	Moderate	Dull red; clearly distinguishable
2.5		

3.0	Severe	Deep, dark red; marked and extensive
Excoriation (scratching present at the target lesion)		
Score	Grade	Description
0	None	No evidence of excoriation
0.5		
1.0	Mild	Mild excoriation present
1.5		
2.0	Moderate	Definite excoriation present
2.5		
3.0	Severe	Marked, deep, or extensive excoriation present
Exudation (oozing or crusting of the Target Lesion)		
Score	Grade	Description
0	None	No oozing or crusting
0.5		
1.0	Mild	Minor or faint signs of oozing
1.5		
2.0	Moderate	Definite oozing or crusting present
2.5		
3.0	Severe	Marked and extensive oozing or crusting present
Lichenification (scratching present at the target lesion)		
Score	Grade	Description
0	None	epidermal thickening of the Target Lesion
0.5		
1.0	Mild	Minor epidermal thickening
1.5		
2.0	Moderate	Moderate epidermal thickening; accentuated skin lines
2.5		
3.0	Severe	Severe epidermal thickening; deeply accentuated skin lines
Pruritus (itching present at the Target Lesion)		
Score	Grade	Description
0	None	No itching
0.5		
1.0	Mild	Occasional, slight itching
1.5		
2.0	Moderate	Constant or intermittent itching; does

		not disturb sleep
2.5		
3.0	Severe	Bothersome itching that disturbs sleep or normal activity

Source: Clinical Study Report for Protocol AN2728-AD-204, page 30

Results

For the primary endpoint, a dose response was evident across the four treatment groups. The greatest improvement was observed in lesions treated with AN2728 Topical Ointment, 2%, BID.

The Division did not consider the intra-subject, bilateral treatment design to be appropriate to evaluate the efficacy and systemic safety of this topical drug product. However, the results were considered sufficient to inform the dosing selection. The Division provided the following comments (EOP2 Meeting Minutes dated 3/6/2014)

> "Although the data submitted to date appears to support your proposed dosing regimen and duration of treatment, we have the following concerns:
>
> The Agency reiterates its previous comments in the Advice Letter (IND 102317; 1/23/2009) that due to the lack of control, within-subject, bilateral trials are limited in assessing dose response as well as limited in providing reliable safety and efficacy data. You are also referred to the minutes from the Pre-IND meeting (IND 77537; 2/13/2008) that in order to power future Phase 3 trials based on previously conducted Phase 2 trials, similar endpoints and patient populations intended for the Phase 3 trials should be assessed in the Phase 2 trials. The primary endpoint for Phase 2 trials (AN2728-AD-204 and AN2728-AD-202*) was based on the Atopic Dermatitis Severity Index (ADSI) of the target lesion only and not on a global disease severity as whole. ADSI is calculated from a number of variables and is not used routinely in clinical settings. Therefore, taking into account that the primary endpoint in trials AN2728-AD-202 and AN2728-AD-204 was based on ADSI, and not on the ISGA scale, and that AN2728-AD-203 was a small open label, non-randomized, safety trial, you run the risk of underpowering your Phase 3 trials."

* Trial AN2728-AD-202 was a 6 Week trial comparing the safety, tolerability and efficacy of crisaborole ointment, 2% to AN2898 ointment, 1% (another formulation) in adult subjects.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The applicant did not conduct a trial designed to evaluate the duration or durability of efficacy effects.

7.1.6. Considerations on Benefit in the Postmarket Setting

There were no significant differences in efficacy in important subpopulations that would be expected to impact the generalizability of benefit to the broader population who may use this product. However, there were insufficient numbers of subjects with atopic dermatitis who were older than age 65 to ensure the same benefit as younger subjects. In addition, the youngest pediatric subjects age 2 to 6 years, experienced numerically greater benefit from EUCRISA than vehicle; among the pediatric subgroups these youngest subjects derived the greatest benefit from the use of the ointment vehicle alone.

Reviewer Comment:

This finding of improvement in AD with an ointment based vehicle in subjects age 2 to 6 years supports the general practice of dermatologists and pediatricians to optimize the use of emollients prior to the initiation of pharmacologic therapy.

7.1.7. Other Relevant Benefits

In the armamentarium of treatments for atopic dermatitis, the addition of a therapeutic option with a favorable safety profile, limited systemic exposure and acceptable efficacy is important. The remitting and relapsing course of AD can result in patients applying treatments beyond the indicated duration of use. Topical corticosteroid (TCS) products and calcineuin inhibitors (TCI) are effective therapies which are associated with significant potential adverse events especially when used over the long term. A relevant benefit of this therapeutic option is the potential reduction in the chronic use of TCSs and TCIs.

7.2. Integrated Assessment of Effectiveness

The applicant submitted efficacy data from 2 adequate and well-controlled Phase 3 trials (AN2728-AD-301 and AN2728-AD-302) to support the approval of EUCRISA (crisaborole) ointment, 2% for the topical treatment of mild to moderate atopic dermatitis (AD). Enrolled subjects were 2 years of age with a body surface area (BSA) involvement ≥ 5% (excluding scalp) and an Investigator's Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate). EUCRISA ointment, 2% was statistically superior to vehicle ointment on the primary and secondary efficacy endpoint in both trials. In addition, a greater proportion of subjects in the EUCRISA arm experienced improvement in all signs and symptoms of AD at Day 29 than subjects in the vehicle arm. Therefore, the applicant provided substantial evidence of effectiveness in the target population and has met the evidentiary standard.

The addition of a therapeutic option with a favorable safety profile, limited systemic exposure and acceptable efficacy represents a clinically meaningful benefit to the population with atopic dermatitis. The approved treatments, topical corticosteroid (TCS) products and calcineuin inhibitors (TCI), are associated with significant potential adverse events with chronic use. The approval of EUCRISA provides an alternative for patients who are unresponsive to the currently

available treatment options or unable to use them based on their adverse event profile.

Refer to Section 6.1 and 6.2 of this review for additional information regarding the individual trials and the Statistical Review by Matthew Guerra, PhD dated 8/19/2016 for a comprehensive analysis of the efficacy data.

Labeling

At the time of this review labeling negotiations were ongoing. Data regarding the primary efficacy outcome measure was presented in labeling. The Division revised the language proposed by the applicant and removed (b) (4). The Division recommended an analysis of success rate over time as recommended by the statistical reviewer in Section 7 of this review.

The Division proposed the following language for Section 14 CLINICAL STUDIES.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials (Trials 1 and 2) enrolled a total of 1522 subjects 2 to 79 years of age ((b) (4)% of subjects were 2 to (b) (4) years of age) with a 5% to 95% treatable body surface area. At baseline, 38.5% of the subjects had an Investigator's Static Global Assessment [ISGA] score of 2 (mild) and 61.5% had an ISGA score of 3 (moderate) in the overall assessment of atopic dermatitis (erythema, induration/papulation, and oozing/crusting) on a severity scale of 0 to (b) (4)

In both trials, subjects were randomized 2:1 to receive EUCRISA or vehicle applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at Day 29 (b) (4) achieved success, defined as an ISGA grade of Clear (score=0) or Almost Clear (score=1) with a ≥2-grade improvement from baseline

Efficacy results from the two trials are summarized in Table 3.

Table 3: Efficacy Outcomes in Subjects with Mild to Moderate Atopic Dermatitis at Day 29

	Trial 1		Trial 2	
	EUCRISA (N=503)	**Vehicle (N=256)**	**EUCRISA (N=513)**	**Vehicle (N=250)**
Success in ISGA[a]	32.8%	25.4%	31.4%	18.0%

[a] Defined as an ISGA score of Clear (0) or Almost Clear (1) with a ≥2-grade improvement from baseline.

In addition, the applicant provided limited data in the population ≥ age 65 years with AD.

The sponsor proposed the following language for **Section 8.5** of labeling:

Per 21 CFR 201.80 this reviewer recommends the following language for Section 8.5

"Clinical studies of EUCRISA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects."

8 Review of Safety

8.1. Safety Review Approach

The applicant conducted two identical randomized, vehicle controlled, Phase 3 trials (AN2728-AD-301 and AN2728-AD-302) in subjects with mild to moderate atopic dermatitis. Pooled data from trials AN2728-AD-301 and AN2728-AD-302 comprised the primary safety database. The safety data analyzed in this review were systemic safety findings such as vital signs, laboratory parameters, ECGs and adverse event reports and local safety findings from active assessments of local tolerability. The applicant submitted long term safety data from a 52- week, open label trial (AN2728-AD-303) which enrolled subjects who had completed one of the two Phase 3 trials without a safety signal which would have precluded further treatment with the proposed product. Data from Phase 2 trials in subjects with AD and plaque psoriasis were not included in the primary safety database because of inadequate intra-subject study designs, differences in indications and study populations and the use of prototype formulations.

Other data analyzed to support the safety of crisaborole included findings from Trial AN2728-TQT-108 and Trial AN2728-RIPT-101 which investigated the effect of the proposed product on cardiac safety and dermal safety, respectively. The Agency granted a waiver of the conduct of phototoxicity and photoallergenicity testing because no components of the drug product absorbed light corresponding to wavelengths of 290 to 700 nm.

There were no local or systemic safety signals identified during the pre-clinical program or early phase trials. The primary focus of this safety evaluation was the local safety assessments. However, based on findings regarding orally administered PDE4 inhibitors such as OTEZLA® (apremilast) tablets, systemic safety considerations included the potential for depression, weight loss, and gastrointestinal adverse events.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The primary safety database was comprised of pooled data from the 2 identical Phase 3 trials, AN2728-AD-301 and AN2728-AD-302. These were randomized, vehicle- controlled, multicenter trials enrolling subjects with mild to moderate atopic dermatitis which were conducted in the United States. Subjects applied the study product twice daily for 28 days in both trials. Due to the differences in study design, study populations, and indications, the safety data from the remaining trials was considered supportive.

In the pooled database, a total of 1021 subjects were randomized to Crisaborole and 506 subjects were randomized to the vehicle. In the Crisaborole arm, 5 subjects were excluded from the safety population due to "no confirmed dose of Study Drug" and 9 were excluded due to "No Post Baseline Assessment" for a total of 1012 subjects. In the vehicle arm, 7 subjects were excluded from the safety population due to "No Post Baseline Assessment" for a total of 499 subjects. The numbers of subjects of the intent to treat (ITT) population, per protocol (PP) population and safety population were tabulated below (Table 29). Refer to Table 41 for a summary of subject completion and reasons for discontinuation from the pooled dataset.

Table 29: Safety Population

Primary Safety Database for Crisaborole ointment, 2%			
Clinical Safety and Efficacy Trials	Crisaborole Ointment, 2%	Vehicle	Totals
AN2728-AD-301	507 subjects randomized 4 excluded from ITT 72 excluded from PP 477 completers 502 safety population	256 subjects randomized 0 excluded from ITT 55 excluded from PP 225 completers 252 safety population	754 safety population
AN2728-AD-302	514 subjects randomized 1 excluded from ITT 60 excluded from PP 483 completers 510 safety population	250 subjects randomized 0 excluded from ITT 42 excluded from PP 213 completers 247 safety population	757 safety population
Total	1012 safety population	499 safety population	

Source: Reviewer's Table

.

Table 30: Summary of Exposure to Crisaborole by Usage in Phase 3 Trials (Safety Population)

	AN2728-AD-301 BID for 28 days (N = 759*)		AN2728-AD-302 BID for 28 days (N = 763*)		AN2728-AD-303 Up to 48 weeks (N = 517**)
	Crisaborole	Vehicle	Crisaborole	Vehicle	Crisaborole
# exposed to	503	256	513	250	517
# applications					
Mean (SD)	55(9)	52 (13)	54 (10)	52 (11)	349 (185)
Median	56	56	56	56	56
Min/Max	1/101	1/88	1/76	1/73	8/748
Total Usage (g)					
Mean (SD)	172 (194)§	167 (187)	167 (169)§	171 (155)	760 (1012)
Median	110	106	120	121	435
Min/Max	2/1602	1/1356	2/1328	7/991	0/9980
Dosing Days					
Mean (SD)	28 (4)	27 (7)	28(5)	27(6)	
Median	29	28	28	28	
Range	1/52	1/46	1/38	1/28	

*ITT population
**Safety population
§Subjects with missing data were not included
Source: Modified from 2.7.4 Summary of Clinical Safety, Table 24

The open-label long-term safety Trial AN2728-AD-303 enrolled 517 subjects, including 454 subjects age 2-17 years, who completed one of the pivotal Phase 3 trials (AN2728-AD-301 or AN2728-AD-302) without safety issues that precluded further treatment. The numbers of subjects participating in the trial for 6 months or greater were 395 and the number of subjects participating for 12 months was 271. The use of rescue therapy was discussed in 7.1.5.

Table 31: Duration of Participation and Potential Exposure in Trial AN2728-303.

Long-term Safety Trial AN2728-AD-303			
Design	Duration of Participation and Potential Exposure to Crisaborole ointment, 2%		
52- week, open label trial in which enrolled subjects were treated as needed	Enrolled	>=6 months	12 months
	N=517	N=396 (76.6%)	N=271 (52.4%)

Source: Reviewer's Table

Reviewer Comment:

- *Because investigators treated subjects as needed during the long-term safety Trial* AN2728-AD-303*, the duration of subject participation was not equivalent to the duration of exposure. However, this strategy reflects real world conditions of use.*
- *The size of the study population was discussed at the EOP2 meeting (Meeting Minutes dated 3/6/2014) and is consistent with the ICH-E1A guideline "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life- Threatening Conditions (March 1995)."*
- *The applicant and Division agreed upon the selection of the trials to be pooled for the integrated analysis of safety. (Pre-NDA Meeting Minutes dated 10/8/2015.)*

8.2.2. Relevant characteristics of the safety population:

The demographic characteristics of subjects included in Trial AN2728-AD-303 and the safety population (Trial AN2728-AD-301 and Trial AN2728-AD-302) and were similar to the ITT populations of the separate Phase 3 trials. The majority of subjects were White, female and not Hispanic/Latino. The mean age of subjects in the pooled crisaborole group (12.3 years) was slightly higher than the mean age of subjects in the vehicle group (12.1 years) and approximately 60% of subjects in both groups were in the 2 to 11 year old age group.

Table 32: Baseline Characteristics and Demographics in the Safety Population

	Pooled Trial AN2728-301 & Trial AN2728-302		Trial AN2728-303 (Long Term Safety)
	Crisaborole (N=1012)	Vehicle (N=499)	Crisaborole (N=506)
Age			
Mean (SD)	12.3 (12.2)	12.1 (10.7)	12.6 (12.7)
Median	9.0	9.0	10.0
Range	2 – 79	2 – 79	2 – 72
Categories			
2-11	625 (61.8%)	311 (62.3%)	308 (59.6%)
2-6	333 (32.9%)	333 (32.9%)	333 (32.9%)
7-11	292 (28.9%	292 (28.9%	292 (28.9%
12-17	246(24%)	122 (24%)	146 (28%)
≥18	141(14%)	66 (13%)	63 (12%)
Gender			
Male	448 (44%)	220 (44%)	211 (41%)
Female	364 (56%)	279 (56%)	306 (59%)
Race			

White	615(61%)	303 (61%)	315 (61%)
Black	283 (28%)	136 (27%)	152 (29%)
Asian/ Pacific Islander	59 (6%)	35 (7%)	29 (6%)
American Indian / Alaska Native	11 (1%)	5 (1%)	1 (0.2%)
Other	44 (4.3%)	44 (4.3%)	44 (4.3%)
ISGA			
Mean (SD)	2.6 (0.5)	2.6 (0.5)	NC
Median	3.0	3.0	NC
Min/Max	2/3	2/3	NC
Ethnicity			
Hispanic or Latino	199 (19.7%)	199 (19.7%)	199 (19.7%)
Not Hispanic or Latino	813 (80.3%)	813 (80.3%)	813 (80.3%)
Treatable %BSA			
Mean (SD)	18.3 (18.02)	18.1 (17.36)	NC
Median	11.0	12.0	NC
Min/Max	5, 95	5, 90	NC

NC=Not calculated
Source: Modified from 2.7.4 Summary of Clinical Safety Table 29

8.2.3. Adequacy of the safety database

The primary safety database (Trial AN2728-AD-301 and Trial AN2728-AD-302) was adequate to assess the safety of EUCRISA in the target population. The safety database included 1012 subjects who were exposed to crisaborole and 499 subjects who were exposed to vehicle. The majority of subjects were female, White, Non-Hispanic/Latino and age 2-11 years. Most of the subjects had AD of moderate severity and reported moderate pruritus. The demographic profile of the two treatment groups was comparable with a mean age of 12, 61% white, 80% Non-Hispanic/Latino and approximately 44% male. The mean treatable BSA of both groups was 18%.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall the quality of the data appears adequate. In conjunction with the JReview consultants, this reviewer found no significant deficiencies in the quality of the data from the pivotal trials. The Statistical Reviewer, Matthew Guerra, PhD confirmed this conclusion.

8.3.2. Categorization of Adverse Events

The applicant recorded adverse events from the onset of treatment and throughout the course

of all trials. To promote review and comparison across trials, the applicant recoded adverse events using a common MedDRA Version 16.1, the version of MedDRA used in the Phase 3 trials. All adverse events (AEs) were considered to represent treatment emergent adverse events (TEAEs) unless otherwise noted.

The applicant categorized adverse events using the following definitions:
Adverse event (AE): any untoward medical occurrence in a subject that might or might not have had a causal relationship with the study drug. An AE therefore included, but was not limited to, any unfavorable and unintended illness, sign, symptom, clinically important laboratory test or electrocardiogram (ECG) abnormality that was not present at Baseline, or disease temporally associated with the use of the study drug(s) that had appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug.

Serious adverse event (SAE): an event that was fatal, was life threatening, required subject hospitalization or prolongation of an existing hospitalization, was a persistent or significant disability/incapacity, or was a congenital anomaly/birth defect in a pregnancy outcome. In addition, SAEs included medically important events that did not result in any of the previously listed outcomes, but nevertheless were judged by the Investigator to jeopardize the subject and required medical or surgical intervention to prevent said outcomes.

Severity of AEs:

Mild:
Symptom(s) barely noticeable to the subject or did not make the subject uncomfortable. The adverse experience did not influence performance or functioning. Prescription drugs were not ordinarily needed for relief of symptom(s).

Moderate:
Symptom(s) of a sufficient severity to have made the subject uncomfortable. Performance of daily activities was influenced. Severity may have caused temporary cessation of treatment with the study drug. Treatment of symptom(s) may have been needed.

Severe:
Symptom(s) of a sufficient severity to have caused the subject severe discomfort. Severity may have caused cessation of treatment with the study drug. Treatment for symptom(s) may have been given.

Causality of AEs:

Unrelated
The event was definitely not associated with study drug administration, and was judged clearly due to causes other than the study drug.

Unlikely to be related
An event that followed a temporal sequence from administration of the study drug such that a relationship was not likely, and could be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Possibly related
An event that followed a reasonable temporal sequence from administration of the study drug, but that may have been due to another cause and could also have been reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Probably related
An event that followed a reasonable temporal sequence from administration of the study drug, that was not easily explained by another cause such as known characteristics of the subject's clinical state or other treatment, and was confirmed by improvement on stopping or slowing administration of the study agent (de-challenge), if applicable.

Definitely related
The AE was clearly related to the study drug: the AE had a temporal relationship to the administration of the investigational agent(s) or research intervention followed a known pattern of response, and no alternative cause was present.

8.3.3. Routine Clinical Tests

The applicant conducted routine laboratory testing and cardiac safety monitoring and assessed vital signs and local tolerability throughout the development program for EUCRISA (crisaborole) ointment, 2%. The assessments from trials which contributed significant safety information were tabulated below. Overall, the safety monitoring performed during the trials supporting this NDA was appropriate and adequate for the evaluation of the proposed product.

