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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review
Snezana Trajkovic, MD
NDA 207695
EUCRISA (crisaborole) Ointment, 2%

Cross-Discipline Team Leader Review

Date	12/5/2016
From	Snezana Trajkovic, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	207695
Applicant	Anacor Pharmaceuticals Inc.
Date of Submission	01/07/2016
PDUFA Goal Date	01/06/2017
Proprietary Name / Non-Proprietary Name	EUCRSA/crisaborole
Dosage form(s) / Strength(s)	Ointment, 2%
Applicant Proposed Indication(s)/Population(s)	Treatment of mild to moderate atopic dermatitis in patients 2 years of age 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

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

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. 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 children, scaly papules and plaques are distributed on flexor surfaces, neck and back. The intense pruritus and resultant scratching produce secondary changes of lichenification and excoriations which are typical features of chronic AD.

Therapeutic options for the treatment of AD include several approved topical corticosteroid (TCS) products: fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%. In addition to TCS products, two calcineurin products are approved for the treatment of AD: tacrolimus ointment, 0.03% and 0.1%; and pimecrolimus cream, 1%.

EUCRISA (crisaborole) ointment, 2% is a topical product proposed for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor. The proposed dosing regimen is to apply a thin layer of EUCRISA twice daily to affected areas.

Two pivotal trials of identical design, AN2728-AD-301 and AN2728-AD-302, enrolled 1523 subjects, 2 years of age and older with mild to moderate AD. In each of two adequate and well-controlled trials, a significantly greater proportion of subjects treated with crisaborole ointment, 2% achieved success on the primary efficacy endpoint compared to subjects treated with vehicle.

The safety database was adequate to characterize the safety of EUCRISA ointment, 2%.

In the two Phase 3 trials, 2 subjects in crisaborole treatment group and 3 subjects in vehicle group have reported application site urticaria. Two excipients in the current formulation of crisaborole ointment, 2% [propylene glycol and butylated hydroxytoluene (BHT)], have been described in medical literature to be associated with allergic contact dermatitis. Therefore, the information regarding urticarial reactions will be included in product labeling under 4 CONTRAINDICATIONS; 5 WARNINGS AND PRECAUTIONS, 5.1 Hypersensitivity Reactions subsection; and 6 ADVERSE REACTIONS.

The most frequently reported adverse reaction was an application site pain, reported in 4.4% of subjects treated with crisaborole and in 1.2% of subjects treated with vehicle.

Prescription and patient labeling as well as routine pharmacovigilance are adequate to manage the risk of EUCRISA ointment, 2% in the post market setting; a Risk Evaluation and Mitigation Strategy (REMS) is not needed.

Recommended postmarketing study includes 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).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- 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. - 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 children, scaly papules and plaques are distributed on flexor surfaces, neck and back. The intense pruritus and resultant scratching produce secondary changes of lichenification and excoriations which are typical features of chronic AD.	The AD is a common condition associated with significant discomfort due to inflammatory skin lesions and intense pruritus causing difficulties with concentration and disruption of sleep.
<u>Current Treatment Options</u>	Approved drug products indicated for the treatment of AD include several topical corticosteroid (TCS) products: fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%. In addition to TCS products, two calcineurin products are approved for the treatment of AD: tacrolimus ointment, 0.03% and 0.1%; and pimecrolimus cream, 1%.	There is a need for additional therapeutic options with improved safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• TCS are associated with local and systemic adverse events. Local adverse events include skin atrophy, striae, telangiectasia, irritation, folliculitis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, and secondary infections. Systemic adverse reactions reported with use of TCS include hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome, hyperglycemia, and unmasking of latent diabetes mellitus. • Labeling for both TCIs include boxed warning regarding reports of skin malignancies (e.g., basal cell carcinoma; squamous cell carcinoma; malignant melanoma) and lymphomas. As a result, TCIs are indicated as a 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.	
<u>Benefit</u>	• Two pivotal trials of identical design, AN2728-AD-301 and AN2728-AD-302, enrolled 1523 subjects, 2 years of age and older with mild to moderate AD [defined as $\geq 5\%$ of body surface area (BSA) involvement; score of mild (2) or moderate (3) on Investigator Static Global Assessment (ISGA) scale]. Subjects applied crisaborole ointment 2% BID or vehicle BID, for 28 consecutive days. The primary efficacy endpoint was the proportion of subjects achieving success on ISGA at Day 29. The success was defined as an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. A significantly greater proportion of subjects treated with crisaborole ointment, 2% achieved success on the primary endpoint compared to subjects treated with vehicle.	The data submitted by the applicant meet the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled.
<u>Risk</u>	• The safety database was adequate to characterize the safety profile of crisaborole ointment, 2%. • In the two Phase 3 trials, 2 subjects in crisaborole treatment group and 3 subjects in vehicle group have reported application site urticaria. Two excipients in the current formulation of crisaborole ointment	The safety profile of crisaborole has been adequately characterized.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2%, propylene glycol and butylated hydroxytoluene (BHT)), have been described in medical literature to be associated with allergic contact dermatitis. Therefore, the information regarding urticarial reactions will be included in product labeling under 4 CONTRAINDICATIONS; 5 WARNINGS AND PRECAUTIONS, 5.1 Hypersensitivity Reactions subsection; and 6 ADVERSE REACTIONS. • The most frequently reported adverse reaction at frequency $\geq 1\%$ was an application site pain, 4.4% in crisaborole treated subjects and 1.2% in vehicle treated subjects.	
<u>Risk Management</u>	• Labeling: Prescription labeling adequately addresses risks identified during product development. A REMS is not recommended.	Prescription and patient labeling as well as routine pharmacovigilance are adequate to manage the risk of crisaborole ointment, 2% in the post market setting; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. Prescription labeling adequately addresses risks identified during product development.