Table 33: Routine Laboratory Tests

Subjects who are Healthy		
Trial	Assessments	Timing of Assessments
AN2728-TQT-108	Hematology, chemistry and urinalysis	Screening, Day -1, and End of Trial/Early Termination
AN2728-RIPT-101	None	
Subjects with Atopic Dermatitis		
Trial	Assessments	Timing of Assessments

AN2728-AD-102	Hematology and chemistry	Screening, Baseline, Day 8, and Day 29/Early Termination
AN2898-AD-202	Hematology and chemistry	Screening, Baseline, Day 28 and Day 42/Early Termination
AN2728-AD-203	Hematology and chemistry	Screening, Baseline, Day 8, and Day 29/Early Termination
AN2728-AD-204	Hematology and chemistry	Screening, Baseline, and Day 29/Early Termination
AN2728-AD-301	Hematology and chemistry	Baseline and Day 29/Early Termination
AN2728-AD-302	Hematology and chemistry	Baseline and Day 29/Early Termination
AN2728-AD-303	Hematology and chemistry	Baseline, Week 12, Week 24, Week 36, and Week 48/End of Study/Early Termination

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Tables 4 and 5

The specific hematology and chemistry testing which was conducted in the Phase 3 trials included the following:

Table 34: Clinical Laboratory Test Parameters

Serum chemistry	Hematology	Pregnancy Testing
Glucose (non-fasting)	Hemoglobin	Urine Pregnancy testing with a minimum analytical sensitivity of 25 mIU/mL
Blood Urea Nitrogen	Hematocrit	
Creatinine	Red blood cell (RBC) count	
Sodium	Platelet count	
Potassium	White blood cell (WBC) count	
Aspartate aminotransferase	Neutrophils	
Alanine aminotransferase	Eosinophils	
Total bilirubin	Monocytes	
Alkaline phosphatase	Basophils	
Albumin	Lymphocytes	
Total protein		

Source: Modified from Protocol AN2728-AD-301 Table 7, page 79

Table 35: Vital Sign Assessments

Subjects who are Healthy		
Trial	Assessments	Timing of Assessments
AN2728-TQT-108	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Day -1, Baseline Day 1-5 and End of Trial
AN2728-RIPT-101	Not done	
Subjects with Atopic Dermatitis		
Trial	Assessments	Timing of Assessments
AN2728-AD-102	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline, Day 2, 5, 8, 9, 15, 22, and Day 29/Early Termination
AN2898-AD-202	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline, Day 14, 28 and Day 42/Early Termination
AN2728-AD-203	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline, Day 2, 4, 6, 8, 9, 15, 22, and Day 29/ End of treatment
AN2728-AD-204	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline, Day 8, 15, 22 and 29/ End of treatment
AN2728-AD-301	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline and Day 8, 15, 22, 29, 36/End of Trial or Early Termination
AN2728-AD-302	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Screening, Baseline and Day 8, 15, 22, 29, 36/End of Trial or Early Termination
AN2728-AD-303	Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature	Baseline and every 28 days through Week 48/End of Study or Early Termination

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Tables 7 and 8]

Table 36: Electrocardiogram Data Collected in Crisaborole Clinical Trials

Subjects with Atopic Dermatitis		
Trial	Assessments	Timing of Assessments
AN2728-AD-301 AN2728-AD-302	12-lead ECGs were performed for a subset of subjects at 56 selected sites across the 2 trials	Baseline, Day 8
Healthy Subjects or Subjects with Psoriasis		
Trial	Assessments	Timing of Assessments
AN2728-PK-101	Single 12-lead ECG	Screening, prior to Day 1 dosing in Period 1, prior to Day 1 morning dosing in Period 2, prior to Day 1 crisaborole morning dosing in Period 3, and at the end of Period 3 or prior to early termination
AN2898-PSR-104	Single 12-lead ECG	Screening, Day -1, 3, 7 pre-dose and 6 hours post-dose
AN2728- PSR-105	Single 12-lead ECG	Screening, Check-in, 24 hours post-dose, and Study Completion
AN2728- PSR-106	Single 12-lead ECG	Screening, Baseline, and Day 9, and Day 15/Early Termination
AN2728- PSR-204	Single 12-lead ECG	Screening, and Day 1,7,14 and 84/ Early Termination

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Tables 10

Table 37: Assessments of Local Tolerability

Healthy Subjects

Trial	Assessments	Timing of Assessments
AN2728-RIPT-101	Local skin irritation was assessed using an 8-point scale (Table 64). A second scale was used to score effects on superficial layers of the skin (Table 66). Other notations could replace a score to explain inability to assign a score or to add to a score to identify damage to the epidermis and/or spreading of a reaction beyond the application site (Table 67).	Cohort 1: Day 1, after removal of each patch, during the Induction Period (nine times), 4 times during Challenge and, if applicable, 4 times during Rechallenge. Cohort 2: Day 1 and QD for 21 days post Day 1.
Subjects with Atopic Dermatitis		
Trial	Assessments	Timing of Assessments
AN2898-AD-202	Application site reactions (ASR) at the target lesion were classified as one of the following: contact dermatitis (either allergic or irritant); worsening AD, either locally at lesion (target lesion only), or widespread, overall worsening of subject's AD, including non-target lesion(s); or other.	Baseline, Day 14,28 and 42/Early Termination
AN2728-AD-203	Symptoms of burning and stinging were assessed using the burning/stinging assessment scale shown in the second column of Table 65.	Baseline, Day 2, 4, 6, 8, 9, 15, 22, and 29
AN2728-AD-204	The Investigator assessed whether an AE at an application site was beyond the normal variation of AD for	Baseline, Day 8, 15, 22, and 29/End of Treatment

	the subject. If an ASR was identified, information was provided about the nature of the observed reaction.	
AN2728-AD-301 AN2728-AD-302	Symptoms of burning and stinging were assessed using the burning/stinging assessment scale shown in the second column of Table 65.	Baseline, Day 8, 15, 22, 29 and 36/Early Termination
AN2728-AD-303	Symptoms of burning and stinging were assessed using the burning/stinging assessment scale shown in the second column of Table 65.	Screening/ Enrollment, Baseline, every 28 days through Week 48/Early Termination and at off treatment visits

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Table 16

Refer to Section 8.7 for the tolerability scales.

8.4. Safety Results

8.4.1. Deaths

The applicant reported no deaths among subjects enrolled in the development program for EUCRISA (crisaborole) ointment, 2%.

8.4.2. Serious Adverse Events

Phase 3 Pooled Data

In the pooled Phase 3 pivotal trials, a total of 8 subjects (0.8%) in the crisaborole group and 1 subject (0.2%) in the vehicle group reported serious adverse events (SAEs) during the treatment period, Day 1 through Day 29. The majority of subjects who experienced SAEs in the crisaborole group were age 2–11 years (6/8, 75%); the remainder (2/8, 25%) were age 12–17 years. The subject in the vehicle group was in the 2–11 year age range. No subjects who were age ≥ 18 years reported a SAE. The investigators concluded that none of the SAEs in the crisaborole group was related to study treatment while the single event reported in the vehicle group was possibly related to study treatment.

The following is a tabulation of serious adverse events by preferred term and treatment arm. All SAEs were reported by one subject each. However, suicide attempt and suicidal ideation are included in the same system organ class (SOC). Refer to Section 8.4.4 of this review for a

discussion of adverse events related to depression and suicidal ideation.

Table 38: Serious Adverse Events-Trials AN2728-AD-301 and AN2728-AD-302

MedDRA Preferred Term	Age/Sex	Severity	Relationship to study Treatment	Action with Regard to Study Drug	Outcome
AN2728-AD-301					
Crisaborole 2% applied BID					
Kawasaki's disease	2/male	Severe	Unlikely related	Drug withdrawn	Recovered with sequelae
Pneumonia	5/ Female	Severe	Not related	Dose not changed	Not *recovered
Asthma	7/Male	Moderate	Not related	Dose not changed	Recovered
Appendicitis	8/ Female	Severe	Not related	Drug Interrupted	Recovered
Suicide attempt	13/ Female	Severe	Not related	Dose not changed	Recovered
Vehicle applied BID					
Cellulitis	4/ Female	Severe	Possibly related	Dose not changed	Recovered
AN2728-AD-302					
Crisaborole 2% applied BID					
Application site infection	3/Male	Moderate	Unlikely related	Dose withdrawn	Recovered
Laceration	9/ Female	Moderate	Not related	Dose not changed	Recovered
Suicidal ideation	14/ Female	Severe	Unlikely related	Dose not changed	Recovered
Vehicle applied BID					
None					

* Onset of pneumonia was 3 days after the subject had completed the study, so study drug had already been discontinued.
BID: twice daily
MedDRA: Medical Dictionary of Medical Activities.
Source: Adapted from the Applicant's submission 2.7.4 Summary of Clinical Safety, Table 61

Narratives
The following are brief narratives of the Serious Adverse Events (SAEs) which occurred in each

Phase 3 trial. The majority of these events were related to infections and infestations system organ class (SOC) or psychiatric disorders SOC.

AN2728-AD-301
The applicant reported a total of 5 SAEs among the 502 subjects (5/502, 1.0 %) in the crisaborole group compared with 1 SAE among the 252 subjects (1/252, 0.4%) in the vehicle group.

Crisaborole Arm
Subject 109004 (Appendicitis), an 8-year-old white female with no relevant past medical history, experienced an acutely inflamed appendix which was treated with a laparoscopic appendectomy on Day 28 of treatment with crisaborole. While she was hospitalized, the investigational drug was interrupted for two days. After the event resolved, she completed the trial. The Principal Investigator and applicant assessed the onset of appendicitis as not related to study drug.

Reviewer Comment:

I agree with the assessment by the Principal Investigator and applicant that this SAE was unrelated. It is difficult to attribute causality to the study product when the subject resumed treatment with crisaborole without further incident.

Subject 114009 (Kawasaki's disease), a 2-year-old white male with a history of pneumonia, reflux, and 14% BSA affected with AD at Screening experienced fever, abdominal pain, and bloody diarrhea on Day 27 of treatment with crisaborole. His status deteriorated and he developed ascites, pulmonary edema/effusions, and hypotension. The subject was intubated and treated in the pediatric intensive care unit with diuretics, antibiotics, vasopressors, corticosteroids, immunosuppressants, and antihistamines. An echocardiogram was performed which showed coronary artery aneurysms. The subject discontinued participation from the trial and crisaborole was withdrawn. The event resolved with the sequelae of ongoing coronary artery aneurysm. The applicant assessed the event as not related to investigational drug while the Principal Investigator assessed the event as unlikely to be related.

Reviewer Comment:

I agree with the assessment by the Principal Investigator that this SAE was unlikely to be related. Kawasaki's disease generally occurs in children less than 5 years of age (median age 2 years in one study). Associated findings in some studies include antecedent respiratory illness and pre-existing eczema.[11] These factors are more likely to place this subject at risk for Kawasaki's disease than exposure to crisaborole.

[11] Newburger JW et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on

Subject 115018 (Suicide attempt), a 13 year old white female, with no psychiatric history and 7% BSA affected with AD at Screening was hospitalized for a suicide attempt 5 days after discontinuing treatment with crisaborole. See Section 8.5.2 of this review for the full narrative.

Reviewer Comment:

I agree with the assessment by the Principal Investigator, Medical Monitor and applicant that this SAE was unrelated. In view of the half -life of crisaborole (4-5 days) and reports of plausible precipitating events, causality cannot be attributed to crisaborole. See Section 8.5.2 and Section 8.11 for a complete discussion of adverse events in the psychiatry SOC.

Subject 126022 (Pneumonia), a 5-year-old white female with a history of asthma, allergic rhinitis, allergies and 20% BSA affected with AD at Screening, was hospitalized with pneumonia and respiratory syncytial virus and bilateral otitis media (non-serious AE). Prior to the onset of the SAE, the subject experienced pyoderma (moderate, not related), and asthma (moderate, not related). At the time of the event, the subject was taking hydroxyzine, montelukast sodium, salbutamol, and prednisolone. She had recently completed a course of cephalexin for pyoderma. The last scheduled dose of investigational drug was applied prior to the onset of the event; therefore, no action was taken with the investigational drug. The event was ongoing at the end of study, because the subject was still receiving treatment for pneumonia. The Principal Investigator and the applicant assessed the event as not related.

Reviewer Comment:

I agree with the assessment by the Principal Investigator and applicant that this SAE was unrelated. The presence of asthma and exposure to corticosteroids for the treatment of asthma were more significant risk factors for pneumonia. [12]

Subject 146008 (Acute asthma exacerbation), a 7-year-old male of mixed race with a history of asthma, frequent exposure to smoke and 20% BSA affected with AD at Screening , was hospitalized for a moderate adverse event of acute asthma exacerbation. His medical history included asthma and frequent exposure to smoke at home. Concomitant medications at the time of the event were azithromycin, inhaled albuterol and budesonide. The subject was hospitalized and treated with steroids, inhalers, continuous positive airway pressure, and antibiotics. No action was taken with the study drug. The event resolved, and the subject completed the study. The event was assessed by the Principal Investigator and the applicant as not related to study drug,

Reviewer Comment:

Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004;110:2747-2771

[12] Barson WJ. Community-acquired pneumonia in children: Clinical features and diagnosis. UpToDate. Accessed August 25, 2016.

I agree with the assessment by the Principal Investigator and applicant that this SAE was unrelated. Exposure to smoking is a common trigger for asthma. It is difficult to attribute causality to the study product when the subject resumed treatment with crisaborole without further incident.

Vehicle Arm

Subject 114012 (Left ankle cellulitis), a 4-year-old white female with 40 % BSA affected with AD at Screening, experienced left ankle cellulitis on Day 7 of treatment with vehicle. The subject completed a 10-day course of oral cephalexin for a positive Staphylococcus aureus wound culture. However, the infection persisted and subsequently worsened. The subject presented to the emergency room with a red, tender, painful ankle and was admitted for additional treatment with clindamycin. Osteomyelitis was not present on x-ray. No action was taken with the investigational drug. The event resolved, and the subject completed the trial. The Principal Investigator judged the event to be possibly related to investigational drug, because the subject was not receiving treatment for her disease. The Sponsor assessed the event as not related.

Reviewer Comment:

None of the SAEs which occurred in Trial AN2728-AD-301 are clearly related to exposure to crisaborole.

- *The underlying diseases of atopic dermatitis and asthma and the medications used to treat them (parenteral corticosteroids), placed the subjects at risk for infections.*
- *The suicide attempt occurred 5 days after completing the treatment course of crisaborole. The subject targets the onset of her stress as 2 months prior to her suicide attempt.*

AN2728-AD-302

The applicant reported a total of 3 SAEs among the 510 subjects (3/510, 0.6 %) in the crisaborole group compared with none SAE among the 247 subjects (1/247, 0.4%) in the vehicle group.

Crisaborole

Subject 201001 (Multiple lacerations), a 9-year-old black female, was hospitalized for multiple lacerations after being struck by a car. The event resolved and the subject completed the trial. The Principal Investigator and applicant assessed the event as not related to the investigational drug.

Reviewer Comment:

I agree with the Principal Investigator and applicant that this SAE was not related to the study product. The subject resumed the study product without incident.

Subject 222001 (Impetigo at application site), a 3-year-old black male with a history of

molluscum contagiosum and 7% BSA affected with AD at Screening, was hospitalized for impetigo at the application site. At Baseline/Day 1, the subject appeared well but had a temperature of 99.1°F. After three doses of investigational drug, the subject developed pustules localized to the treatment area on the forehead. No other treated areas were affected. Culture results from the pustules were positive for gram positive cocci, Staphylococcus aureus, and Streptococcus pyogenes. The subject was treated with antibiotics and systemic and topical corticosteroids. The investigator withdrew the study drug and discontinued the subject from the trial. The Principal Investigator assessed the event as unlikely related to study drug and the applicant assessed the event as not related.

Reviewer Comment

Due to the mechanism of action, the contribution of the study product to the promotion of infection cannot be excluded. Children with eczema are more likely to experience cutaneous infections due to scratching associated with chronic pruritus.

Subject 233005 (Suicidal ideation), a 14-year-old Hawaiian or other Pacific Islander female with a history of an arachnoid cyst on the brain (diagnosed in April 2012), depression (ongoing since 2013), and bipolar disorder (ongoing since 2013), was hospitalized for suicidal ideation. See Section 8.5.2 of this review for the full narrative.

Reviewer Comment
This SAE is confounded by the presence of other concomitant medications which may have contributed to suicidal ideation. However, because the subject was able to resume the study product without another event of suicidal ideation, causality cannot be attributed to the study product. See Section 8.5.2 and Section 8.11 for a complete discussion of adverse events in the psychiatry SOC.

None of the SAEs which occurred in Trial AN2728-AD-301 are clearly related to exposure to crisaborole.

- *The subject who developed the application site infection, was likely to have been colonized with Staphylococcus aureus at Baseline. The low grade temperature and development of the infection after only 3 doses of the study product, does not support causality related to the study product.*
- *The subject with suicidal ideation experienced a worsening of her bipolar disease 3 days after initiating treatment with crisaborole. Based on the limited systemic exposure of this topical product, it appears unlikely that the exacerbation of her bipolar disease and subsequent suicidal ideation was attributable to the study product.*

Phase 3 Long Term Safety Trial AN2728-AD-303
(Subjects enrolled from Trials AN2728-AD-301 and AN2728-AD-302)

In the long-term open-label safety Trial AN2728-AD-303, 7 subjects reported SAEs. The two subjects who experienced SAEs during the pivotal trials [laceration in AN2728-AD-301 (Subject 201001) and appendicitis in AN2728-AD-302 (Subject 109004)] and subsequently enrolled in Trial AN2728-AD-303 are not included in Table 39. When these 2 subjects are excluded, the incidence of SAEs is in the long-term safety study is 1.4%. The investigators concluded that none of the SAEs was related to the study treatment. All subjects reporting SAEs were <18 years of age at Baseline in the Phase 3 trials. Among the 7 subjects experiencing SAEs, 4 were in the 2-11 year old age group (1.3%) and 3 were in the 12 to 17 year old age group.

Refer to Section 8.4.4 of this review for a discussion of adverse events related to application site reaction, depression and suicidal ideation.

Table 39: Serious Adverse Events-Trial AN2728-AD-303

MedDRA SOC/ Preferred Term	Age/Sex	Severity	Relationship to study Treatment	Action with Regard to Study Drug	Outcome
AN2728-AD-303					
Crisaborole 2% applied BID for 28 days per cycle					
Infections and infestations/ Application site infection 131001	2/Male	Severe	Not related	Dose not changed	Recovered
Infections and infestations/Upper respiratory tract infection 128006	3/Male	Severe	Not related	Dose not changed	Recovered
Nervous system disorders/ CNS ventriculitis 2201053	6/Female	Severe	Not related	Dose not changed	Recovered
Respiratory, thoracic and mediastinal disorders/ Asthma 201051	11/Male	Severe	Not related	Dose not changed	Recovered
Psychiatric disorders/ Suicide attempt 220016	12/Female	Severe	Not related	Dose not changed	Recovered
Psychiatric disorders/	13/Female	Severe	Not related	Dose not	Recovered

Depression 115012				changed	
Immune system disorders/ Anaphylactic reaction 113015	15/Female	Severe	Not related	Dose not changed	Recovered

Source: Adapted from the Applicant's submission 2.7.4 Summary of Clinical Safety, Table 62
SOC: MedDRA System Organ Class

These serious adverse events are summarized in the following brief narratives:

Aged 2–11 years

Subject 128006 (Upper respiratory infection), a 3-year-old black male was admitted to the hospital with fever, cough, tachypnea, and vomiting. The chest x-ray was normal. His physician initiated treatment with inhalation therapy and corticosteroids for a severe upper respiratory tract infection. Investigators took no action with the study drug. The event resolved and the subject completed the trial. The investigator and Medical monitor assessed the event as not related to study drug.

Reviewer Comment:

Upper respiratory tract infections (URI) are the most frequent human illnesses and generally resolve without complications.[13] Children younger than six years of age experience an average of six to eight URIs per year with duration of symptoms up to 14 days. This event resolved, the subject resumed crisaborole and completed the trial. There is no data to support relationship of this common adverse event with the study product. I agree with the investigator and Medical monitor assessed the event as not related to study drug.

Subject 131001 (Superinfection of eczema at application site), a 2-year-old Filipino male with a history of febrile seizures ,upper cleft lip repair, septorhinoplasty and bilateral myringotomy was admitted to the hospital with superinfection of eczema at the application site. His mother applied crisaborole starting 3 days prior to hospitalization for 2 consecutive days, but discontinued administration 2 days prior to hospitalization. The subject had been scratching the treatment site on the right anterior knee. While treating the wound with Neosporin Ointment, the subject developed a fever of 102 F and a tender lesion on the right knee. On evaluation in the emergency room, the subject tested positive for methicillin-resistant Staphylococcus aureus (MRSA). The subject was subsequently admitted to the intensive care unit, and had magnetic resonance imaging of the right, swollen knee, which revealed subcutaneous edema with no osteomyelitis. Treatment for the event included clindamycin, prednisolone, mupirocin, acyclovir, and desonide. Application of the study drug was interrupted by the mother. The

[13] Pappas DE. The common cold in children: Clinical features and diagnosis. UpToDate .Accessed 8/25/2016

event resolved but the subject experienced burning at the application sites and withdrew from the trial. The investigator and Medical Monitor assessed the event as not related to crisaborole.

Reviewer Comment:

Children with eczema are more likely to experience cutaneous infections due to scratching associated with chronic pruritus. Due to the history of scratching at the site of infection, the event was not likely to be related to crisaborole.

Subject 201051 (Asthma exacerbation), an 11-year-old black male with history of asthma and allergic rhinitis was hospitalized for an asthma exacerbation. He was treated with inhalation therapy and the event resolved. No action was taken with study drug because the subject was not currently using study drug at the time of the event (last dose approximately 26 days prior to event). The Principal Investigator and Medical Monitor assessed the adverse event as not related to study drug.

Reviewer Comment:

I agree with the Principal Investigator and applicant that this SAE was not related to the study product. Because the last dose of the study product was 26 days prior to the SAE, there was no reasonable temporal relationship.

Subject 201053 (MRSA ventriculitis), a 6-year-old black female with history of hydrocephalus, spina bifida and ventriculo-peritoneal shunt, was hospitalized with a severe AE of methicillin-resistant *Staphylococcus aureus* (MRSA) ventriculitis. The subject underwent a shunt revision and was treated with antibiotics. The event resolved and the subject was discharged. No action was taken with the study drug in response to the event and the subject completed the trial. The Principal Investigator and Medical Monitor assessed the adverse event as not related to study drug.

Reviewer Comment:

I agree with the Principal Investigator and Medical Monitor that this SAE was not related to the study product. This subject had sufficient pre-disposing factors, a history of hydrocephalus, spina bifida and ventriculo-peritoneal shunt, to account for this SAE.

Aged 12–17 years

Subject 113015 (Anaphylaxis), a 15-year-old white female, with a history of nut allergy was hospitalized for anaphylaxis due to nut ingestion and was treated with dexamethasone, diphenhydramine, and epinephrine. The subject had applied the last dose of crisaborole 2 weeks prior to event. The event resolved and the Principal Investigator and Medical Monitor assessed the adverse event as not related to study drug.

Reviewer Comment:

I agree with the Principal Investigator and applicant that this SAE was not related to the study product. The subject resumed the study product without incident.

Subject 115012 (Exacerbation of depression), a 13-year-old white female was admitted to the hospital for an exacerbation of depression. See Section 8.5.2 of this review for the full narrative.

Reviewer Comment:

I agree with the Principal Investigator and Medical Monitor that the adverse event was not related to study drug. See Section 8.5.2 and Section 8.11 for a complete discussion of adverse events in the psychiatry SOC.

Subject 220016 (Suicide attempt), a 12-year-old black female with a history of being bullied in school due to her AD reported depression and a suicide attempt. After a single crisaborole application following a 24- day non-treatment period, the subject took an overdose of diphenhydramine hydrochloride. See Section 8.5.2 of this review for the full narrative.

Reviewer Comment:

Due to the temporal relationship of the event to exposure to the study product, I agree with the Principal Investigator and Medical Monitor that the adverse event was not related to study drug

In 2014, an estimated 11.4% of the U.S. population aged 12 to 17 experienced at least one major depressive episode in the past year, the prevalence rising sharply from 5.7% at age 12 years to 15.1 % at age 17 years. Females were affected 3 times more frequently than males.[12-month prevalence data for major depressive episode from the National Survey on Drug Use and Health (NSDUH)] Other survey data in the pediatric population age 8 to 15 years indicated a 12-month prevalence of major depressive disorder of 2.7% and any mood disorder of 3.7%.[The Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES)]

Thus, although there is an imbalance in the treatment arms, the incidence of suicidal ideation and behavior in the study population is not greater than the general population.

Phase 1 and 2 Trials

In Phase 1 and Phase 2 trials in the development program, 1 of 985 subjects (0.1%) who received crisaborole had an SAE. A subject with psoriasis who received crisaborole 5% and vehicle (bilateral application) in Trial AN2728-PSR-202 experienced an SAE of drug eruption 3 days after receiving an intramuscular injection of penicillin for symptoms of pharyngitis. The Investigator considered the event possibly related to study drug even though the AE occurred

35 days following the last treatment.

Table 40: Serious Adverse Events in Subjects Who Received Crisaborole, Phase 1 and Phase 2 Clinical Trials

MedDRA Preferred Term/ Subject ID	Age/Sex	Severity	Relationship to study Treatment	Action with Regard to Study Drug	Outcome
AN2728-PSR-202					
Crisaborole 5% and vehicle applied BID					
Drug eruption 01-07	38/male	Severe	Possibly related	Dose not changed	Not Recovered

Source: Adapted from the Applicant's submission 2.7.4 Summary of Clinical Safety, Table 60

Reviewer Comment:

The assessment of causality is confounded by the concurrent use of penicillin which is the more likely etiologic agent for this drug eruption.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The majority of the subjects completed their participation in the Phase 3 trials (crisaborole, 94.0%; vehicle, 86.6%). The most common reasons for early discontinuation from the trials were the following: withdrawn by parent/guardian (crisaborole, 2.5%; vehicle, 7.5%) and AE (crisaborole, 1.2%; vehicle, 1.2%).

Investigators informed subjects and their parents/guardians that they were permitted to discontinue the study drug, withdraw from further study participation at any time and to withdraw consent/assent without penalty or loss of benefits to which they were otherwise entitled. The decision to withdraw subjects from the trial for an abnormal finding or adverse event was based primarily on the Investigator's evaluation of the event. The applicant specified that subjects who experienced a persistent 2-grade worsening of any specific sign of AD assessed in two consecutive visits must be withdrawn from the trials. There were no other pre-specified objective criteria for subject withdrawal. This approach was reasonable because early phase trials and non-clinical data did not identify a safety signal. The most important assessments were related to local safety.

Reviewer Comment:

The Division agreed with the subject withdrawal criteria. Their implementation did not impact the collection or interpretation of the data.

Table 41 provides a summary of the reasons for discontinuation from the pooled dataset (Trial AN2728-AD-301 and AN2728-AD-302.)

Table 41: Summary of Subject Completion/Discontinuation Pooled Dataset

	Pooled Trial AN2728-AD-301 and AN2728-AD-302	
	Crisaborole Ointment, 2% (N=1021)	**Vehicle Ointment (N=506)**
Completed	960 (94.0%)	438 (86.6%)
Discontinued	61 (6.0%)	68 (13.4%)
Reason for discontinuation		
Adverse Event	12 (1.2%)	6 (1.2%))
Lost to Follow-Up	9 (0.9%)	8 (1.6%)
Other	5 (0.5%)	7 (1.4%)
Withdrawal by Parent/Guardian	26 (2.5%)	38 (7.5%)
Withdrawal by Subject	9 (0.9%)	9 (1.8%)

Source: Adapted from Applicant's submission, 2.7.3 Summary of Clinical Efficacy, Table 10

The adverse events that resulted in the discontinuation of subjects from the pivotal Phase 3 trials are listed below. In the crisaborole group, the majority of subjects who withdrew from the trials experienced adverse events related to the application site. In the vehicle group, the most frequent AE leading to trial discontinuation was atopic dermatitis. In both treatment groups, the majority of subjects who discontinued were 2–11 years of age (crisaborole, 10 of 12 subjects; vehicle, 4 of 6 subjects). No subject ≥18 years of age discontinued from the study due to an AE.

Table 42: Subjects Who Withdrew due to Adverse Events-Trials AN2728-AD-301 and AN2728-AD-302

MedDRA Preferred Term/ Subject ID	Age/Sex	Severity	Relationship to study Treatment	Outcome
AN2728-AD-301				
Crisaborole 2% applied BID				
Application site pain 110013	2/Female	Severe	Definitely related	Recovered
Kawasaki's disease 114009	2/Male	Severe	Unlikely related	Recovered with sequelae
Application site pain 149006	3/ Male	Moderate	Definitely related	Recovered
Impetigo 135021	7/Male	Moderate	Possibly related	Not recovered
Pharyngitis 116024	10/ Male	Severe	Unlikely related	Recovered
Application site urticaria 129016	12/Male	Mild	Probably related	Recovered
Application site urticaria 138015	16/ Female	Moderate	Probably related	Recovered
Vehicle applied BID				
Dermatitis atopic 152012	2/ Female	Severe	Possibly related	Not recovered
AN2728-AD-302				
Crisaborole 2% applied BID				
Application site irritation 212024	2/ Female	Mild	Probably related	Recovered
Application site infection 222001	3/Male	Moderate	Unlikely related	Recovered
Application site pain 246005	4/ Male	Mild	Definitely related	Recovered
Eczema 232023	8/ Female	Moderate	Unlikely related	Recovered
Application site rash 247020	10/ Female	Moderate	Probably related	Not recovered
Vehicle applied BID				

MedDRA Preferred Term/ Subject ID	Age/Sex	Severity	Relationship to study Treatment	Outcome
Dermatitis atopic 219016	2/Male	Moderate	Not related	Not recovered
Henoch-Schonlein purpura 239030	5/Female	Moderate	Possibly related	Not recovered
Swelling face 247014	11/Female	Mild	Possibly related	Recovered
Photosensitivity reaction 237012	14/Male	Moderate	Unlikely related	Recovered
Urticaria 210011	15/male	Moderate	Possibly related	Recovered

Source: Modified from Applicant's Table 65, 2.7.4 Summary of Clinical Safety

In addition, 10 subjects (2%) in the safety population who were exposed to crisaborole withdrew from treatment due to an adverse event but did not withdraw from the trial compared with zero subjects who were exposed to vehicle.

In the long-term safety Trial AN2728-AD-303, 9 subjects (3.7%) withdrew from the trial due to AEs. These subjects are listed in

Table 43. Six of the 9 subjects withdrew from the trial due to atopic dermatitis or eczema, and the other 3 discontinued due to AEs involving the application site. Most of these AEs were of moderate severity and related to treatment with EUCRISA ointment. The majority of subjects, 5 of the 9 subjects, who withdrew were 11 years old or younger, 3 subjects were greater than 18 years old and 2 were between the ages of 12 to 17 years.

Table 43: Subjects Who withdrew From the Trial Due to Adverse Events, Long-Term Safety Trial AN2728-AD-303

MedDRA Preferred Term/Subject ID	Age/Sex	Severity	Relationship to study Treatment	Outcome
AN2728-AD-303				
Crisaborole 2% applied BID				
Eczema 106008	2/Male	Mild	Not related	Not recovered
Application site pain	2/Male	Moderate	Possibly	Not

MedDRA Preferred Term/Subject ID	Age/Sex	Severity	Relationship to study Treatment	Outcome
131001			related	recovered
Application site pain 240014	3/ Male	Moderate	Definitely related	Recovered
Dermatitis atopic 210005	6/Male	Moderate	Possibly related	Not recovered
Dermatitis atopic 131005	10/ Female	Severe	Possibly related	Not recovered
Dermatitis atopic 221027	15/Female	Moderate	Definitely related	Not recovered
Dermatitis atopic 131002	21/ Female	Moderate	Probably related	Not recovered
Dermatitis atopic 210032	26/Female	Moderate	Possibly related	Not recovered
Application site dermatitis 107006	46/Female	Moderate	Definitely related	Recovered

Source: Modified from Applicant's Table 66, 2.7.4 Summary of Clinical Safety

In Phase 1 and Phase 2 trials conducted in subjects with atopic dermatitis (AN2728-AD-102, AN2728-AD-203 and AN2728-AD-204) or psoriasis (AN2728-PSR-203 and AN2728-PSR-204), the adverse events that resulted in discontinuation from the trials included application site reactions [pain(2), dermatitis (1), pruritus (1), rash (1) or contact dermatitis (1)] or worsening of the primary condition [AD (1) or psoriasis(2)]. Healthy subjects who were exposed to crisaborole (AN2728-PSR-104 and AN2728-RIPT-101) and withdrawn from the trial due to AEs experienced urticaria (1) and contact dermatitis (2).

Reviewer Comment:

As indicated above, the most common reasons for withdrawal of subjects from the trials were anticipated local effects from the investigational product or insufficient response to treatment (atopic dermatitis).

Treatment discontinuation due to AE

In the pooled Phase 3 Trials AN2728-AD-301 and AN2728-AD-302, 17 subjects discontinued treatment with the investigational product due to an AE but did not withdraw from the trials; there were 15 subjects in the crisaborole group (1.5%) and 2 subjects (0.4%) in the vehicle group. Among the subjects treated with crisaborole, the AEs that led to withdrawal of study

drug were application site pain (6 subjects), application site erythema (2 subjects), and asthma, blepharitis, erythema, application site acne, eczema, atopic dermatitis, and impetigo (1 subject each). Among the subjects treated with vehicle, the AEs that led to withdrawal of study drug were urticaria and eczema. When these subjects are assessed together with those who discontinued the trial due to adverse events then 27/1021 (2.6 %) discontinued crisaborole during the pivotal trials due to adverse events compared with 8/506 (1.6%) who discontinued vehicle.

In the crisaborole group, the majority of the AEs that led to withdrawal/permanent interruption of treatment were considered possibly, probably, or definitely related to study drug. In the vehicle group, only urticaria was considered possibly related to study drug.

In long-term safety Trial AN2728-AD-303, 8 subjects (1.7%) continued to participate in the trial after the investigational product was withdrawn due to an AE. These adverse events included: atopic dermatitis (2 subjects), application site infection (2 subjects), eczema (1 subject), staphylococcal skin infection (1 subject), application site pain (1 subject), and application site folliculitis (1 subject).

Reviewer Comment:

The reasons stated by the applicant for withdrawal of some subjects from the trial do not always reflect the actual cause for withdrawal. For example, some subjects resumed the investigational product after experiencing an AE but subsequently were withdrawn by their parents. These subjects were categorized as withdrawn by the parent not withdrawn due to an adverse event (e.g. Subject 220016 who reported a suicide attempt was withdrawn from the trial by her parents after experiencing ongoing mental health issues).

8.4.4. Significant Adverse Events

The applicant defined significant adverse events as those which resulted in discontinuation from the trials or withdrawal of the investigational product (Discussed in Section 8.4.3) and those related to a set of system organ classes (SOCs) which may represent potential safety signals (Discussed in Section 8.5). Other significant adverse events were those with severe intensity as discussed below.

Severe adverse events were uncommon in the pivotal Phase 3 trials. As presented below in Table 44, severe adverse events were observed in approximately 2% of subjects in the crisaborole group and 1% of subjects in the vehicle group in the pooled pivotal trials.

Table 44: Severity of Adverse Events (Safety Population)

Subjects With:	Trial AN2728-AD-301		Trial AN2728-AD-302		Pooled Trials Trial AN2728-AD-301 Trial AN2728-AD-302	
	Crisaborole Ointment, (N=502)	Vehicle (N=252)	Crisaborole Ointment, (N=510)	Vehicle (N=247)	Crisaborole Ointment, (N=1012)	Vehicle (N=499)
Any TEAEs	147 (29%)	50 (20%)	150 (29%)	79 (32%)	297 (29%)	129 (26%)
Maximum Severity of TEAE						
Mild	77 (15%)	26 (10%)	88 (17%)	44 (18%)	165 (16%)	70 (14%)
Moderate	62 (12%)	20 (8%)	52 (10%)	33 (13%)	114 (11%)	53 (11%)
Severe	8 (2%)	4 (2%)	10 (2%)	2 (1%)	18 (2%)	6 (1%)
Any Serious AEs	4 (1%)	1 (<1%)	3 (1%)	0	7 (1%)	1 (<1%)
Any TEAEs Leading to Discontinuation	7 (1%)	2 (1%)	5 (1%)	4 (2%)	12 (1%)	6 (1%)

Source: Adapted from Applicant's submission pg. 93 of Summary of Clinical Safety

Many of the severe adverse events were reported by one subject each. Among the severe adverse events experienced by more than 1 subject was application site pain which was reported by 8 subjects (0.8%) in the crisaborole group and by no subjects in the vehicle group (0.0%). The table below includes severe adverse events reported by more than one subject in either treatment group.

Table 45: Treatment-Emergent Severe Adverse Events Reported by More Than One Subject in Either Treatment Group through Day 29, Trials AN2728-AD-301 and AN2728-AD-302 (Safety Population)

AN2728-AD-301 and AN272-AD-302 Pooled Trials		
Adverse Event[a]	**Crisaborole 2% BID**	**Vehicle BID**
	N = 1012	N = 499
Application site pain	8 (0.8%)	0
Dermatitis atopic	3 (0.3%)	2 (0.4%)
Pruritus	2 (0.2%)	1(0.2%)
a) By MedDRA preferred term; counts reflect numbers of subjects reporting one or more severe adverse events that map to MedDRA. Subjects were counted once under the greatest reported severity.		

Source: Adapted from Applicant's submission, Table 45

There were no additional significant adverse events identified by this reviewer.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse Events

Treatment-emergent adverse events (AEs) that were reported by ≥1% of subjects in the crisaborole group in the pooled Phase 3 pivotal trials included application site pain, upper respiratory tract infection, pyrexia, nasopharyngitis, vomiting, cough, headache, and oropharyngeal pain. In long-term safety trial AN2728-AD-303, the AEs reported by the greatest proportion of subjects were atopic dermatitis, upper respiratory tract infection, and nasopharyngitis.

Table 46: Treatment-Emergent Adverse Events (TEAE) Reported by ≥1% of Subjects

	Trial AN2728-AD-301		Trial AN2728-AD-302		Pooled Trials Trial AN2728-AD-301 Trial AN2728-AD-302	
System Organ Class / Preferred Term	Crisaborole Ointment, N=502	Vehicle N=252	Crisaborole Ointment, N=510	Vehicle N=247	Crisaborole Ointment N=1012	Vehicle N=499
Gastrointestinal disorders						
Diarrhea	3 (1%)	0 (0%)	6 (1%)	2 (1%)	9 (1%)	2 (<1%)
Vomiting	8 (2%)	3 (1%)	7 (1%)	2 (1%)	15 (1%)	6 (1%)
General disorders and administration site conditions						
Application site pain	31 (6%)	3 (1%)	14 (3%)	3 (1%)	45 (4%)	6 (1%)
Application site pruritus	4 (1%)	3 (1%)	1 (<1%)	3 (1%)	5 (<1%)	6 (1%)
Application site urticaria	2 (<1%)	0 (0%)	0 (0%)	3 (1%)	2 (<1%)	3 (1%)
Pyrexia	12 (2%)	3 (1%)	7 (1%)	4 (2%)	19 (2%)	7 (1%)
Infections and infestations						
Nasopharyngitis	9 (2%)	0 (0%)	9 (2%)	6 (2%)	18 (2%)	6 (1%)
Staph skin infection	0 (0%)	1 (<1%)	1 (<1%)	4 (2%)	1 (<1%)	5 (1%)
Upper resp tract infection	14 (3%)	10 (4%)	16 (3%)	5 (2%)	30 (3%)	15 (3%)
Nervous System disorders						
Headache	5 (1%)	0 (0%)	6 (1%)	1 (<1%)	11 (1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders						
Cough	5 (1%)	1 (<1%)	7 (1%)	7 (3%)	12 (1%)	8 (2%)
Nasal congestion	7 (1%)	0 (0%)	1 (<1%)	2 (1%)	8 (1%)	2 (<1%)
Oropharyngeal pain	4 (1%)	0 (0%)	7 (1%)	2 (1%)	11 (1%)	2 (<1%)
Skin and subcutaneous tissue disorders						
Dermatitis atopic	3 (1%)	2 (1%)	4 (1%)	6 (2%)	7 (1%)	8 (2%)
Eczema	1 (<1%)	0 (0%)	3 (1%)	3 (1%)	4 (<1%)	3 (1%)
Pruritus	2 (<1%)	0 (0%)	4 (1%)	3 (1%)	6 (1%)	3 (1%)

Source: Study Report for Trial AN2728-AD-301 page 243-255, Study Report for Trial AN2728-AD-302 page. 239-251 and Table 42 Summary of Clinical Safety page 95

Adverse Reactions

In the pooled pivotal trials, the majority of the adverse reactions were from the following SOCs: General disorders and Administration Site Conditions, Skin and Subcutaneous Tissue Disorders and Infections and Infestations. Among these adverse reactions, only application site pain was reported by ≥1% of subjects in the crisaborole group and greater than the vehicle group (crisaborole, 4.4% of subjects; vehicle, 1.2% of subjects; p = 0.001). The MedDRA preferred term of "application site pain" captured various verbatim terms describing a stinging and burning sensation or pain at the application site.

Table 47: Treatment-Emergent Adverse Events from Trials AN2728-AD-301 and AN2728-AD-302 with the Relationship to the Study Drug (Safety Population)

	Trial AN2728-AD-301		**Trial AN2728-AD-302**		**Pooled Trials Trial AN2728-AD-301 Trial AN2728-AD-302**	
	Crisaborole N=502	Vehicle N=252	Crisaborole N=510	Vehicle N=247	Crisaborole N=1012	Vehicle N=499
Subjects with AEs	147 (29.3%)	50 (19.8%)	150 (29.4%)	79 (32.0%)	297 (29.3%)	129 (25.9%)
Subjects with SAEs	4 (0.8%)	1 (0.4%)	3 (0.6%)	0	7 (0.7%)	1 (0.2%)
Subjects D/C due to AE	7 (1.4%)	2 (0.8%)	5 (1.0%)	4 (1.6%)	12 (1.2%)	6 (1.2%)
Relationship to Study Drug						
Not related	78 (15.5%)	29 (11.5%)	100 (19.6%)	55 (22.3%)	178 (17.6%)	84 (16.8%)
Unlikely	21 (4.2%)	9 (3.6%)	24 (4.7%)	11 (4.5%)	45 (4.4%)	20 (4.0%)
Possible	11 (2.2%)	5 (2.0%)	7 (1.4%)	8 (3.2%)	18 (1.8%)	13 (2.6%)
Probable	16 (3.2%)	3 (1.2%)	5 (1.0%)	4 (1.6%)	21 (2.1%)	7 (1.4%)
Definite	21 (4.2%)	4 (1.6%)	14 (2.7%)	1 (0.4%)	35 (3.5%)	5 (1.0%)

Source: Adapted from the applicant's Table 41, 2.7.4 Summary of Clinical Safety

Table 48: Adverse Reactions Reported by at Least 0.5 Percent of Subjects in At Least One Treatment Group

System Organ Class Preferred Term	**Crisaborole N=1012**	**Vehicle N=499**
General disorders and administration site conditions	56 (5.5%)	13 (2.6%)
Application site pain	45 (4.4%)	6 (1.2%)
Application site pruritus	4 (0.4%)	4 (0.8%)
Infections and infestations	9 (0.9%)	3 (0.6%)
Skin and subcutaneous tissue disorders	10 (1.0%)	9 (1.8%)
Dermatitis atopic	5 (0.5%)	4 (0.8%)

Source: Modified from applicant's Table 14.3.1.1.8.3, ISS

8.4.6. Laboratory Findings

The results of the analysis of the laboratory data indicated that a similar percentage of subjects in both treatment arms had a shift from a normal value at baseline to a level above or below normal at Day 29.

8.4.7. Vital Signs

Results of the vital signs assessments are similar across treatment visits. A similar percentage of subjects in both treatment arms had a shift from a normal value at baseline to a level above or below normal at Day 29.

Subgroup Analysis
The most important subgroup analysis for a product indicated for the treatment of atopic dermatitis is age group. The median and mean vaues for systolic and diastolic blood pressure, temperature and pulse were similar across treatment arms in all age groups. Generally, subjects whose parameters were beyond the normal range at baseline remained outside the normal range.

8.4.8. Electrocardiograms (ECGs)

The applicant conducted cardiac safety monitoring during multiple trials throughout the development program as summarized in Table 36. In addition, the applicant conducted a thorough QT Study (AN2728-TQT -108) which is discussed in Section 8.4.9.

During the pivotal Phase 3 trials (AN2728-AD -301 and AN2728-AD -302), 12-lead ECGs were performed at Baseline and Day 8 in a subset of subjects at 56 selected sites across the 2 trials. A total of 695 subjects (330 male, 365 female) were randomized, received at least one dose of study drug and had ECG data. The distribution by age group was as follows: 459 subjects age 2-11 years, 159 subjects age 12-17 years and 77 subjects age ≥18 years. Among these subjects, 462 applied crisaborole (308 subjects age 2-11 years, 99 subjects age 12-17 years and 55 subjects age ≥18 years) while 233 applied vehicle (151 subjects age 2-11 years, 60 subjects age 12-17 years and 22 subjects age ≥18 years).

The ECG safety population, defined as all subjects who had both Baseline and Day 8 ECGs, included 615 subjects. The distribution by age group is summarized in

Table 49: ECG safety population

Crisaborole: Subjects with Baseline and Day 8 ECGs						
Males			Females			Total
2-11 years	12-17 years	≥ 18 years	2-11 years	12-17 years	≥ 18 years	
139	34	17	140	56	30	416
Vehicle: Subjects with Baseline and Day 8 ECGs						
72	24	7	60	25	11	199
Totals (All subjects with Baseline and Day 8 ECGs): 615						

Source: Modified from the Cardiovascular Safety Report Table 2 page 20

The results indicated that 2 subjects in the crisaborole group age ≥ 18 years had QTcF values in the range of >450 to ≤480 msec (0.5% of all subjects in the crisaborole group.) In addition, 5 subjects age 2-11 years and 5 subjects age 12-17 years on crisaborole had increases of QTcF of >30 to ≤60 msec. However, investigators observed no subjects with QTcF >480 msec and no change of QTcF values >60 msec.

Brief narratives of subjects in the crisaborole group with QTcF values >450 to ≤480 msec

- **Subject 227022** was a 79 year old white female with a history of atopic dermatitis since 1940, seasonal allergies, arthritis, hypertension, left bundle branch block, and obesity. Her concomitant medications included lisinopril. She reported no adverse events. At Baseline her QTcF value was 455 msec and at Day 8 her QTcF value was 458 msec.
- **Subject 223008** was a 64 year old black male with a history of atopic dermatitis and arthritis in his left shoulder. His concomitant medications included Tylenol with codeine. He reported no adverse events. At Baseline his QTcF value was 435 msec and at Day 8 his QTcF value was 462 msec.

The Division consulted with the QT Interdisciplinary Review Team (QTIRT) team to review the ECG data from the Phase 3 trials and provide an assessment of the cardiovascular safety of this drug product and recommendations regarding labeling if needed. QT-IRT comments for DDDP included the following:

> "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. ECG monitoring in Phase 3 trials is not adequate for QT assessment (or ruling out clinically relevant QT effect)." (Review by Jiang Liu dated 4/20/2016.)

Refer to Section 4.5.2 for the QTIRT team labeling recommendations.

8.4.9. QT

The Division recommended that the sponsor conduct a Thorough QT (TQT) trial with their proposed topical product because the results of pre-clinical safety pharmacology studies indicated that crisaborole was a low-potency hERG-channel blocker and the product was an NME with some systemic absorption. (EOP2 meeting Minutes dated 3/6/2014.) On 10/12/2012, the applicant submitted a TQT protocol for review by the Interdisciplinary Review Team (IRT) entitled,

> "A Randomized, Parallel Study of the Effects of AN2728 Topical Ointment, 2% on QT/QTc Intervals Compared to Vehicle and Moxifloxacin Positive Control in Healthy Subjects" (AN2728-TQT-108)

The primary objective of the trial was to evaluate the electrocardiogram (ECG) effects of crisaborole compared to vehicle following of twice daily administration to 30% or 60% BSA.

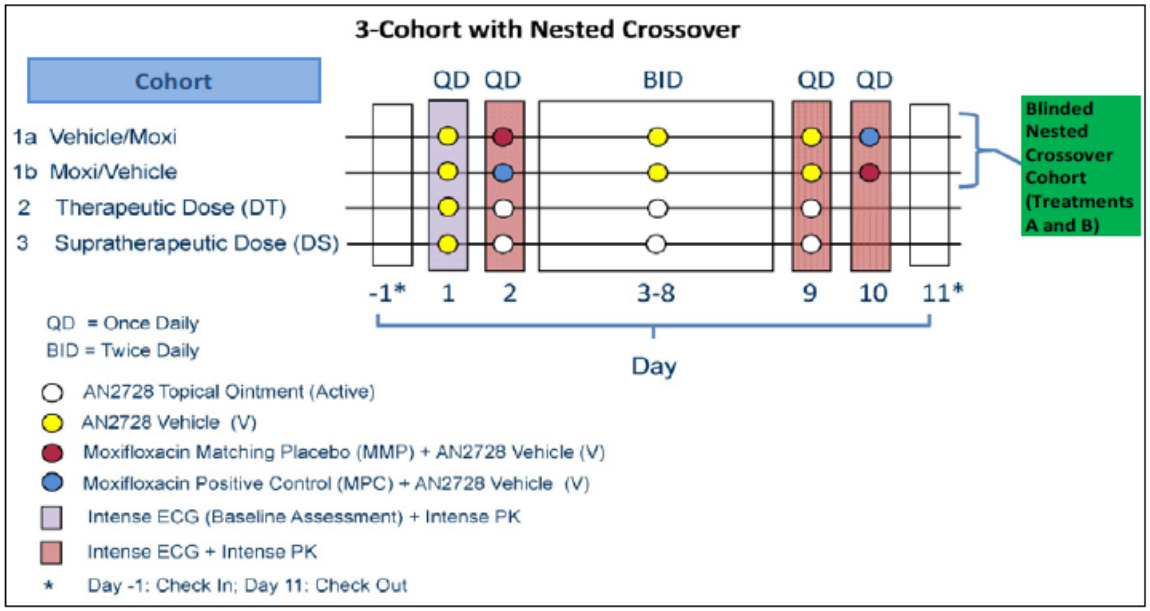
This was a single-center, randomized, parallel-cohort nested crossover trial in 180 healthy adult male and female subjects. Subjects were randomized to 1 of 3 cohorts in a 1:1:1 ratio. The randomization of subjects was stratified by gender to ensure adequate representation of males and females within each cohort. Investigators administered the following drug products:

- **V** = Vehicle ointment
- **MMP** = Moxifloxacin Matching Placebo
- **MPC** = Moxifloxacin Positive Control (400 mg)
- **DT** = Therapeutic Dose (15 g) of crisaborole ointment, 2%, applied to designated treatment areas (representing approximately 30% of BSA)
- **DS** = Supra-therapeutic Dose (45 g) of crisaborole ointment, 2%, applied to designated treatment areas (representing approximately 60% of BSA)

Cohort 1, the nested crossover cohort, was a vehicle- and positive-control cohort. Subjects enrolled in this cohort were further randomized to 1 of 2 blinded sequences (Cohorts 1a and 1b) which were used to assess assay sensitivity. Subjects enrolled in **Cohort 2 (60 subjects)**, received vehicle on Day 1 followed by 8 days of therapeutic doses (DT-15 g) of crisaborole applied to approximately 30% BSA (QD on Days 2 and 9 and BID on Days 3–8). Subjects enrolled in **Cohort 3** (60 subjects) received vehicle on Day 1 followed by 8 days of a supra-therapeutic dose (DS-45 g) of crisaborole applied to approximately 60% BSA. Investigators collected 12-lead ECGs from continuous 24-hour Holter monitor data. At Days 1, 2, 9, and 10, triplicate cardiodynamic ECGs were recorded at the following timepoints: Hour 0 (prior to dosing) and at Hours 0.5, 1, 2, 3, 4, 5, 6.5, 8, 10, 12, 15, and at approximately 23.5 hours postdose.

The primary endpoint was the vehicle-corrected change from baseline in QTcF (ΔΔQTcF) on Day 9.

Table 50: Trial AN2728-TQT-108-three cohort with nested crossover design



Source: Applicant's submission-Section 2.7.4 Summary of Clinical Safety, Figure 2

Results

Among the 180 subjects who enrolled, 175 subjects (78 females and 97 males) completed the trial (97%). The majority or the subjects were male (54%), White, Hispanic/Latino (87%) with a mean age of 33 years (range 18 to 45 years) and a mean weight of 69 kg. The demographic characteristics were similar across cohorts.

Most of the subjects who discontinued the trial were from Cohort 1 (4/5) and did not receive crisaborole. Two subjects withdrew due to AEs (mild vomiting possibly related to moxifloxacin and anxiety related to confinement) and 2 subjects withdrew consent. One subject in Cohort 3 who received only vehicle discontinued due to AEs (application site pain, feeling cold, and generalized pruritus assessed as mild in severity and probably/possibly related). Overall, three subjects discontinued the trial due to adverse events (2%) and 2 subjects withdrew consent (1%).

Among the 119 subjects who were exposed to crisaborole, all subjects applied 14 doses. However, total exposure during the trial ranged from 210g to 610g as documented below.

Table 51: Summary of Exposure to Crisaborole in Trial AN2728- TQT-108

Crisaborole 2% or Vehicle (N = 180)	
No. of subjects exposed to crisaborole	119
No. of applications	
Mean (SD)	14(0)
Median	14
Min/ max	14/14
Total study drug usage (g)	
Mean (SD)	418 (210)
Median	210
Min/ max	210/630

Source: Modified from Applicant's table, Summary of Clinical Safety Table 20

Key findings

Plasma Concentration Results

The plasma concentrations in the TQT trial (AN2728-TQT-108) enrolling healthy adult subjects were less than those observed in the pharmacokinetic trial conducted under maximal use conditions enrolling pediatric subjects with atopic dermatitis (AN2728-AD-102). The table below presents the mean Cmax values (±SD) for all subjects in the pharmacokinetic trial compared with subjects assigned to the supratherapeutic dose group in the TQT trial. Per FDA advice, the applicant performed additional analyses of this data to further explore the potential for QT interval prolongation at drug concentrations that might potentially be achieved in patients with AD. The applicant evaluated data from subjects in the TQT trial whose C_{max} values exceeded the mean C_{max} observed in subjects with AD in the pharmacokinetic trial and observed no correlation between Cmax and QTcF data in those subjects. They concluded that multiple applications of crisaborole at therapeutic doses (15 g) and supra-therapeutic doses (45 g) did not prolong the QTcF interval.

Table 52: Mean Maximum Plasma Concentration Results from MUSE (AN2728-AD-102) and TQT (AN2728-TQT-108) Trials

	MUSE (Pediatric subjects with Atopic Dermatitis, 2-17 years) (AN2728-AD-102) 27% - 92% BSA		TQT (Healthy Adult Subjects) (AN2728-TQT-108) 60% BSA	
Crisaborole PK Parameter	Day 1 (N = 34)	Day 8 (N = 34)	Day 2 (N=59)	Day 9 (N=59)
Mean Cmax in ng/mL (SD)	111 (113)	127 (196)	56.4 (26.3)	87.4 (29.6)

Source: Modified Applicant's Table 15, 2.7.2 Summary of Clinical Pharmacology Studies page 77.

QTIRT Comment

Per QTIRT Review by Qianyu Dang (5/20/2014), no subject had a QTcF above 480 msec. In addition, the results of a categorical analysis indicated that no subject had a change from baseline above 60 ms. For a substantive discussion of this issue refer to the Clinical Pharmacology review by Chinmay Shukla, PHD.

Safety

There were no deaths or serious adverse events which were reported in this trial. A total of 111 subjects (62%) reported 327 treatment-emergent adverse events (TEAEs). The majority of the adverse events were mild (270/327, 83%) and the remainder (57/327, 17%) were moderate. The incidence of adverse events was similar in the therapeutic dose group (53%) and supra-therapeutic dose group (60%) and significantly higher than the vehicle group. Overall, the most commonly reported adverse event was contact dermatitis, primarily attributable to ECG electrode placement, followed by headache and application site pruritus.

QT-IRT Team discussion and conclusion

QT-IRT reviewer Jiang Liu, PhD., provided the following comments regarding the QT assessments:

> "The thorough QT study demonstrates that no significant QTc prolongation effect of crisaborole at a dose of 2% crisaborole ointment up to 45 g/day (designated treatment areas which represented ~ 60% of body surface area (BSA)); however the highest concentration in the TQT study was <180 ng/mL (with mean steady state Cmax of 87.4 ng/mL at the 45 g/day dose). In the MUSE pediatric AD study (AN2728-AD-102), the mean crisaborole C_{max} of 205 ng/mL was observed in the group of subjects of age 6 to 11 years old (with highest C_{max} value of 1,170 ng/mL). Although according to the sponsor, no safety signals were noted upon review of treatment emergent AEs in those subjects, the effect of crisaborole on the QTc interval in those patients cannot be reliably predicted based on currently available preclinical and clinical information." (Review dated 4/20/2016)

In another review, Jiang Liu, PhD., concluded:

1. "Although the TQT study was negative at the doses/exposures evaluated and there was no evidence of a crisaborole-QTc relationship, the limitation of the study is the exposures achieved do not cover the clinical exposures to crisaborole in patients enrolled in the phase 3 clinical trials.
2. The applicant submitted safety ECGs collected at baseline and Day 8 in in the two Phase 3 trials as supportive evidence that there are no effects on the QTc interval. We agree that there are no findings in these limited safety ECGs based on categorical analysis of the QTc intervals—no subjects had QTcF >480 ms or a change in QTcF from baseline >30

ms. These data, however, cannot be used to exclude a mean increase in QTc interval around the regulatory threshold (<10 ms) per the ICH E14 guidelines.

3. Based on the totality of clinical data presented in the cardiac safety report and TQT study, there is no evidence that crisaborole has a clinically meaningful effect on the QTc interval, and we are not recommending that the applicant performs any additional QT assessments.
4. With regards to the label, we recommend that the description of the TQT study acknowledges the limitation in dose/exposure."(Review dated 8/2/2016)

Refer to Section 4.5.2 for the QTIRT team labeling recommendations.

Reviewer Comment:

This reviewer does not recommend that the applicant conduct an additional TQT trial for several reasons. First, data from the TQT trial and all trials which included ECG monitoring did not indicated a cardiovascular safety signal. Second, this proposed product is not indicated for patients with BSA > 60 affected with AD which represents severe disease. Third, because this product has a modest treatment effect, patients with a BSA > 60 affected with AD are less likely to be treated with this product.

8.4.10. Immunogenicity

As the proposed product is not a therapeutic protein, the potential for immunogenicity was not anticipated or assessed.

8.5. Analysis of Submission-Specific Safety Issues

The applicant identified a set of system organ classes (SOCs) to evaluate for potential safety signals. These SOCs were selected because they included adverse events of special interest. The adverse events were identified based on the underlying disease, the mechanism of action and potential previous exposure to other therapeutic products indicated for atopic dermatitis such as topical corticosteroids. 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. The applicant also evaluated immunosuppression and the risk of systemic or cutaneous infections or neoplasms and local cutaneous effects.

Reviewer Comment:

Phosphodiesterases are grouped into families which have slightly different functions and tissue specificity. The PDE-4 isoenzyme is distributed in the brain, leukocytes, skeletal, visceral and vascular muscles and testes. Thus, the predictable effects are related to inflammation, vascular and visceral muscle tone, depression, and reproduction. [14]Although systemic exposure is limited

after topical application, the threshold concentration needed to induce these effects is not known.

The applicant evaluated the adverse events of special interest according to SOC and selected some preferred terms such as upper respiratory infection or nasopharyngitis for separate analysis. However, the applicant did not evaluate the adverse reaction of weight loss which is associated with exposure to PDE-4 inhibitors [OTEZLA® (apremilast) tablets labeling].

8.5.1. Gastrointestinal Disorders

In the pooled pivotal Phase 3 trials, 2.7% of subjects in the crisaborole group and 2.4% of subjects in the vehicle group reported AEs mapping to the gastrointestinal disorders SOC (See Section 8.6 below). No subjects reported SAEs related to the gastrointestinal system.
In long-term safety trial AN2728-AD-303, 8.5% of subjects reported AEs mapping to the gastrointestinal disorders SOC. The preferred terms which were most frequently documented by investigators were vomiting (2.9% of subjects), diarrhea (2.3%), and nausea (1.4%) (AN2728-AD-303 CSR, Table 14.3.1.1.3). As expected, the age group reporting symptoms of vomiting and diarrhea at the highest rate was the 2-11 year old age group. See Table 53.

Table 53: Selected Gastrointestinal System Adverse Events by Age

Crisaborole Ointment, 2%				
Age				
Dictionary Derived Term	2-6 Years	7-11 Years	12-17 Years	18 Years and Older
Abdominal pain upper	1 (0.10%)	1 (0.10%)	1 (0.10%)	0 (0.00%)
Vomiting	9 (0.89%)	7 (0.69%)	1 (0.10%)	0 (0.00%)
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain	0 (0.00%)	1 (0.10%)	0 (0.00%)	0 (0.00%)
Diarrhea	7 (0.69%)	3 (0.30%)	0 (0.00%)	0 (0.00%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	3 (0.30%)	1 (0.10%)	0 (0.00%)	1 (0.10%)
Vehicle				

[14] Moustafa, F and Feldman, S R. A Review of phosphodiesterase-inhibition and the potential role for phosphodiesterase 4-inhibitors in clinical dermatology. Dermatology Online Journal, 20(5).2014.

Age				
Dictionary Derived Term	2-6 Years	7-11 Years	12-17 Years	18 Years and Older
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
Vomiting	3 (0.60%)	1 (0.20%)	1 (0.20%)	0 (0.00%)
Abdominal discomfort	0 (0.00%)	1 (0.20%)	0 (0.00%)	0 (0.00%)
Abdominal pain	1 (0.20%)	0 (0.00%)	0 (0.00%)	1 (0.20%)
Diarrhea	1 (0.20%)	0 (0.00%)	1 (0.20%)	1 (0.20%)
Dyspepsia	0 (0.00%)	1 (0.20%)	0 (0.00%)	0 (0.00%)
Nausea	1 (0.20%)	0 (0.00%)	0 (0.00%)	1 (0.20%)

Source: Reviewer's Table

8.5.2. Psychiatric Disorders

In the pooled Phase 3 pivotal trials, adverse events (AEs) in the psychiatric disorders SOC were reported in 0.6% of subjects treated with crisaborole and 0.2% of subjects treated with vehicle. Among 1527 subjects in the safety population, 6 subjects in the crisaborole group and 1 subject in the vehicle group reported adverse events in the psychiatric disorders system organ class (SOC). These adverse events are summarized in Table 54. No subjects 18 years of age or older reported psychiatric events.

Table 54: Adverse Events in the Psychiatric SOC by Preferred Term in the Pooled Phase 3 Trials AN2728-AD-301 and AN2728-AD-302

System Organ Class SOC/ Preferred Term	Crisaborole	Vehicle
Psychiatric Disorders		
Agitation	1 (0.10%)	0 (0.0%)
Anxiety	1 (0.10%)	0 (0.0%)
Confusional State	1 (0.10%)	0 (0.0%)
Depression*	3 (0.30%)	0 (0.0%)
Insomnia	0 (0.0%)	1 (0.2%)
Listless	1 (0.10%)	0 (0.0%)
Suicidal Ideation	1 (0.10%)	0 (0.0%)
Suicide Attempt	1 (0.10%)	0 (0.0%)
Totals	1012	499

Source: Reviewer's Table, JReview confirms findings by Jean Kim, MD
Note: Some subjects reported more than one adverse event.

* Difference is non-significant (p=0.56; 2-tailed Fishers exact test.

Among 517 subjects enrolled in the long term safety Trial AN2728-AD-303, 12 subjects (2.3%) who were treated intermittently with crisaborole reported adverse events in the psychiatric disorders system organ class (SOC). These adverse events are summarized in Table 55. Only one of these 12 subjects was 18 years of age or older.

Table 55: Adverse Events in the Psychiatric SOC by Preferred Term in Phase 3 Trial AN2728-AD-303

System Organ Class SOC	Preferred Term	Subjects N (%)
Psychiatric Disorders	Anxiety	2 (0.39%)
	Attention deficit/hyperactivity disorder	4 (0.77%)
	Depression	4 (0.77%)
	Insomnia	2 (0.39%)
	Suicidal Ideation	1 (0.19%)
	Suicide Attempt	1 (0.19%)

Source: Reviewer's Table, JReview confirms findings by Jean Kim, MD
Note: Some subjects reported more than one adverse event.

Serious Adverse Events (SAEs) and Suicidal Ideation and Behaviors (SIBs) Compared with Systemic Exposure

In the following tables, the cases involving SAEs related to psychiatric disorders and suicidal ideation and behaviors (SIBs) are summarized in association with the available exposure data. The range of exposures varied widely. Greater exposure did not correlate with reports of significant AEs in the psychiatric disorders SOC.

Table 56: Serious Adverse Events (SAEs) Related to Psychiatric Disorders

Trial	Serious Adverse Event	Subject Number	Event Date	%BSA	Total Amount Used/ No. Applications
AN2728-AD-301	Suicide attempt	Subject 115018	Day 27	Baseline: 7%	During 301: 23 g 42 applications 0.55 g/application
AN2728-AD-302	Suicidal ideation	Subject 233005	Day 20	Baseline: 9%	During 302: 226.8 g 52 applications 4.4 g/application
AN2728-AD-303	Depression	Subject 115012*	Day 159,229,258 **	Baseline: 12%	During 303: 1012.8 g

Trial	Serious Adverse Event	Subject Number	Event Date	%BSA	Total Amount Used/ No. Applications
					467 applications 2 2 g/application
AN2728-AD-303	Suicide attempt	Subject 220016	Day 198 **	Baseline: 18%	During 303: 1144 g 327 applications 3.5 g/application

Source: Data from Psychiatry Review by Jean Kim, MD dated 6/23/2016 and exposure data provide by the Statistical Reviewer, Matthew Guerra, PhD
*Depression was considered an SAE because treatment included hospitalization.
**From entrance into the first trial (Subject 115012 entered AN2728-AD-301 and Subject 220016 entered AN2728-AD-302 first then enrolled in AN2728-AD-303)

Table 57: Suicidal ideation and behavior (SIB)

Trial	Serious Adverse Event	Subject Number	Event Date	%BSA	Amount Used/ No. Applications
AN2728-AD-301	Suicide attempt	Subject 115018	Day 27	Baseline: 7%	During 301: 23 g 42 applications 0.55 g/application
AN2728-AD-302	Suicidal ideation	Subject 233005	Day 20	Baseline: 9%	During 302: 226.8 g 52 applications 4.4 g/application
AN2728-AD-303	Suicidal ideation	Subject 204041	Day 52	Baseline: 5%	During 303: 621.2 g 349 application 1.8 g/application
AN2728-AD-303	Suicide attempt	Subject 220016	Day 198	Baseline:18%	During 303: 1144 g 327 applications 3.5 g/application
AN2728-AD-202	0	0	0		
AN2728-AD-204	0	0	0		

Source: Data from Psychiatry Review by Jean Kim, MD dated 6/23/2016 and exposure data provide by the Statistical Reviewer, Matthew Guerra, PhD

Reviewer's comment

Because no pharmacokinetic data was collected during the Phase 3 trials, the actual systemic exposure to the topical application of crisaborole is not known for this group of subjects.

Narratives

The following narratives provide additional information regarding the subjects who reported SAEs and the SIBs as tabulated above.

AN2728-AD-301

Subject 115018 (*Suicide attempt*), a 13 year old white female, with no psychiatric history and 7% BSA affected with AD at Screening was hospitalized for a suicide attempt 5 days after discontinuing treatment with crisaborole. The subject had reported a 2 month history of stress due to transitioning to high school and took eight 0.5 mg lorazepam tablets (total dose of 4 mg), four 325 mg acetylsalicylic acid tablets (total dose of 1300 mg), and two 200 mg ibuprofen pills (total dose of 400 mg). The subject was diagnosed with depression and discharged after 6 days on Prozac. The event of suicide attempt resolved, and the AE of depression was reported as ongoing. The subject was withdrawn from the trial by her parents. The investigator took no action with regard to the investigational drug. The Principal Investigator, applicant and Medical Monitor assessed the event as not related to the investigational drug.

Reviewer's comment
The subject completed 42 applications of crisaborole and discontinued the study product 5 days prior to the suicide attempt. The timing alone supports the conclusion by the applicant that the adverse event of suicide attempt was not related. The investigators continued to evaluate the severity of her atopic dermatitis as moderate and the lack of treatment success may be associated with her behavior. The psychiatry consultant assessed this adverse event of suicidal ideation and behavior as "unlikely" related to crisaborole.

AN2728-AD-302

Subject 233005 (*Suicidal ideation*), a 14-year-old Hawaiian or other Pacific Islander female with a history of an arachnoid cyst (diagnosed in April 2012), depression (ongoing since 2013), and bipolar disorder (ongoing since 2013), was hospitalized for suicidal ideation. Three days after initiating study drug, the subject reported worsening bipolar disorder which was treated with lorazepam. Approximately 16 days later, the subject reported suicidal ideation. At the time of the suicidal ideation, the subject was taking the following concomitant medications: lorazepam and lamotrigine. She was hospitalized and treated with quetiapine and a reduced dose of dose of lamotrigine (150 mg to 75 mg). The investigator took no action with regard to the investigational drug. The event resolved, and the subject completed the trial. The Principal Investigator assessed the event as unlikely related to study drug and the applicant assessed the event as not related.

Reviewer's comment
Among the subjects with suicidal ideation or an SAE of depression, this subject applied the largest dose of crisaborole per application. However, worsening bipolar disorder was reported after only 3 days of treatment. After topical application, steady state is achieved within 4–6 days (AN2728-AD-203). The investigators continued to evaluate the severity of her atopic dermatitis as moderate and the lack of treatment success may be associated with her behavior. The evaluation of the adverse event of suicidal ideation is confounded by the concomitant use of lamotrigine which may increase the risk of suicidal thoughts or behavior in patients taking these drugs per labeling. The psychiatry consultant assessed this adverse event of suicidal ideation and behavior as "possibly" related to crisaborole. In her clinical experience, she has not observed an increase in SIB with exposure to lamotrigine.

AN2728-AD-303
Subject 115012 (Exacerbation of depression), a 13-year-old white female was admitted to the hospital for an exacerbation of depression. She was initially diagnosed with moderately severe, depression approximately 3 months earlier while using crisaborole. The initial adverse event of depression was judged to be unrelated to the study product. Prior to the initial diagnosis she applied crisaborole intermittently for 5 months. The subject was not treated with medication for the initial diagnosis of depression. The depression worsened in severity, and 5 days after initiating another cycle of crisaborole she required inpatient management for depression. She was treated with fluoxetine during a one-month hospitalization, and was discharged on fluoxetine, melatonin, trazodone, and ziprasidone. Adverse events related to depression were reported on Day 159, 229 and 258. Concomitant medications initiated during the trial included ethinyl estradiol for menstrual irregularities. The investigators took no action with regard to the study drug and the subject completed the trial. The Principal Investigator and Medical Monitor assessed the adverse event as not related to study drug. The Principal Investigator described the event as "situational depression" caused by family issues.

Reviewer's comment
During trial AN2728-AD-301, the subject was assigned to treatment with vehicle ointment. She initiated crisaborole periodically starting on July 24, 2014 in trial AN2728-AD-303. The subject had 12% BSA at baseline and applied a total of 467 doses of crisaborole during intermittent 28-Day cycles. Due to the onset of depression after such a long duration of exposure to crisaborole (4 of 5 months on treatment), the causality is unlikely. The role of ethinyl estradiol in the course of her depression is unclear. The psychiatry consultant assessed this adverse event of depression as "unlikely" related to crisaborole.

Subject 220016 (Suicide attempt), a 12-year-old black female with a history of being bullied in school due to her AD, reported depression and a suicide attempt. The subject applied crisaborole intermittently for approximately 6 months prior to the event. After a single crisaborole application following a 24- day non-treatment period, the subject took an overdose

of diphenhydramine hydrochloride on Day 198. In the emergency room, the subject was diagnosed with depression, treated with observation and counseling and prescribed Trazadone. She was released from the emergency room on the same day. The investigator did not discontinue the study product. However, her parents withdrew the subject from the trial 32 days later. The applicant noted that the completed suicide of another student at her school within the previous year continued to impact the subject. The Principal Investigator and Medical Monitor assessed the adverse event as not related to study drug.

Reviewer's comment
The subject completed 327 applications of crisaborole during intermittent 28-Day cycles. She had not used the study product for approximately 24 days and then applied a single dose prior to the suicide attempt. The timing alone supports the conclusion by the applicant that the adverse event of suicide attempt was not related. At baseline the subject had 18% BSA of involvement with AD which worsened to 30% BSA during the first 28 days while she was treated with vehicle. The severity of her AD and the need for ongoing treatment may have contributed to her suicidal behavior. The psychiatry consultant assessed this adverse event of suicidal ideation and behavior as "possibly" related to crisaborole.

Subject 204041 (*Suicidal ideation*), a 13-year-old white female with no history of depression or other psychiatric diagnosis wrote a suicide note on Day 52. The subject was referred for counseling but received no medication.

Reviewer's comment
The subject had 5% BSA at baseline and completed 349 applications of crisaborole during intermittent 28-Day cycles. The applicant provided no narrative regarding this case because it was not assessed as an SAE. The patient profile indicates that the subject reported no concomitant medications at baseline and that her disease severity remained moderate at the completion of the first 28 day treatment cycle. There is insufficient data to evaluate this adverse event. The psychiatry consultant assessed this adverse event of suicidal ideation as "unassessible" due to lack of information

Comparison with epidemiologic data
The applicant compared the prevalence of psychiatric disorders observed in their study population with other pediatric populations. Survey data from adolescents in the United States from 2010 and 2011 indicated a 1-year prevalence of major depression of 8% (Bonin et al, UpToDate . 2015). Other survey data from 2001, 2003, 2005, and 2007, indicated that approximately 7-9% of adolescents had attempted suicide in the previous 12 months (Kennebeck et al, UpToDate ,2015). The applicant stated that rates of suicidal ideation in patients with eczema are even higher than those without eczema according to one author (15.5% versus 9.1%). In the subpopulation with both eczema and itch, the prevalence of suicidal ideation was 23.8% (Halvorsen et al, 2014; survey data in a population age 18-19 years). These

rates of psychiatric disorders far exceed those observed among crisaborole treated subjects in the trials. Therefore, the applicant concludes that exposure to crisaborole is not associated with excess risk for psychiatric disorders.

Reviewer Comment:

In a more recent evaluation of mental health disorders in the pediatric population with AD using a large population-based survey of 91,642 children up to 17 years of age in the United States, the authors confirmed that children with AD are at increased risk for mental health disorders. The authors found a statistically significant increase in the prevalence of ADHD, anxiety, depression, conduct disorders, and autism in patients with AD. In addition, the prevalence of mental health disorders strongly correlated with AD severity (Yaghmaie 2013).For example, the prevalence of depression was 3.4% in children without eczema and 7.2% and 14.4% in those with moderate and severe eczema, respectively. This recent data provides support for the applicant's assertion that that there is no excess risk for mental health disorders associated with their product. However, this data was not analyzed by age group and the prevalence of mental health disorders increases with age in the pediatric population.

Consultation from the Division of Psychiatry Products (DPP)

Jean Kim, MD, MA, Division of Psychiatry Products (DPP), evaluated the data from the development program for trends in psychiatric adverse events (AE) which might represent a safety signal. The Psychiatry Reviewer noted that the overall rates of psychiatric adverse events were low and the difference in the incidence of these AEs in the active treatment group compared to the vehicle group in the pooled Phase 3 trials was not statistically significant.

The Psychiatry Reviewer provided the following conclusions and recommendations:

> "It is difficult to know for certain if there is no psychiatric risk, or minimal risk, based on the currently available safety data on crisaborole. The overall rates of psychiatric AEs appear extremely low in these Phase 3 studies, although there was also no formal psychiatric monitoring.
>
> I recommend use of screening tools such as the C-SSRS and/or the Physician Depression Questionnaire (PDQ) prospectively for future clinical trials with crisaborole. I would note that all screening tools for suicidality are limited in terms of any ability to predict or prevent SIB (Suicidal Ideation and Behavior) events.
>
> I also recommend a general advisory/addition in labeling such as the following in the Adverse Reactions section of labeling:

> In Phase 3 clinical trials, there were four cases of suicidal ideation and behavior noted in the treatment group versus none in placebo, out of a study population of about 1013 subjects on the study drug and 503 on placebo.

…it may be worth considering whether a class-wide warning or precaution in labeling should be considered…"

Reviewer Comment:

The data indicated an imbalance in the incidence of adverse events in the psychiatric disorders SOC with exposure to crisaborole compared with vehicle. However, the incidence of psychiatric disorders was far below the expected rates for patients in this age group with atopic dermatitis. I agree with the psychiatry consultant that the low numbers may be due in part to the lack of a sensitive screening instrument for depression and suicidal ideation. However, due to the timing of the event or use of a concomitant medication, none of the five cases supported a clear association of the severe depression or SIB event with administration of crisaborole. Because of the lack of clear causality, I would not recommend that these cases be included in labeling at this time; but I would concur with the acquisition of prospective data using a validated tool in future trials where possible. See Section 8.11.

8.5.3. Infections and Infestations

In the pooled pivotal Phase 3 trials, 11.7% of subjects in the crisaborole group and 11.8 % of subjects in the vehicle group reported AEs mapping to the infections and infestations SOC. The preferred terms which were most frequently documented by investigators were upper respiratory tract infection (crisaborole, 3.0%; vehicle 3.0%) and nasopharyngitis (crisaborole, 1.8%; vehicle, 1.2%).

The incidence of infections and infestations varied by age group. Among subjects age 2 to 11 years, a greater proportion of subjects in the vehicle group reported infections and infestations (15.4 %) compared to the crisaborole group (12.8 %). However, among subjects age 12 to 17 years, a greater proportion of subjects in the crisaborole group (9.3 %) reported infections and infestations compared to the vehicle group (8.2 %). The greatest difference in reporting AEs in this SOC occurred among subjects who were ≥ 18 years of age (10.6 % in the crisaborole group and 1.5 % in the vehicle group). The preferred terms which were reported by more than one subject included upper respiratory infection (3.5%) and nasopharyngitis (1.4%) in the crisaborole group and upper respiratory infection (1.5%) in the vehicle group.

In long-term safety trial AN2728-AD-303, 43.9 % of subjects reported AEs mapping to the infections and infestations SOC. The preferred terms which were most frequently documented by investigators were upper respiratory tract infection (10.3% of subjects), nasopharyngitis (7.7%), and sinusitis (4.8%).

There were 2 infections categorized as SAEs in the Phase 3 trials among subjects treated with crisaborole (See Section 8.4.2 for additional information):

Pneumonia (Trial AN2728-AD-301, Subject 126022)
A 5-year-old white female with a history of asthma, allergic rhinitis, allergies, was hospitalized with an SAE of pneumonia and AEs of respiratory syncytial virus and bilateral otitis media. The subject had a prior adverse event of asthma. Treatment included salbutamol, antibiotics, and corticosteroids. The SAE occurred after the course of treatment with crisaborole was completed. The investigators assessed these adverse events as not related to study drug.

Upper respiratory infection (Trial AN2728-AD-303, Subject 128006)
A 3-year-old black male was admitted to the hospital with a severe upper respiratory infection. His chest x-ray was normal and physicians initiated treatment with inhalation therapy and corticosteroids. The event resolved without withdrawal of the study product. Investigators assessed the event as not related to study drug.

Reviewer Comment:

Patients with atopic dermatitis experience an increased incidence of skin infections due to their compromised epidermal barrier and severe pruritus. In addition, subjects may be at increased risk for some systemic infections such as pneumonia and upper respiratory infections due to associated disorders (e.g. asthma.)

The greatest disparity in the frequency of infections and infestations between the crisaborole group and vehicle group occurred in the adult population. This may be attributed, in part, to the small number of subjects in this age group compared with the other age groups in the safety population; less than 15 % of the safety population was ≥ 18 years of age.

8.5.4. Pyrexia

In the pooled pivotal Phase 3 trials (AN2728-AD-301 and AN2728-AD-302), a similar percentage of subjects reported pyrexia, 1.9% of subjects in the crisaborole group compared with 1.4% of subjects in the vehicle group. Pediatric subjects in the age group 2 to 11 years experienced the majority of the events of pyrexia.

Similarly, in the long-term safety trial AN2728-AD-303, the frequency of pyrexia reports was 8.8% in the 2 to 11 year old age group and 1.4% in the 12-17 year old age group. The frequency of viral and bacterial infections was also the highest in the younger age group.

Reviewer Comment:

The generally accepted levels which define fever are a rectal temperature, tympanic membrane or forehead [temporal artery] temperature above 100.4 ^{0}F, oral temperature above 100 ^{0}F or an axillary temperature above 99^0 F. [15] In the safety population 0.89% (9 subjects) had a temperature of 100.5 or above in the crisaborole arm whereas 1.2% (6 subjects) had a temperature of 100.5 or above in the vehicle arm. However, the Phase 3 trial protocols do not specify the site of the temperature assessments. Thus, the results may represent assessments of temperature conducted at different body sites and may not be meaningful.

In addition, because pyrexia is a sign of an underlying condition, the small observed differences in the rates of pyrexia alone are not meaningful without a recognizable source. (See Section 8.5.3) Although viral or bacterial infections are the most common causes of pyrexia, a variety of conditions such as vaccines, allergies, medications, environmental conditions, collagen vascular disease etc. may be associated with transient elevations in temperature.[16]

8.5.5. Immune System Disorders

In the pooled pivotal Phase 3 trials (AN2728-AD-301 and AN2728-AD-302), 0.5% of subjects in the crisaborole group reported adverse events mapping to the immune system disorders SOC compared with 0% of subjects in the vehicle group. The most common adverse events by preferred term were food allergy (0.2%), seasonal allergy (0.2%), allergy to animal (0.1%) and hypersensitivity (0.1%). The Investigator assessed the hypersensitivity reaction as unrelated to the study product. There were no reports of immune mediated diseases such as connective tissue disorders or inflammatory bowel diseases in either treatment arm.

In long-term safety trial AN2728-AD-303, 2.9% of subjects reported AEs mapping to the immune system disorders SOC. The most common adverse events by preferred term were seasonal allergy (11 subjects, 2.1%), hypersensitivity (2 subjects, 0.4%), food allergy (1 subject, 0.2%) anaphylaxis (1 subject, 0.1%, see Section 8.4.2). Investigators assessed both hypersensitivity reactions and the anaphylactic reaction to be unrelated to the study products. There were no reports of immune mediated diseases such as connective tissue disorders or inflammatory bowel diseases.

8.5.6. Weight Loss

The evaluation of weight loss with exposure to crisaborole ointment included data from the 2 vehicle controlled 28- day, Phase 3 trials (AN2728-AD-301 and AN2728-AD-302) and the long-term, open-label, safety extension trial (AN2728-AD-303). Investigators documented the weight of enrolled subjects at baseline, Week 24 and Week 48. Overall, investigators recorded weight

[15] Ward MA et al. Patient information: Fever in children (Beyond the Basics) . UpToDate. Accessed 7/11/2016.
[16] Allen CH. Fever without a source in children 3 to 36 months of age. UpToDate. Accessed 7/12/2016.

loss in 15% of subjects at Week 24 and 15% of subjects at Week 48. A greater proportion of subjects in the 12 to 17 year old age group had weight loss compared with other pediatric age groups. In addition, there were more subjects in this age group (12-17 years) with a greater than 10% weight loss at any timepoint as summarized in the following tables.

Table 58: Categories of Weight Loss by Age (Trial AN2728-AD-303)

	Age				
	2 - 6	7 - 11	12 - 17	18+	Overall
Week 24	N=129	N=94	N=112	N=50	N=385
Lost +15	0	0	4 (3.6%)	0	4 (1.0%)
10 ≤ Lost < 15	0	0	2 (1.8%)	3 (6.0%)	5 (1.3%)
5 ≤ Lost < 10	1 (0.8%)	1 (1.1%)	5 (4.5%)	5 (10%)	12 (3.1%)
3 ≤ Lost < 5	1 (0.8%)	0	6 (5.4%)	8 (16%)	15 (3.9%)
0 < Lost <3	5 (3.9%)	3 (3.2%)	6 (5.4%)	8 (16.0%)	22 (5.7%)
No Change	4 (3.1%)	1 (1.1%)	3 (2.7%)	2 (4.0%)	10 (2.6%)
0 < Gained <3	52 (40.3%)	20 (21.3%)	21 (18.8%)	11 (22.0%)	104 (27.0%)
3 ≤ Gained < 5	47 (36.4%)	17 (18.1%)	16 (14.3%)	2 (4.0%)	82 (21.3%)
5 ≤ Gained < 10	16 (12.4%)	31 (33.0%)	21 (18.8%)	6 (12.0%)	74 (19.2%)
10 ≤ Gained < 15	2 (1.6%)	12 (12.8%)	17 (15.2%)	2 (4.0%)	33 (8.6%)
Gained +15	1 (0.8%)	9 (9.6%)	11 (9.8%)	3 (6.0%)	24 (6.2%)
Week 48	N=81	N=71	N=79	N=40	N=271
Lost +15	0	0	2 (2.5%)	0	2 (0.7%)
10 ≤ Lost < 15	0	0	0	4 (10.0%)	4 (1.5%)
5 ≤ Lost < 10	0	1 (1.4%)	7 (8.9%)	6 (15.0%)	14 (5.2%)
3 ≤ Lost < 5	0	0	4 (5.1%)	7 (17.5%)	11 (4.1%)
0 < Lost <3	1 (1.2%)	0	6 (7.6%)	3 (7.5%)	10 (3.7%)
No Change	1 (1.2%)	2 (2.8%)	1 (1.3%)	1 (2.5%)	5 (1.9%)
0 < Gained <3	12 (14.8%)	3 (4.2%)	6 (7.6%)	4 (10.0%)	25 (9.2%)
3 ≤ Gained < 5	30 (37.0%)	12 (16.9%)	6 (7.6%)	2 (5.0%)	50 (18.5%)
5 ≤ Gained < 10	32 (39.5%)	11 (15.5%)	13 (16.5%)	9 (22.5%)	65 (24.0%)
10 ≤ Gained < 15	3 (3.7%)	14 (19.7%)	10 (12.7%)	0	27 (10.0%)
Gained +15	2 (2.5%)	28 (39.4%)	24 (30.4%)	4 (10.0%)	58 (21.4%)

Source: Adapted from an analysis by Matthew Guerra, PhD.

Table 59: Long- Term Weight Loss ≥ 10 % at Any Timepoint by Age Group

Subject	Age	Age Group	baseline weight	Week 24	Week 48	Change Week	Change Week	% Change	% Change

			(LB)	weight	weight	24	48	Wk 24	Wk 48
301-139007	2	2-6 Years	60	52	64	-8	4	-13.33	6.67
302-202008	7	7-11 Years	55	56	48	1	-7	1.82	-12.73
301-139005	12	12-17 Years	154	135	157	-19	3	-12.34	1.95
302-201042	12	12-17 Years	127	109.5	124	-17.5	-3	-13.78	-2.36
301-139009	15	12-17 Years	190	126	156	-64	-34	-33.68	-17.89

Source: Reviewer's Table, Based on data from the Statistical Analysis by Matthew Guerra, PhD

Reviewer's comment

- *Examination of JReview patient profiles, did not suggest an etiology for weight loss observed among these subjects. The majority reported no contributory adverse events. Some subjects had associated disorders (asthma and allergies) with concomitant medications (e.g. 302-201042) but other subjects were otherwise healthy. Specifically, with regard to Subject 301-139009, the data do not suggest an etiology for the finding of weight loss ≥ 15 % from baseline. The lack of significant shifts in her laboratory data supports the conclusion that the value for her weight was recorded in error. The conclusion that weights were not recorded accurately in some cases was confirmed by the investigators. (Response to an Information Request dated 7/14/2016 regarding Subject # 302-202008 and 301-139005.)*

Weight change from baseline to Week 48 versus exposure to EUCRISA ointment

To evaluate whether weight loss was related to increased exposure to EUCRISA, the statistical reviewer analyzed the observed weight change by the total amount of EUCRISA ointment used by age group during 48 weeks of exposure. The results are displayed in the following figures:

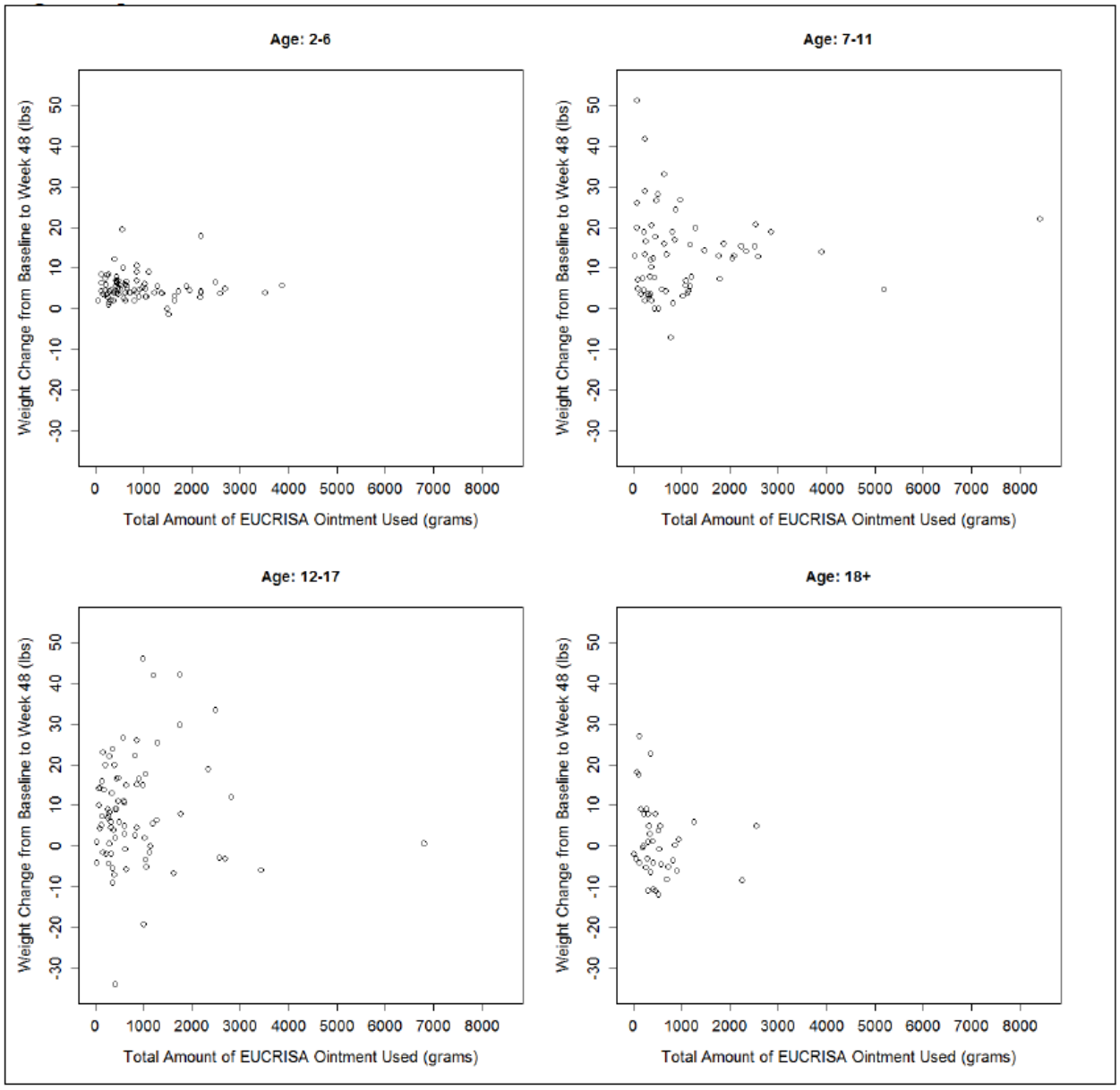


Figure 6: Weight Change from Baseline to Week 48 vs. Total Amount of EUCRISA Ointment Used by Age Groups

Source: Analysis by Matthew Guerra, PhD, Statistical Reviewer

This regression analysis did not support a correlation between exposure and weight loss (large p-values and very small regression coefficients). The data is presented below.

Table 60: Correlation between Weight Change from Baseline to Week 48 and Total Amount of EUCRISA Ointment Used by Age Group

Age Range (years)	Number (N)	Correlation Coefficient	p-value
2-6	78	-0.044	0.7043
7-11	64	0.036	0.7780
12-17	76	0.026	0.8221
18+	39	-0.190	0.2479
Overall	259	0.063	
2-9	114	0.023	

Source: Data provided by Matthew Guerra, PhD.

The statistician conducted another analysis of weight change in the subgroup age 2 to 9 years because all subjects in this age group should observe weight gain. In older pediatric age groups, the increase in growth is less predictable and may be confounded by other factors (e.g. social impact of obesity and others.) Overall, 14 subjects in the age group 2-9 years had no reported weight gain at Week 24 and 4 subjects had no reported weight gain at Week 48. Similar to analyses in other age groups, results of the regression analysis, showed no correlation between exposure and weight loss.

Table 61: Weight Change Categorized at Week 24 and Week 48 for Subjects Age 2 to 9 Years

Weight Change lbs.	Age 2 – 9 years
Week 24	N=184
Lost +15	0
10 ≤ Lost < 15	0
5 ≤ Lost < 10	2 (1.1%)
3 ≤ Lost < 5	1 (0.5%)
0 < Lost <3	6 (3.3%)
No Change	5 (2.7%)
0 < Gained <3	69 (37.5%)

Weight Change lbs.	Age 2 – 9 years
3 ≤ Gained < 5	57 (31.0%)
5 ≤ Gained < 10	31 (16.9%)
10 ≤ Gained < 15	8 (4.4%)
Gained +15	5 (2.7%)
Week 48	N=120
Lost +15	0
10 ≤ Lost < 15	0
5 ≤ Lost < 10	1 (0.8%)
3 ≤ Lost < 5	0
0 < Lost <3	1 (0.8%)
No Change	2 (1.7%)
0 < Gained <3	14 (11.7%)
3 ≤ Gained < 5	38 (31.7%)
5 ≤ Gained < 10	40 (33.3%)
10 ≤ Gained < 15	8 (6.7%)
Gained +15	16 (13.3%)

Source: Analysis by Matthew Guerra, PhD

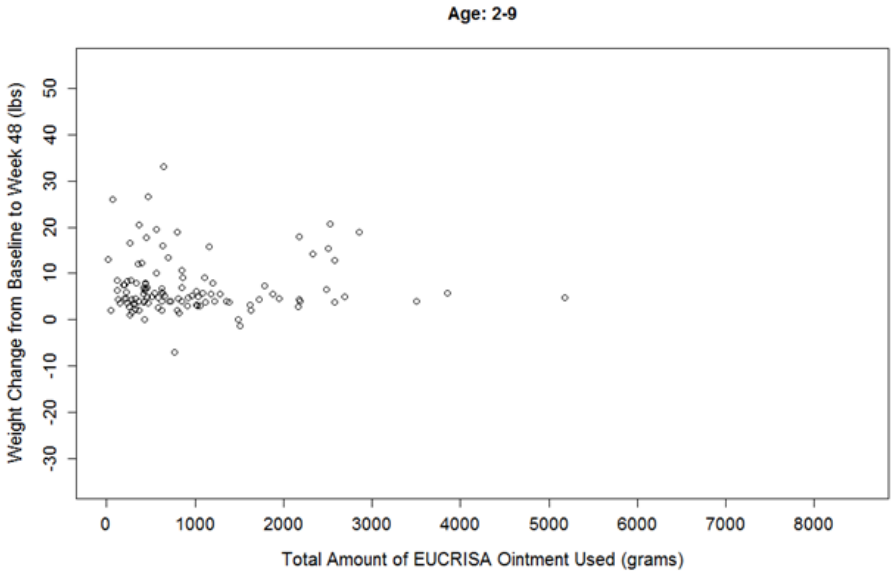


Figure 7: Weight Change from Baseline to Week 48 vs. Total Amount of EUCRISA Ointment Used (Age 2-9)

Source: Analysis by Matthew Guerra, PhD.

In addition, Erica Radden, M.D., from the Division of the Pediatric and Maternal Health (DPMH) provided the following comments regarding further evaluation of the potential for weight loss with the topical administration of crisaborole (Review dated 9/29/2016,):

1. "DPMH does not recommend a formal study to evaluate growth in the pediatric population that has already been studied in the clinical development program for crisaborole.

2. With regards to the planned post-approval long-term safety study in patients 3 months to 2 years of age which will be issued as a PREA PMR, the lack of a long term comparator and the amount of variability of growth typically seen in patients less than 3 years of age, will likely limit a reliable growth assessment in this age group. However, DPMH recommends DDDP consider including growth measurements in this study [redacted] The study protocol should specify how height (or length in patients <2 years of age) and weight measurements will be replicated (at least 3), standardized and performed. The steps that will be taken to reduce measurement errors should also be outlined. The study protocol should incorporate recommendations from the March 2007 Guidance for Industry on Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children.

DPMH recommends the sponsor submit the study protocol for review by the Agency before initiating the study. Consider the following general recommendations:

- All weights should be measured on a calibrated scale.
- Length should be measured for patients < 2 years of age using a fixed headboard.
- Standing height should be measured in patients 2 years and older using stadiometer.
- Measurements should be obtained for a long enough interval to detect changes (e.g., 1 year).
- Changes in growth are best detected during the period of linear growth, between 3 years of age and prior to puberty. Thus, growth studies in this population are deemed most clinically relevant and Tanner staging should also be performed, when applicable."

Reviewer Comment:

The systemic exposure and effects of crisaborole on weight are substantially less than other members of the class of PDE-4 inhibitors which are administered by the oral route. Interpretation of this data is limited by the study design, number of timepoints where data was collected and the study population. In this population of predominantly pediatric subjects, the anticipated weight gain may obscure any minor changes in weight related to exposure to the drug product. Because the number of subjects with documented severe weight loss was small, not correlated with greater exposure to the drug product or associated with diarrhea, it is difficult to categorize these findings as representing a class effect. I do not recommend that language regarding weight loss be included in labeling at this time.

8.5.7. Local Tolerability

The applicant evaluated local tolerability during their development program using a variety of measures and scales as summarized in Table 37. The evaluation of local tolerability was distinct from application site reactions reported as AEs. Generally, the number of reports of moderate and severe stinging and burning decreased with time in both treatment groups during the Phase 3 trials.

8.5.8. Immunosuppression

Local immunosuppression may be characterized by an increased risk of infections and neoplasms. The incidence of infections by treatment group was discussed in Section 8.5.3. In the pooled Phase 3 pivotal trials (AN2728-AD-301 and AN2728-AD-302), 0.2% (2 /1012) of subjects in the crisaborole group experienced adverse events (AEs) in the Neoplasms SOC compared with 0.0% (0 / 499) of subjects in the vehicle group. Both events were benign lesions (2 papillomas) which occurred in the pediatric age group 12 to 17 years. The incidence of neoplasms was also low in the long-term safety Trial AN2728-AD-303, 0.8% (4/517). Three pediatric subjects reported papillomas and 1 subject reported a lipoma. There were no neoplasms reported in subjects age ≥ 18 years.

8.6. Safety Analyses by Demographic Subgroups

The youngest subjects reported Treatment-Emergent Adverse Events (TEAEs) with greater frequency than older subjects. There were no other clear trends in the rates of TEAEs by sex, race or ethnicity.

Table 62: Summary of Treatment-Emergent Adverse Events (TEAEs) Reported by At Least One Percent of Subjects in at Least One Treatment Group by Age Group

MedDRA System Organ Class	Crisaborole 2% BID				Vehicle BID			
	Age (years)			Total	Age (years)			Total
	2-11	12-17	≥18		2-11	12-17	≥18	
	N=625	N=246	N=141	N =1012	N=311	N=122	N=66	N=499
Infections and infestations	80 (12.8%)	23 (9.3%)	15 (10.6%)	118 (11.75)	48 (15.4%)	10 (8.2%)	1 (1.5%)	59 (11.8%)
General disorders and administrative site conditions	54 (8.6%)	13 (5.3%)	8 (5.7%)	75 (7.4%)	1 (3.5%)	7 (5.7%)	7 (10.6%)	25 (5.0%)
Respiratory, thoracic and mediastinal disorders	36 (5.8%)	8 (3.3%)	3 (2.1%)	47 (4.6%)	11 (3.5%)	3 (2.5%)	1 (1.5%)	15 (3.0%)
Skin and subcutaneous tissue disorders	22 (3.5%)	11 (4.5%)	4 (2.8%)	37 (3.7%)	13 (4.2%)	6 (4.9%)	2 (3.0%)	21 (4.2%)
Gastrointestinal disorders	23	3	1	27	9	2	1 (1.5%)	12

MedDRA System Organ Class	Crisaborole 2% BID				Vehicle BID			
	Age (years)			Total	Age (years)			Total
	2-11	12-17	≥18		2-11	12-17	≥18	
	N=625	N=246	N=141	N =1012	N=311	N=122	N=66	N=499
	(3.7%)	(1.2%)	(0.7%)	(2.7%)	(2.9%)	(1.6%)		(2.4%)
Injury, poisoning and procedural complications	14 (2.2%)	3 (1.2%)	3 (2.1%)	20 (2.0%)	6 (1.9%)	2 (1.6%)	1 (1.5%)	9 (1.8%)
Nervous system disorders	4 (0.6%)	6 (2.4%)	4 (2.8%)	14 (1.4%)	1 (0.3%)	0	1 (1.5%)	2 (0.4%)
Investigations	6 (1.0%)	2 (0.8%)	2 (1.4%)	10 (1.0 %)	3 (1.0%)	1 (0.8%)	2 (3.0%)	6 (1.2%)
Musculoskeletal and connective tissue disorders	2 (0.3%)	6 (2.4%)	1 (0.7%)	9 (0.9%)	0	0	1 (1.5%)	1 (0.2%)
Eye disorders	5 (0.8%)	2 (0.8%)	0	7 (0.7%)	2 (0.6%)	1 (0.8%)	1 (1.5%)	4 (0.8%)
Psychiatric disorders	1 (0.2%)	5 (2.0%)	0	6 (0.6%)	1 (0.3%)	0	0	1 (0.2%)
Vascular disorders	2 (0.3%)	1 (0.4%)	3 (2.1%)	6 (0.6%)	0	0	0	0
Immune system disorders	3 (0.5%)	2 (0.8%)	0	5 (0.5%)	0	0	0	0
Metabolism and nutrition disorders	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.3%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.8%)	0	2 (0.2%)	0	0	0	0
Ear and labyrinth disorders	2 (0.3%)	0	2 (1.4%)	2 (0.2%)	0	0	0	0
Blood and lymphatic system disorders	0	1 (0.4%)	0	1 (01%)	3 (1.0%)	0	0	3 (0.6%)
Reproductive system and breast disorders	0	0	1 (0.7%)	1 (01%)	0	0	0	0
Cardiac disorders	0	0	0	0	1 (0.3%)			1 (0.2%)
Renal and urinary disorders	0	0	0	0	1 (0.3%)			1 (0.2%)

Source: Adapted from Applicant's Table 68, 2.7.4 Summary of Clinical Safety

8.7. Specific Safety Studies/Clinical Trials

For the evaluation of their topical drug product, the applicant conducted Trial AN2728-PSR-107 to evaluate local tolerability in intertriginous and "sensitive skin areas" and dermal safety studies which included Trial AN2728-RIPT-101 to evaluate the potential for irritation and sensitization. The Division determined that Protocol AN2728-RIPT-101 was adequate to provide data to meet the stated objectives. As the Division did not review Protocol AN2728-

PSR-107 which was a foreign clinical trial (not conducted under an IND), this NDA review includes only a brief summary of the design and results. The Agency waived the recommended evaluation of phototoxicity and photoallergenicity because none of the components of the drug product absorbed light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible). (See EOP2 Meeting Minutes dated 11/3/2011).

In addition, for the evaluation of the long- term safety of their topical drug product, the applicant conducted open-label, Phase 3 Trial AN2728- AD-303. The study population included subjects who participated in Trial AN2728-AD-301 or AN2728-AD-302 who did not experience an adverse event which would preclude further participation.

Trial AN2728-PSR-107 (Conducted 10/31/2011-12/12/2011 in Australia)
Title: "Local Tolerability of AN2728 Topical Ointment, 2% in Sensitive Areas"

Objective:
Primary Objective:

- To evaluate the local tolerability of crisaborole ointment, 2% compared to vehicle ointment in sensitive skin areas of healthy volunteers.

Study Population
The trial enrolled a total of 32 (16 males and 16 females) healthy, Caucasian subjects aged 18 - 55 years with no clinically significant medical condition or abnormal findings on screening physical examination or laboratory evaluation. Women of childbearing potential were required to use acceptable methods of contraception (abstinence, hormone method, tubal ligation, intrauterine device, condom with spermicide, vasectomized male partner) until 4 weeks after the last dose of the study product.

Study Plan
This was a single-center, randomized, double-blind, vehicle-controlled trial in healthy volunteers to assess the local tolerability of crisaborole ointment applied twice daily for 21 days in "sensitive areas". Eligible subjects were randomized to crisaborole ointment or vehicle in a 3:1 ratio. Subjects self-administered all doses. However, the site staff supervised the application of the study product on Days 1, 3, 7, 10, 14 and 17 at the assessment visits. Subjects returned to the study site on Day 22, the day after last application for final study assessments. At each clinic visit, the site staff conducted an evaluation of local tolerability using the Local Tolerability Scale for burning/stinging, pruritus and erythema and recorded adverse events. Vital signs and safety laboratory parameters were collected at Screening, Baseline and Day 22.

Application Instructions
The site staff instructed subjects to apply a thin layer of the study product and rub into the skin at least 15 minutes after bathing/showering. The intended dose for each treatment area was

0.5 to 1 Finger Tip Unit (FTU) which covers approximately 2% BSA.

Compliance
The site staff weighed the tubes of investigational product when dispensed and returned.

Assessments

- Systemic safety: incidence of SAEs, observed values and changes in vital signs(screening, baseline and Day 22), laboratory tests (hematology/chemistry-screening, baseline and Day 22); frequency and severity of AE and TEAE (all visits), pregnancy testing (screening, baseline and Day 22)
- Local tolerability: frequency and severity of local tolerability symptoms, including burning/stinging, erythema, and pruritus using the following scale

Table 63: Grading of Local Tolerability Symptoms

Grade	Burning/Stinging	Pruritus	Erythema
0 (None)	No stinging/burning	No pruritus	No detectable erythema, skin of normal color
1 (Mild)	Slight warm, tingling sensation; not really bothersome	Occasional, slight itching/scratching	Slight pinkness present
2 (Moderate)	Definite warm, tingling sensation that is somewhat bothersome	Constant or intermittent itching/scratching which is not disturbing sleep	Definite redness, easily recognized
3 (Severe)	Hot, tingling/stinging sensation that has caused definite discomfort	Bothersome itching/scratching which is disturbing sleep	Intense redness

Note: Grades of 0.5, 1.5 & 2.5 were allowed as midpoints between the definite grades of 0, 1, 2 & 3.
Source: Clinical Study Report, Table 9.5.3.1 page 30

Results
The demographic characteristics of the treatment groups were comparable with a mean age in the crisaborole group of 30.2 (range 18-52 years) and the vehicle group of 29.1 years (range 19-53).The majority of subjects applied 42 doses. One subject in each treatment group applied fewer than 42 doses (41 doses of crisaborole group and $\geq$ 36 dosed of vehicle).

Local Tolerability
Most (99%) assessments of local tolerability were graded as 0 (none), and only 0.1% of assessments graded higher than 1 (mild). There were no marked differences in burning/stinging, erythema or pruritus at any of the 13 application sites over the course of the

trial between subjects who applied crisaborole or vehicle.

Other Safety Results

There were no deaths or SAEs and no subjects were withdrawn from the trial due to adverse events. Twenty two of 32 subjects (69%) reported a total of 38 TEAEs (17 in the crisaborole group (71%) and 5 in the vehicle group (63%)). TEAEs classified as severe were reported by 4 subjects (dental caries, upper respiratory tract infection, oropharyngeal pain and seasonal allergy) but none of these AEs was assessed as related. TEAEs of moderate severity were reported by 8 subjects (headache, back pain, upper respiratory tract infection, musculoskeletal chest pain, limb injury, gastroenteritis and nasopharyngitis) but all of these AEs were assessed as not related or unlikely related. One subject reported 3 adverse reactions (application site pain) of mild severity which were definitely related to crisaborole.

Commonly occurring TEAEs were headache and sunburn. These occurred in a similar rate in both treatment groups.

Reviewer Comment:

Under the conditions of this trial, crisaborole was well tolerated even in intertriginous areas where other treatment options may be associated with an increased incidence of adverse reactions.

Trial AN2728-RIPT-101

Title: "A Randomized, Controlled Study to Evaluate the Sensitizing Potential and Cumulative Irritation Potential of AN2728 Topical Ointment, 2%, in Healthy Volunteers Using a Repeat Insult Patch Test and Cumulative Irritation Design" (AN2728-RIPT-101)

Objective:

Primary Objective:

- To determine the potential of crisaborole ointment, 2% to induce sensitization or to cause irritation by repeated topical application to normal skin of healthy volunteers under controlled conditions.

Secondary Objectives:

- to evaluate the safety by evaluation of any adverse events (AEs) reported during the study

Study Population:

The trial enrolled healthy male and female subjects age 18 years and older of any race with any skin type which would allow the assessment of erythema and free of dermatologic disorders that would interfere with trial results or increase the risk of adverse events. A total of 238 subjects enrolled in Cohort 1(sensitization) and 40 enrolled in Cohort 2 (irritation).

Key Inclusion Criteria:

- Females of childbearing potential (FCBP) must use an acceptable form of birth control and have a negative urine pregnancy test at Day 1
- FCBP must be willing to complete pregnancy testing during the Challenge Period prior to patch application (Cohort 1) and at the end of study (EOS)

Key Exclusion Criteria:

- Visible skin disease or damaged skin at the application site
- Psoriasis and/or active atopic dermatitis/eczema
- Not willing to refrain from using any topical/systemic analgesics such as aspirin
- Using systemic/topical corticosteroids for 3 weeks prior to and during the study, or systemic/topical antihistamines for 72 hours prior to and during the study
- Pregnant, plan to become pregnant during the study, or are breast-feeding a child
- Using medication which, in the opinion of the investigative personnel, will interfere with the study results, including anti-inflammatory medications
- Any known sensitivity to adhesives;
- Received treatment for any type of internal cancer within 5 years prior to study entry; or have a history of, or are currently being treated for skin cancer;

Study Products

Cohort 1: Sensitization Potential Evaluation

A) AN2728 Topical Ointment, 2%, 0.2 g
B) AN2728 Topical Ointment, Vehicle 0.2 g
C) 0.1% sodium lauryl sulfate (SLS), 0.2 mL positive control.
D) 0.9% saline, 0.2 mL, a negative control.

Cohort 2: Cumulative Irritancy Potential Evaluation

A) AN2728 Topical Ointment, 2%, 0.2 g
B) AN2728 Topical Ointment, Vehicle 0.2 g
C) 0.5% sodium lauryl sulfate (SLS), 0.2 mL positive control.
D) 0.9% saline, 0.2 mL, negative control

Study Plan:

This was a single-center, randomized, controlled, within-subject comparison trial to assess sensitization and irritation. After a 14 day screening period, eligible subjects (as determined by review of the inclusion/exclusion criteria) were assigned to one of two cohorts with separate treatment schedules and procedures.

Cohort 1: Sensitization Potential Evaluation

During the 3-week Induction Period of the trial, the investigational staff applied the study products (listed above) to the infrascapular area of the back of each subject under semi-

occlusive patch conditions, 3 times weekly for a total of 9 applications. Following Induction, all subjects entered a 10 to 14-day Rest Period, followed by a single 48-hour patch application to a naïve site on the side of the back during the Challenge Period. Trained and blinded observers performed the scoring of skin reactions and patch adherence at each patch removal, using the scales presented below. During Challenge phase, observers graded the sites at 30 minutes, 24 hours, 48 hours, and 72 hours after patch removal.

Cohort 2: Cumulative Irritancy Potential Evaluation
During the 3-week Induction Period of the trial, the investigational staff applied the study products (listed above) to the infrascapular area of the back of each subject under semi-occlusive patch conditions, once daily for a total of 21 applications. In Cohort 2, investigators removed the patch from any site where they observed a cutaneous response of grade 4 (definite edema) or higher.

Safety variables for Trial AN2728-RIPT-101 included:
- Local cutaneous signs of irritation and/or sensitization.
- All local and systemic adverse events observed by or reported to the Investigators

Table 64: Scale for Assessing Localized Skin Reactions

Score	Description
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema, or minimal popular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Table 12

Table 65: Local Tolerability Assessment Scales

Grade	Burning/Stinging	Pruritus	Erythema
0 (none)	No stinging/burning	No pruritus	No detectable erythema, skin of normal color
1 (mild)	Slight warm, tingling sensation, not really bothersome	Occasional, slight itching/scratching	Slight pinkness present
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome	Constant or intermittent itching/scratching which is not disturbing sleep	Definite redness, easily recognized
3	Hot, tingling/stinging sensation	Bothersome	Intense redness

(severe)	that has caused definite discomfort	itching/scratching which is disturbing sleep	

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Table 13

Table 66: Effects on Superficial Layers of the Skin

Symbol	Score	Response
A	0	Slight glazed appearance
C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch
H	3	Small petechial erosions and/or scabs
Scale utilized in Study AN2728-RIPT-101.		

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Table 14

Table 67: Additional Notations for Assessing Local Tolerability

Notation	Definition
X	Subject absent
B	Burning or stinging sensation
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation
I	Itching
D	Damage of the epidermis: oozing, crusting and/or superficial erosions
P	Papular response
PV	Papulovesicular response
S	Spreading of reaction beyond application site (i.e., reaction where study material did not come in contact with skin)
Scale utilized in Study AN2728-RIPT-101.	

Source: Adapted from Applicant's submission, 2.7.4 Summary of Clinical Safety, Table 15

Reviewer Comment:

Generally, positive controls are not utilized in trials to assess sensitization for ethical and practical reasons. There is no substance that represents a sensitizer for all individuals and it is unethical to induce contact sensitization with a positive control in a healthy subject. However,

the risks of the study procedures were conveyed to the subjects in the informed consent and subjects could decline to participate if this is a concern.

Results
Cohort 1:
A total of 207 subjects were included in the sensitization analysis and 238 subjects were included in the safety analysis. No subject developed sensitization to any investigational product. During the induction phase, 1 subject experienced erythema, edema and papules (grade 5) at the crisaborole site. When investigators moved the patch to a naïve site under open conditions, they observed no further reactions. The most severe reaction to the vehicle was definite erythema, readily visible (grade 2) and the most severe reaction to the positive and negative control patches was minimal erythema, barely perceptible (grade 1).

There were 5 treatment-emergent adverse events (TEAEs) reported by 5 subjects in Cohort 1. No TEAE was considered serious or related to the study product. Two (2) TEAEs were severe (contact dermatitis to the adhesive tape used to apply the patches) and led to discontinuation from the trial. Three (3) TEAEs were mild (2 eye infections and a furuncle).

Cohort 2:
A total of 40 subjects were included in the analysis of cumulative irritation potential and safety. The most severe reactions to crisaborole and vehicle were grade 1, the most severe reactions to 0.9% saline site were grade 2, and the most severe reactions to 0.5% sodium lauryl sulfate (SLS) were grade 3. Investigators observed no dose limiting irritation reactions or adverse events. The mean cumulative irritation scores for crisaborole, vehicle, saline and SLS were 0.03 (SD 0.11), 0.05 (SD 0.16), 0.29 (SD 0.33) and 0.93 (SD 0.66), respectively.

There were no deaths or Serious Adverse Events (SAEs) reported by subjects during the trial. All female subjects of childbearing potential in both Cohorts had negative urine pregnancy test (UPT) results at Day 1 and at end of study (EOS).

Trial AN2728-AD-303
Title:
"A Multicenter, Open-Label Study of the Long-Term Safety of AN2728 Topical Ointment, 2% in the Treatment of Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis."

Objective:
Primary Objective:

- To evaluate the long-term safety of open-label treatment with crisaborole (AN2728 Topical Ointment, 2%) in subjects ages 2 years and older with mild-to-moderate atopic dermatitis (AD).

Study Population:
The trial enrolled 517 healthy male and female subjects age 2 years and older with the clinical diagnosis of AD, involvement ≥ 5% Treatable %BSA (excluding the scalp), ISGA score of Mild (2) or Moderate (3)} and successfully completed AN2728-AD-301 or AN2728-AD-302 through Day 36.

Study Sites: 41 US sites

Key Inclusion Criteria:
- Completed Trial AN2728-AD-301 or AN2728-AD-302
- Met eligibility criteria for AN2728-AD-301 or AN2728-AD-302. See 6.1 and 6.2.
- Females of childbearing potential (FCBP) using an acceptable form of birth control with a negative urine pregnancy test at Day 1
- Has safety laboratory results from the Day 29 Visit in AN2728-AD-301 or AN2728-AD-302 that are judged clinically acceptable by the investigator

Key Exclusion Criteria:
- Experienced a related or probably or possibly related AE or SAE during participation in Trial AN2728-AD-301 or AN2728-AD-302, which precluded further treatment with AN2728 Topical Ointment, 2%, in the judgment of the PI
- Significant active systemic or localized infection, including known actively infected AD
- Anticipated concomitant use of systemic or topical therapies that might alter the course of AD
- FCBP who was breastfeeding or pregnant or intended to become pregnant

Study Plan:
This was multicenter, long-term, open-label safety trial to evaluate crisaborole for the treatment of mild-to-moderate atopic dermatitis (AD.) Subjects/care givers administered the study product twice daily during 28-day treatment periods to all treatable AD-involved areas. Following each On-Treatment period, investigators assessed the severity of the atopic dermatitis on the Investigator's Static Global Assessment (ISGA) scale and identified the remaining treatment areas for each subject. Subjects with severity of mild (2) or greater were instructed to initiate another treatment cycle of 28 days (On-Treatment Period). Subjects applied the study treatment for a variable number of 28 day cycles during the 48 weeks of study participation.

Investigators discontinued treatment with crisaborole for any subject who experienced no improvement in ISGA after three consecutive cycles of treatment.

If AD became "intolerable" during the On-Treatment period, the investigator could instruct the subject /parent to discontinue crisaborole and use recue therapy with a low- to mid-potency topical corticosteroid (TCS). Intolerable AD was defined as an exacerbation of AD that significantly affected normal function or promoted harmful behavior (e.g. scratching.) If AD recurred or worsened during an Off-Treatment Period, investigators could arrange an unscheduled visit to provide a sufficient quantity of the study product for the remainder of a given 28-day period.

If the investigator assessed the AD severity as Clear (0) or Almost Clear (1) on the ISGA during an in-clinic visit, then the subject would discontinue treatment and enter an Off-Treatment Period. During Off-Treatment Periods, the subject could apply an acceptable bland emollient, as needed. Subjects who entered an Off-Treatment Period, returned to the clinic for evaluation every 4 weeks to determine the severity of their AD. If ISGA reached a grade of Mild (2) or greater, then the investigator would initiate another treatment cycle of crisaborole.

Assessments

- Vital signs (temperature, respiratory rate, pulse rate, BP): all clinic visits
- Height and weight: Day 169 (Week 24) and 337 (Week 48; End of Study)
- Disease-focused physical examination of all AD-involved areas: (Day 29 in AN2728-AD-301 or AN2728-AD-302 will serve as the baseline) Study Days 169 (Week 24) and 337 (Week 48; End of Study)
- Concomitant medications, including confirming that subject is not taking any prohibited medications: all visits
- AEs and SAEs: all visits
- Clinical laboratory tests (Serum chemistry and hematology): (Baseline, Week 24 and Week 48)
- Local tolerability: Screening, all clinic visits
- Urine pregnancy test; Screening, Day 1 of each On-Treatment cycle, end of treatment
- Investigator's Static Global Assessment (IGSA): Screening, all clinic visits (Table 7)
- Dermatology-related quality of life questionnaires: Children's Dermatology Life Quality Index (CDLQI) or Dermatology Life Quality Index (DLQI) and Dermatology Family Index Questionnaire (DFI) (if applicable)
- Weigh tubes upon dispensing and return: Each On-Treatment cycle

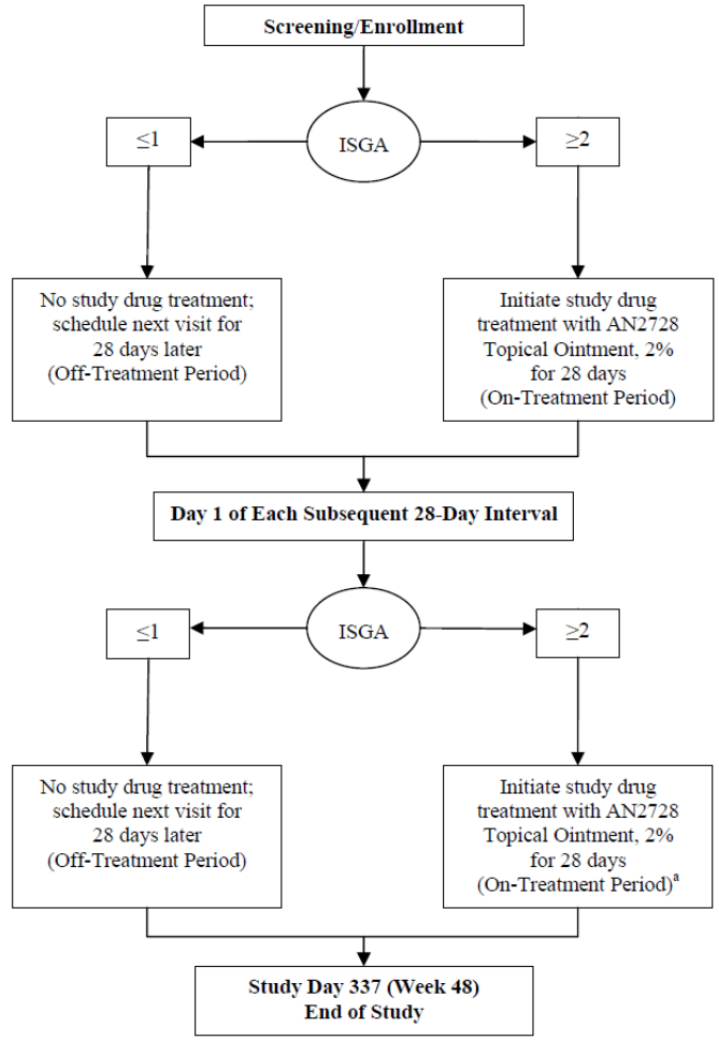


Figure 8: Trial Flow Diagram- Trial AN2728-AD-303

Prohibited Systemic Medications

- Systemic (oral, parenteral) corticosteroids
- Systemic immunosuppressive agents {e.g. methotrexate, cyclosporine, azathioprine, hydroxychloroquine, and mycophenolate mofetil (MMF)}
- Systemic antibiotics except short courses (≤ 14 days)

Prohibited Topical Medications (prohibited anywhere on the body throughout the study)

- low- to mid-potency topical corticosteroids (TCS), or calcineurin inhibitors unless prescribed by the investigator or designee as recue therapy

- Sunbathing, tanning bed use or light therapy within 14 days prior to Baseline

Medications Permitted During the Study

- Use of acceptable bland emollient(s) - Written instruction will be provided and a list of acceptable choices
- During On-Treatment Periods: use of acceptable bland emollient(s) to manage dry skin in areas surrounding the treatable AD-involved areas
- During Off-Treatment Periods: use of acceptable bland emollient(s) is permitted in all areas , as needed
- Short courses (≤ 14 days) systemic antibiotics for new onset infections
- Nonsteroidal anti-inflammatory drugs
- Routine preventative immunizations are permitted
- For female subjects of childbearing potential: Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception
- Concomitant medications for other chronic medical conditions (unless specifically prohibited in the protocol)

Endpoints:
Primary endpoints: frequency of AEs including TEAEs and SAEs, local tolerability and changes in disease severity including the need for topical corticosteroids or calcineurin inhibitors as rescue therapy.

Data Analysis:

- All analyses were performed using the Safety Population which included all subjects who receive at least one confirmed dose of study drug and have at least one post-baseline assessment.

Results
A total of 271 subjects completed Trial AN2728-AD-303. Among the 246 subjects who discontinued participation in the trial, common reasons included withdrawn by a parent or guardian (63 subjects), lost to follow-up (36 subjects), withdrawn by subject (23 subjects), adverse event (9 subjects) and other (115 subjects).

Table 68: Exposure by Age Group- Long-Term Safety Trial AN2728-AD-303 (Safety Population)

	Crisaborole 2% BID			
	Age (years)			Total
	2-11	12-17	≥18	
	N=308	N=146	N=63	N =517
Number of Applications				

	Crisaborole 2% BID			
	Age (years)			Total
	2-11	12-17	≥18	
	N=308	N=146	N=63	N =517
Number of subjects	304	146	60	510
Mean (SD)	349.0 (179.57)	349.4 (193.21)	347.7 (180.33)	348.9 (183.30)
Median	345.0	362.5	341.0	347.5
Min to Max	16 to 748	8 to 748	33 to 663	8 to 748
Amount of Drug Used (g)				
Number of subjects	308	146	63	517
Mean (SD)	793.46 (1039.62)	791.13 (1052.15)	528.32 (722.22)	760.49 (1012.07)
Median	486.50	469.70	335.70	435.10
Min to Max	0 to 9979.7	0 to 8025.3	0 to 4803.5	0 to 9979.7
Amount of Drug Used (g) per Application				
Number of subjects	304	146	60	510
Mean (SD)	2.403 (2.4979)	2.293 (2.3791)	2.104 (3.1979)	2.337 (2.5537)
Median	1.545	1.602	1.210	1.504
Min to Max	0.00 to 16.39	0.10 to 15.99	0.15 to 21.71	0.00 to 21.71
Number of On-Treatment Periods				
Number of subjects	308	146	63	517
Mean (SD)	6.2 (3.14)	6.3 (3.35)	5.9 (3.12)	6.2 (3.20)
Median	6.0	6.5	6.0	6.0
Min to Max	0 to 13	1 to 13	0 to 11	0 to 13
Duration of On-Treatment Periods (days)				
Number of On-Treatment Periods	1903	921	370	3194
Mean (SD)	28.4 (5.83)	28.3 (6.52)	28.6 (6.40)	28.4 (6.10)
Median	29	29	29	29
Min to Max	1 to 73	1 to 71	1 to 62	1 to 73
< 21 Days	118 (6.2%)	69 (7.5%)	23 (6.2%)	210 (6.6%)
21-35 Days	1654 (86.9%)	772 (83.8%)	317 (85.7%)	2743 (85.9%)
>35 Days	131 (6.9%)	80 (8.7%)	30 (8.1%)	241 (7.5%)

Max= maximum; min= minimum; SD= standard deviation
Source: Modified from Clinical Study Report for AN2728-AD-303, Table 10 page 58

A limited number of subjects withdrew from the trial due to an adverse event. Most of these adverse events were related to the application site or worsening eczema. Additionally, investigators withdrew crisaborole treatment from 8 subjects who remained in the trial. Among these subjects, 2 subjects interrupted treatment only to the location of the AE but continued treatment to other affected areas. See the summary below.

Table 69: Number of Subjects Who Discontinued From the Trial Due to Adverse Events, Long-Term Safety Study AN2728-AD-303 (Safety Population)

Crisaborole 2% BID (N = 517)	
Total number of subjects who discontinued from the study due to an AE	9 (1.7%)
AEs leading to discontinuation	
Dermatitis atopic	5 (1.0%)
Application site pain	2 (0.4%)
Application site dermatitis	1 (0.2%)
Eczema	1 (0.2%)

If a subject reported the same MedDRA preferred term more than once, that subject was counted only once for that preferred term.
Study drug was administered in 28-day treatment periods, which were initiated when a subject's ISGA score was Mild (2) or higher.
Source: 2.7.4 Summary of Clinical Safety Table 52 page 107

Table 70: Number of Subjects Who Had Study Drug Withdrawn Due to an Adverse Event but Continued in the Study, Long-Term Safety Study AN2728-AD-303 (Safety Population)

Crisaborole 2% BID (N = 517)	
AEs leading to discontinuation of the study drug	
Application site pain	2 (0.4%)
Application site infection	2 (0.4%)
Dermatitis atopic	5 (1.0%)
Application site folliculitis	1 (0.2%)
Eczema	1 (0.2%)
Eczema herpeticum	1 (0.2%)
Lymphadenopathy	1 (0.2%)
Staphylococcal skin infection	1 (0.2%)

These subjects had treatment interrupted and not restarted. Subjects are counted once per preferred term.
Source: Applicant's Table-2.7.4 Summary of Clinical Safety page 108 Table 53

SAEs reported by subjects in Trial AN2728-AD-303 included anaphylactic reaction (to nuts), application site infection, worsening asthma, CNS ventriculitis, depression, suicide attempt, and upper respiratory tract infection. Each of these AEs was reported by a single pediatric subject (0.2%) and none were assessed as related. For a discussion of the SAEs reported by subjects in Trial AN2728-AD-303 see 8.4.2.

Table 71: Treatment-Emergent Adverse Events Reported by ≥2% of Subjects, Long-Term Safety Trial AN2728-AD-303, by Decreasing Frequency (Safety Population)

Adverse Events	Crisaborole 2% BID (N = 517)
Dermatitis atopic	58 (11.2%)
Upper respiratory tract infection	53 (10.3%)
Nasopharyngitis	40 (7.7%)
Cough	35 (6.8%)
Pyrexia	29 (5.6%)
Sinusitis	25 (4.8%)
Pharyngitis streptococcal	20 (3.9%)
Oropharyngeal pain	19 (3.7%)
Application site infection	18 (3.5%)
Dermatitis contact	16 (3.1%)
Asthma	16 (3.1%)
Vomiting	15 (2.9%)
Eczema	13 (2.5%)
Diarrhea	12 (2.3%)
Application site pain	12 (2.3%)
Ear infection	12 (2.3%)
Pharyngitis	12 (2.3%)
Influenza	12 (2.3%)
Seasonal allergy	11 (2.1%)
Otitis media	11 (2.1%)
Headache	11 (2.1%)
Viral infection	11 (2.1%)

Source: Modified from applicant's Table 48, 2.7.4 Summary of Clinical Safety

Table 72: Adverse Reactions Reported by ≥1% of Subjects, Long-Term Safety Study AN2728-AD-303 (Safety Population)

Adverse Reactions Trial AN2728-AD-303	Crisaborole 2% BID (N = 517)
Number of subjects who reported at least one treatment-related AE	
Possible	34 (6.6%)
Probable	11 (2.1%)
Definite	8 (1.5%)
Treatment-related AEs	
Dermatitis atopic	
Possible	11 (2.1%)
Probable	4 (0.8%)
Definite	1 (0.2%)
Application site pain	
Possible	2 (0.4%)
Probable	3 (0.6%)
Definite	7 (1.4%)
Application site infection	
Possible	6 (1.2%)
Probable	0
Definite	0

Source: Modified from the Applicant's Table 49, NDA 207695 / Sequence No. 0000 Crisaborole Topical Ointment, 2%; 2.7.4 Summary of Clinical Safety
Note that subjects reporting the same adverse event more than once are counted only once for that preferred term.

Multiple Consecutive Treatment Courses

Overall, 29.2% (151/517) of subjects received study drug for 3 or more consecutive cycles without improvement in the ISGA. The use of study drug for 3 or more consecutive cycles was more frequent in the younger age groups, with 31.5% (97/308) subjects in the 2–11 year age group, 26.0% (38/146) of subjects in the 12–17 year age group, and 25.4% (16/63) subjects ≥18 year age group.

Rescue Therapy

Per protocol, investigators prescribed low-to-mid potency TCS or calcineurin inhibitors as "rescue" therapy based on pre-specified IGSA scores or safety or tolerability findings. As requested by the FDA (Pre-NDA Meeting Minutes dated 10/8/2015), the applicant analyzed the

trends in rescue medication prescribing. Overall, 22.2% (115/517) subjects used 178 concomitant medications designated as rescue medications. Subjects in all age groups used rescue medications: 22.4% (69/308) subjects in the age group 7-11 years, 26.0% (38/146) subjects in the age group 12-17 years, and 12.7% (8/63) subjects in the age group ≥18 years. The medications were initiated following an average of 150 days after enrollment in the trial. Low- to- mid-potency topical corticosteroids such as triamcinolone, hydrocortisone, and desonide were the most commonly prescribed rescue medications. Calcineurin inhibitors such as pimecrolimus and tacrolimus were less frequently prescribed.

Reviewer Comment:

With regard to rescue therapy, the applicant indicates that the intermittent use of topical corticosteroids or calcineurin inhibitors reflects "real world conditions".

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development of crisaborole ointment, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. However, no subjects enrolled in the Phase 3 trials reported malignant neoplasms; a total of 4 subjects reported benign papillomas and 1 subject reported a lipoma.

With regard to the non-clinical evaluation of carcinogenicity, refer to Section 4.4 of this review for the Agency proposed labeling for Section 13 NONCLINICAL TOXICOLOGY.

8.8.2. Human Reproduction and Pregnancy

During the development of crisaborole ointment, all female subjects of childbearing potential were required to use acceptable methods of contraception from the Screening Visit continuously until 30 days after stopping the study drug. Trial staff performed pregnancy testing at Screening/Baseline and Day 29/End of Treatment during the pivotal trials. During the long term extension trial, staff performed pregnancy testing at Screening/Enrollment and on Day 1 of each treatment cycle. Per protocol, pregnant and lactating females were excluded from the trials. If subjects reported pregnancy, the investigators discontinued the investigational product and followed the pregnancy to delivery or final outcome.

A total of 4 subjects became pregnant in the Phase 3 trials to evaluate crisaborole ointment. No subjects enrolled in the Phase 1 and Phase 2 trials became pregnant and no female subjects exposed neonates to the study product through lactation. Among the subjects who became

pregnant, 3 subjects applied crisaborole ointment and one subject applied vehicle. The narratives are as follows:

AN2728-AD-301

Subject 150001, a 21-year-old white female with 59% BSA affected with AD, initiated treatment with crisaborole on (b) (6). The subject chose abstinence as her form of contraception. She had a negative urine pregnancy test result at Baseline/Day 1. After 28 days of treatment, the subject had a positive urine pregnancy test. An obstetrician confirmed the pregnancy with an estimated date of delivery of (b) (6). The subject was lost to follow-up approximately 5 months prior to the anticipated delivery date. As of the last contact date of December 9, 2014, the subject reported that the pregnancy was uneventful and all testing was normal.

AN2728-AD-302

Subject 215008, a 21-year-old white female, with 11% BSA affected with AD, initiated treatment with vehicle on April 28, 2014. She had a negative urine pregnancy test result at Baseline/Day 1. The subject chose Natazia as her form of contraception. Approximately 16 days later, the subject had a positive urine pregnancy test. The investigator withdrew the subject from the trial. After an uncomplicated pregnancy, the subject delivered a healthy infant. The applicant planned no additional follow-up.

Subject 233007, a 20-year-old American Indian/Alaska Native female with 9% BSA affected with AD, initiated treatment with crisaborole on (b) (6). She had a negative urine pregnancy test result at Baseline/Day 1. The subject chose Camrese as her form of contraception. After 28 days of treatment, the subject had positive urine and serum pregnancy tests. The investigator discontinued the study drug and the subject completed the trial. A healthcare provider confirmed the pregnancy with an estimated date of delivery of (b) (6) After an uncomplicated pregnancy, the subject delivered a healthy infant on The applicant planned no additional follow-up.

AN2728-AD-303

Subject 201004, a 26-year-old black female, with a history of hypertension since 2012, initiated treatment with crisaborole on April 14, 2014 during Trial AN2728-AD-302. The subject chose Mirena (levonorgestrel) as her form of contraception. The subject enrolled in AN2728-AD-303 on May 19, 2014. The subject had a negative urine pregnancy test result at Week 4 of AN2728-AD-303 (June 17, 2014). Her last dose of the study product (July 14, 2014) was more than 6 months prior to her positive urine pregnancy test at Week 48/End-of-study (April 20, 2015). A healthcare provider confirmed the pregnancy with an estimated date of delivery in December 2015. At the end to the trial she reported an uncomplicated pregnancy without need for additional diagnostic testing. However, the subject experienced a spontaneous abortion on August 13, 2015 which was attributed to underlying hypertension. The applicant considered this outcome to be unrelated to the study product because of the long latency period between

the potential conception date and her last exposure to crisaborole.

Reviewer Comment:

I agree with the conclusion of the investigator. Because the interval between the exposure to crisaborole and conception was greater than 6 months, the negative pregnancy outcome for Subject 201004 is not related to exposure to crisaborole.

Division of Pediatric and Maternal Health Consultation

The Agency began to implement the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" also known as Pregnancy and Lactation Labeling Rule (PLLR) on June 30, 2015. The PLLR requirements include the removal of pregnancy categories (A, B, C, D and X) from prescription drug and biological product labeling and the addition of information about the risks and benefits of using these products during pregnancy and lactation.

The Applicant did not conduct a search of published literature. The content of proposed labeling only included data from the crisaborole development program. The applicant submitted draft labeling for Sections 8.1, 8.2 and 8.4.

The Division consulted with the Maternal Health Division of Pediatric and Maternal Health (DPMH) team to provide comments regarding the appropriate format and content of the pregnancy and lactation sections of EUCRISA (crisaborole) Ointment, 2% labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format. After reviewing the data the DPMH Reviewer, Jane Liedtka, MD, concluded the following:

- "Human pregnancy outcome data for topical crisaborole were not found in the published literature. The limited numbers of cases from the applicant's files from the phase 3 trials are not sufficient to rule out a drug-associated risk to the fetus. However, pharmacokinetic data suggest systemic exposure with topical use is likely to be low and the animal data does not suggest a significant risk.

- There are no data on the presence of crisaborole in human milk. Crisaborole has characteristics (molecular weight <800 Daltons), which may increase the presence of the drug in maternal circulation and may increase transfer of the drug into breast milk. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breast milk. Given the lack of severe adverse events in adults in clinical trials and minimal systemic exposure following topical administration, DPMH agrees with the applicant that the following risk/benefit statement be included in section 8.2 of labeling:

  The development and health benefits of breastfeeding should be considered along

with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

- Animal reproductive studies of administration of crisaborole did not show any adverse effects on fertility. Since there is no information available on the effect of crisaborole on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in crisaborole labeling."

In consultation with the DPMH Reviewer, the Division recommended the following language for Sections 8.1, 8.2 and 8.4 of labeling for EUCRISA:

8.1 Pregnancy

Risk Summary

There are no available data with EUCRISA in pregnant women to inform the drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to 5 and 3 times, respectively, the maximum recommended human dose (MRHD) [see Data].

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

Data

Animal Data

Rat and rabbit embryo-fetal development was assessed after oral administration of crisaborole. Crisaborole did not cause adverse effects to the fetus at oral doses up to 300 mg/kg/day in pregnant rats during the period of organogenesis (5 times the MRHD on an AUC comparison basis). No treatment-related fetal malformations were noted after oral treatment with crisaborole in pregnant rats at dose up to 600 mg/kg/day (18 times the MRHD on an AUC comparison basis) during the period of organogenesis. Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of decreased fetal body weight and delayed skeletal ossification. Crisaborole did not cause adverse effects to the fetus at oral doses up to the highest dose tested of 100 mg/kg/day in pregnant rabbits during the period of organogenesis (3 times the MRHD on an AUC comparison basis).

In a prenatal/postnatal development study, pregnant rats were treated with crisaborole at doses of 150, 300 and 600 mg/kg/day by oral gavage during gestation and lactation

(from gestation day 7 through day 20 of lactation). Crisaborole did not have any adverse effects on fetal development at doses up to 600 mg/kg/day (18 times the MRHD on an AUC comparison basis). Maternal toxicity was produced at the high dose of 600 mg/kg/day in pregnant rats and was associated with findings of stillbirths, pup mortality and reduced pup weights.

8.2 Lactation

Risk Summary

There is no information available on the presence of EUCRISA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of EUCRISA to a breast fed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EUCRISA and any potential adverse effects on the breastfed infant from EUCRISA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of EUCRISA in pediatric patients below the age of 2 years have not been established."

Refer to DPMH Review by Jane Liedtka, MD dated 8/4/2016 for additional discussion regarding the format and content of the pregnancy and lactation sections of EUCRISA (crisaborole) Ointment, 2%. Labeling negotiations are ongoing at the time of this review.

8.8.3. Pediatrics and Assessment of Effects on Growth

The applicant evaluated pediatric subjects in all trials which were the primary source of data to support the safety and efficacy of crisaborole ointment for the treatment of atopic dermatitis. The Phase 3 trials enrolled subjects age 2 years and older. The entry criteria specified that at least 20 % of the subjects enrolled in the study would be between the ages of 2 and 6 years, and up to 15 % of the enrolled subjects would be adults.

Pediatric Study Plan

On April 24, 2014 the applicant submitted an initial Pediatric Study Plan (iPSP) which included a request for a partial waiver for assessments in the pediatric population from birth to less than 3 months old. The stated reason was because "Studies are highly impractical because the diagnosis of atopic dermatitis is uncommon and often unreliably made before age 3 months." The applicant also requested a deferral of the evaluation of pediatric subjects age 3 months to 2 years.

During a teleconference (May 21, 2014) the Division recommended that the iPSP include a protocol synopsis for a pharmacokinetic (PK) trial to be conducted in subjects age 3 months to less than 2 years of age under maximal use conditions, an increased sample size for the proposed Phase 4 trial to 100 subjects and additional laboratory monitoring.

On June 18, 2014, PeRC discussed the proposed iPSP and provided the following summary of their comments:

- Concurred with the Division that because this product was an NME, it was acceptable to review the long-term safety data (48 weeks) before initiating studies in younger children.
- Recommended that although juvenile toxicity studies were needed because the product was an NME, neonatal studies might not need to be conducted in 2 species.
- Nonclinical studies should be initiated as soon as feasible and not be delayed until after NDA submission/approval.

In an Advice letter dated July 7, 2014, the Division provided comments regarding the acceleration of the timeline, rationale for the deferral (to allow Agency review of the safety data from Phase 3 trials) and required non-clinical data to support the evaluation of subjects age 3 months to 2 years.

In the Agreed initial Pediatric Study Plan (iPSP) (dated October 6, 2014), the applicant proposed to conduct an open-label, Phase 4 pharmacokinetic and safety trial in 100 subjects age 3 months to < 2 years with mild-to-moderate AD involving at least 5% Treatable percent body surface area (%BSA), (b) (4) A total of 16 subjects with at least 35% Treatable %BSA will be included in a subgroup for pharmacokinetic (PK) assessment. The applicant proposed to initiate the trial in the 4th quarter of 2017 and complete the trial by the 4th quarter of 2018.

NDA submission

In the NDA submission (Section 1.9.1), the applicant included a request to waive the requirement to conduct clinical studies with Crisaborole Ointment, 2% in pediatric subjects ages birth to less than 3 months old. The justification for waiving the required pediatric assessment was:

> "Studies are highly impractical because the diagnosis of atopic dermatitis is uncommon and often unreliably made before age 3 months. For example, the AD involvement of the scalp, common in this age group, is often confused with seborrheic dermatitis."

In addition, the applicant included a request to defer the requirement to conduct clinical studies with Crisaborole Topical Ointment, 2% in pediatric subjects ages 3 months to less than 2 years. The justification for deferring the required pediatric assessment was:

> "Anacor is requesting a deferral of Clinical Study …to allow the Agency to review safety data from the Phase 3 trials in pediatric subjects age ≥2 years (b) (4) ."

The Division presented the Pediatric Study Plan to the Pediatric Review Committee (PeRC) on August 10, 2016. The following were the key comments from the PeRC summary (draft):

Eucrisa (crisaborole ointment, 2%) Partial Waiver/Deferral/Plan/Assessment (with Agreed iPSP)

- "This product triggers PREA as a new indication, new dosage form and new route of administration.
- The division continues to agree with the plan as presented in the agreed iPSP.
- The division clarified that there was a potential concern in other PDE4 inhibitors taken orally that weight loss was observed. The sponsor did not provide analysis of the effect of use of this product on growth in the pediatric patients studied in the clinical trials. The PeRC recommended that the sponsor provide an analysis (by patient) of growth during the trial and follow up period. If there is evidence of poor growth in treated patients, then additional information may be required to be collected in the deferred study in patients 3 months-2 years (e.g., additional longer-term follow up)."

Post-marketing Requirement:
Per the Pediatric Study Plan, the applicant agreed to conduct the following pediatric assessment:

> Deferred Trial Under Pediatric Research Equity Act (PREA)
> Conduct an open-label safety trial in 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 (b) (4) in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).
>
> Protocol Submission: 11/2016
> Date of Initiation: 12/2017
> Study Completion: 04/2019
> Study Submission: 09/2019

Reviewer Comment:

This reviewer agrees with the proposed Pediatric Study Plan and the proposed evaluation of pediatric subjects age 3 months to < 2 years as a deferred pediatric study as required by PREA. We are deferring submission of the data from the pediatric trial as described above for ages 3 months to <2 years for this application because this product is ready for approval for use in adults and the pediatric trial has not been completed. At the time of this review, discussions

regarding the language and content of the PMR are ongoing.

Other Pediatric Issues

Pediatric Division of the Pediatric and Maternal Health (DPMH) team
The Division consulted with the Pediatric Division of the Pediatric and Maternal Health (DPMH) team to provide comments regarding the evaluation of the potential for weight loss with the topical administration of crisaborole. See Section 8.5.6 of this review.

(b) (4)

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not report any cases of overdose with crisaborole in the development program. Overdose would be characterized by headache, gastrointestinal symptoms, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension (DALIRESP (roflumilast) tablets labeling.)

Based on the mechanism of action there is no reason to anticipate any potential for abuse or dependency. Therefore, the review team did not consult with the Controlled Substance Staff (CSS).

The applicant did not design or conduct trials to evaluate subjects for withdrawal or rebound. However, labeling for another product in this class (OTEZLA® (apremilast) tablets) included language regarding the potential for rebound in a limited number of cases. Labeling for the other approved PDE4 inhibitor (DALIRESP (roflumilast) tablets labeling) does not include similar language. Thus, this reviewer does not recommend including language to document potential rebound as a class effect.

8.9. Safety in the Postmarket Setting

The applicant is not currently marketing the proposed product in any country. There are no ongoing nonclinical or clinical trials that could provide additional data to inform the current or anticipated safety evaluation for this product (NDA 207695 SD 6, 4-Month Safety Update Report dated 4/27/2016).

8.10. Additional Safety Issues From Other Disciplines

There are no additional safety issues that were not adequately captured in earlier sections of the safety review. Refer to Section 8.

8.11. Integrated Assessment of Safety

The safety profile of EUCRISA (crisaborole) ointment, 2% was well characterized in the population age 2 to 79 years with mild to moderate atopic dermatitis. The applicant evaluated the local, systemic and long-term safety of their product in an adequate number of subjects to identify relevant safety issues. There were no deaths and no serious adverse events that were attributed to the study product. Generally, the adverse events observed with exposure to crisaborole were not unexpected for the pediatric age groups in which the disease commonly occurs. Many of these events related to local safety, common pediatric illnesses and disorders associated with atopic dermatitis such as asthma and allergies. The only adverse reaction observed in greater than 1% of subjects compared with vehicle was application site pain. The review team identified no safety signals that required mitigation.

The design of the long -term safety trial which involved intermittent treatment periods did not allow some potential adverse reactions to be completely characterized. The areas in which the risks associated with exposure to EUCRISA are still somewhat uncertain are depression and weight loss. Both of these events are included in the Warnings and Precautions sections of labeling for the approved, orally administered phosphodiesterase inhibitors. Although these moieties are different than crisaborole with greater anticipated exposure than a topical product, the occurrence of these potential class effects was carefully evaluated by the review team.

In addition, there was some uncertainty regarding the adequacy of the evaluation of effects of EUCRISA on the QT interval. However, these uncertainties were carefully adjudicated in collaboration with the QT Interdisciplinary Review Team (QTIRT) team.

<u>Suicidal Ideation and Depression</u>
The data indicated an imbalance in the incidence of adverse events in the psychiatric disorders SOC with exposure to crisaborole compared with vehicle. Although the incidence of these

adverse events was low during the development program, there is mechanistic plausibility that increased levels of cAMP may have central nervous system effects including effects on mood and memory. These potential effects were more rigorously evaluated in the case of the orally administered phosphodiesterase inhibitors, DALIRESP ® (roflumilast) tablets (NDA 22522), and OTEZLA® (apremilast) tablets (NDA 205437).

With regard to both orally administered phosphodiesterase inhibitors, there was no signal for suicidal ideation or behavior (SIB) events. In the case of roflumilast, an adequately conducted Columbia Classification Algorithm of Suicide Assessment (C-CASA) demonstrated no statistically significant difference in suicidality-related events between the active groups and placebo groups in subjects with COPD. (See Review by Phillip D. Kronstein, M.D, Division of Psychiatry Products 11/16/2010) In the case of apremilast, the C-CASA analyses of the data in subjects with psoriatic arthritis and subjects with psoriasis were inadequate (See Review by Phillip D. Kronstein, M.D, Division of Psychiatry Products dated 1/21/2014). Dr. Kronstein determined that there was no substantial signal for suicidal ideation or behavior. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) concluded that the data did not represent a clear signal for a psychiatric safety concern. However, because some of the events were clinically significant and causality could not be excluded, DPARP decided to include information about possible treatment emergent adverse events of depression and suicidal thinking and behavior in labeling. (b) (4)

With regard to this topically administered phosphodiesterase inhibitor, there was no definitive signal for suicidal ideation or behavior (SIB) events. Due to the timing of the event or use of a concomitant medication, none of the five cases indicated a clear association of severe depression or SIB events with administration of crisaborole. (Refer to Section 8.5.2) In addition, the systemic exposure after topically application of crisaborole is significantly less than after oral administration of roflumilast or apremilast. The mean C_{max} of crisaborole on Day 8 observed in the maximal use PK trial (AN2728-AD-102) was 127 ng/mL. In contrast, the mean C_{max} of roflumilast was 3060 ng/mL following oral doses of 250 mg daily for 12 days (NDA 22522, Clinical Pharmacology Review by Ping Ji, Ph.D., Agrawal Arun, Ph.D. dated 3/23/2010, page 18) and the mean C_{max} of apremilast tablets was 352 ng/mL following oral doses of 30 mg twice daily for 5 days (NDA 205437, Final Study Report for Trial CC-10004-PK-008, Table 4 and Clinical Pharmacology Review by Chinmay Shukla dated 5/2/2014)).

Considering the limited systemic exposure, paucity of cases and lack of clear causality, this reviewer does not recommend the development of a Warnings and Precautions section of labeling to include language regarding the risk of SIB events at this time. (b) (4)

(b) (4)

Weight Loss

The data to support an effect of crisaborole on weight was substantially less persuasive than the data for other members of the class of PDE-4 inhibitors such as orally administered OTEZLA (apremilast) tablets. (b) (4) In contrast to this well documented association, the data regarding the effect of EUCRISA on weight change was difficult to interpret for a variety of reasons which included the following:

- First, the majority of subjects in the study population were pediatric subjects who were expected to gain weight. Therefore, effects on weight may not be evident as weight loss but as failure to experience adequate weight gain. The anticipated weight gain may obscure any minor changes in weight related to exposure to the drug product.
- Second, the duration of the vehicle controlled period was only 28 days and weight was not assessed at the end of this period. Investigators measured weight once during the vehicle- controlled period and twice during the 48- week, open- label period. Without a vehicle control after Day 28, the long term findings from a limited number of data points were difficult to interpret.
- Third, the study staff received no specific training in the assessment of weight and height in pediatric subjects. In the case of the youngest pediatric subjects, dermatology offices may not have possessed the expertise and equipment to collect this data accurately. Notably, three of the 5 subjects with documented weight loss greater than 10% were enrolled in the same study site. When queried about one of these subjects, the principal investigator and suggested that measurement and/or documentation errors accounted for the apparent weight loss. This admission increases the likelihood that a staff member may have measured or recorded the values for weight incorrectly for multiple subjects.

The submitted data was insufficient to support the conclusion that weight loss is a class effect that may be observed with exposure to topical EUCRISA. Unlike apremilast, the number of subjects identified in this analysis with severe weight loss was small and documented weight loss did not appear to be correlated with greater exposure to the drug product or occur in association with diarrhea. Although a relationship cannot be excluded with certainty, I do not recommend that language regarding weight loss be included in labeling at this time.

Effects on Cardiovascular Safety

In Trial AN2728-TQT-108, the applicant evaluated the effects of supra-therapeutic doses of crisaborole ointment, 2% on QT/QTc interval compared to vehicle and moxifloxacin positive control in healthy subjects. The supra-therapeutic dose was defined as application of the study product to 60% BSA. The systemic concentrations of crisaborole following the supra-therapeutic dose in healthy subjects were approximately 30% lower than those achieved in the maximal use PK trial in pediatric subjects with AD (AN2728-AD-102). As a result, the applicant conducted routine cardiac safety monitoring as part of the safety evaluation during the pivotal Phase 3 trials. The conclusion reached by the Clinical Pharmacology team in collaboration with the QTIRT team was that there was no evidence that crisaborole has a clinically meaningful effect on the QTc interval.

9 Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling recommendations are contained within the body of this document. Labeling negotiations with the applicant are ongoing at the time of this review.

10.2. Patient Labeling

The applicant included PATIENT INFORMATION in this NDA submission for EUCRISA.
In a collaborative review dated August 10, 2016, Tara Turner, PharmD, MPH, Office of Prescription Drug Promotion (OPDP) and Sharon R. Mills, BSN, RN, CCRP, Division of Medical Policy Programs (DMPP) provided comments regarding the Patient Package Insert (PPI). In an effort to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication, the reviewers implemented formatting changes, reorganized the content, removed statements that were not product specific.

The recommended comments to the applicant from DMPP included the following:

- We deleted the section "(b) (4)?" because it is not a standard section in patient labeling, and is not relevant to include in the PPI.

OPDP Concurred

- We support deletion of the section "[redacted (b) (4)]?" and the statement "[redacted (b) (4)]" because of potential promotional implications. For instance, this statement could be used in comparative safety or efficacy claims. [redacted (b) (4)]

The reviewers concluded the following:
"The PPI is acceptable with our recommended changes."

Labeling negotiations with the applicant were ongoing at the time of this review.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this topical drug product, risk mitigation measures beyond professional labeling are not warranted at this time. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

12 Postmarketing Requirements and Commitments

Refer to Section 8.8.3 for additional information regarding the deferred trial required under the Pediatric Research Equity Act (PREA).

Deferred trial under Pediatric Research Equity Act (PREA)
Conduct an open-label safety trial in 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 [redacted (b) (4)] in 16 evaluable subjects with moderate atopic dermatitis and at least 35% treatable percent body surface area (%BSA).

Timeline
Protocol Submission: 11/2016
Date of Initiation: 12/2017
Study Completion: 04/2019
Study Submission: 09/2019

Pediatric Review Committee (PeRC) concurred with this assessment in the pediatric population age 3 months to < 2 years and the proposed milestones. However, as discussed in Section 8.8.3, PeRC expressed concern regarding the potential for this topical PDE4 to be associated with weight loss as a class effect. Comments from internal consultation with Division of Pediatric and Maternal Health are pending at the time of this review.

13 Appendices

13.1. References

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

Silverberg JI and Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol 2013. 24: 476–486.

Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011 Jan;131(1):67-73.

Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol. 2013 Aug; 24(5):476-86.

Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population-based study. J Allergy Clin Immunol. 2013 Oct 3. doi:pii: S0091-6749(13)01366-3. 10.1016/j.jaci.2013.08.031. [Epub ahead of print].

Williams HC. Atopic Dermatitis. N Engl J Med 2005;352:2314-24.

Yaghmaie, P et al. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol. 2013. 131: 428-433.

Zuberbier T,. Orlow SJ, Paller AS et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol 2006.118: 226-232.

13.2. Financial Disclosure

The covered clinical studies as defined in 21 CFR 54.2(e) include Trial AN2728-AD-301 and Trial AN2728-AD-302 which provide the primary data to establish effectiveness and safety of this drug product. The applicant also includes investigator information in an attachment to Form 3454 regarding Trial AN2728-AD-202, Trial AN2728-AD-204, Trial AN2728-TQT-108 and Trial AN2728-RIPT-101.

Covered Clinical Study (Name and/or Number):
AN2728-AD-301
AN2728-AD-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: AD-301: 48 sites. AD-302: 42 sites		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigators: Stock held by 2 Investigators 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	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The applicant provides Form FDA 3455 for the investigator, (b) (6), and sub-investigator, (b) (6), participating in Trial AN2728-AD-301 at (b) (6) Both investigators reported a significant equity interest in Anacor Stock (ANAC) above $50,000. (b) (6) purchased 515 shares of Anacor Pharmaceuticals, Inc. Stock on (b) (6) prior to the initiation of the trial (first subject enrolled 12 May 2014).The value at purchase was approximately $9810 and the value on (b) (6) was $53, 895. (b) (6) purchased a total of 1000 shares of ANAC stock from (b) (6) to (b) (6). Two other family members purchased 270 shares each of ANAC stock on (b) (6), (b) (6), and (b) (6). On (b) (6) the 2 family members each sold 100 shares. The value of the stock owned by (b) (6) on (b) (6) was $104,650 and the value of the stock owned by each family member was $17,791.

The applicant stated that the steps that minimized the potential for bias included:

1. Clinical Study AN2728-AD-301 was a randomized, double-blind, vehicle-controlled, multi-center, parallel-group study.
2. An IWRS was utilized for the study and there is no evidence that the blind was breached for site (PI for Site .
3. (Contract Research Organization for Anacor) conducted seven interim monitoring visits and a close-out visit at the site. There were no significant protocol deviations or compliance issues identified at these monitoring visits.

Reviewer Comment:

The approach to minimize bias is acceptable. The data from this single site is not likely to impact the outcome of the evaluation of efficacy or safety.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELINDA L MCCORD
11/02/2016

SNEZANA TRAJKOVIC
11/03/2016