2. Background

Crisaborole ointment, 2% is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. The active ingredient, crisaborole, is a topical phosphodiesterase-4 (PDE-4) inhibitor. Crisaborole is a new molecular entity which is not marketed as a drug in the United States.

Crisaborole ointment, 2% was developed under the IND 77537 by Anacor Pharmaceuticals Inc. During their development program, the applicant interacted with the Agency at two milestone meetings: Pre-IND meeting (February 13, 2008); End-of-Phase 2 Meeting (February 26, 2014); and Pre-NDA Meeting (September 23, 2015).

During the pre-IND meeting the Agency provided general comments regarding the development of static global assessment (ISGA) scale.

During the End-of-Phase 2 meeting the Agency agreed with the applicant that the primary efficacy endpoint for the Phase 3 trials be the proportion of subjects achieving success in ISGA at Day 29, where success is defined as a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. The Agency also commented on three secondary endpoints:

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

In regard to proposed secondary endpoints, the Agency stated the following that “the secondary endpoints that the Division recommends include an evaluation of the signs and symptoms of atopic dermatitis (e.g. erythema, induration/population, 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).” During the meeting, the applicant stated that they will include signs and symptoms of atopic dermatitis as exploratory endpoints which are not intended for labeling. In addition, the applicant agreed not to use time to improvement of pruritus as a secondary endpoint. The applicant stated that time to improvement of pruritus will be used as an exploratory endpoint which is not intended for labeling.

During a pre-NDA meeting, the content and format of the pending NDA submission were discussed.

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 pruritus and red, dry, scaly papules and plaques. 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. Approved drug products indicated for the treatment of atopic dermatitis include topical corticosteroids [fluticasone propionate cream, 0.05%; hydrocortisone butyrate cream, 0.1%; mometasone furoate cream, 0.1%; mometasone furoate lotion, 0.1%; halobetasol propionate 0.05%; desonide gel, 0.05%; desonide foam, 0.05%; fluocinonide cream, 0.1%] and calcineurin inhibitor products (tacrolimus ointment, 0.03% and pimecrolimus cream, 1%).

3. Product Quality

EUCRISA (crisaborole) ointment, 2% contains crisaborole as the active ingredient. The chemical name of crisaborole is: 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-[2,1]-benzoxaborole. Crisaborole is , white to off-white solid that has empirical formula of C₁₄H₁₀NO₃ and the molecular weight of 251.1 g/mol. Crisaborole is manufactured by Anacor Pharmaceuticals, Inc.

Drug Product

The drug product, crisaborole topical ointment, 2% is white to off-white, petrolatum based ointment containing 2.0% of crisaborole. The drug product, EUCRISA (crisaborole) ointment, 2% has the following composition:

Table 1: 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 applicants submission, Quality Assessment, page 73.

Crisaborole ointment is packaged in laminate tubes with 3 packaging presentations: 60 g, 100 g and a physician sample.

Impurity Profile

On September 9, 2016, in response to Agency's Information Request from April 4, 2016 (regarding potential genotoxic/carcinogenic impurities (b) (4)

(b) (4) the applicant informed the Agency of presence of potential mutagenic impurities (b) (4). The applicant stated the following: "... a DEREK report was found which stated that th (b) (4)

On October 19, 2016, the applicant informed the Agency that they plan to revise the crisaborole drug substance specification to include controls for the two mutagenic impurities observed in the final drug substance, (b) (4), at the threshold of toxicological concern (TTC) of (b) (4) ppm.

On October 26, 2016, the applicant submitted an amendment that included information on a new testing site, Pfizer Groton (Pfizer Laboratories Div, Pfizer, Inc.), which was added to the NDA for the two new specified impurities. On November 21, 2016, the

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applicant submitted another amendment providing summaries of validation reports of the (b) (4) analytical methods used in the determination of the aforementioned two new specified impurities [(b) (4)].

The amendments were reviewed by drug substance reviewer, Dr. Joseph Leginus, who concluded that the control strategy for reducing these impurities and the acceptance criteria for (b) (4) with limits of “NMT (b) (4) ppm” in the crisaborole drug substance specification, were acceptable. Additionally, descriptions of the analytical methods for (b) (4) in the proposed drug substance specification and the method validation reports were deemed acceptable.

The amendment submitted on November 21, 2016 was also reviewed by Dr. Barbara Hill, a pharmacology/toxicology supervisor who concluded that applicant’s proposed specification for (b) (4), was acceptable.

Stability and Shelf-life

An expiration dating period of 24 months is recommended for the 60 g and 100 g presentations and 22 months for the physician sample presentation of crisaborole ointment, 2% based on statistical analysis of the 12 months of long-term primary stability data.

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

The product quality review team made the following conclusion: “The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.”

4. Nonclinical Pharmacology/Toxicology

In support of this application, the applicant submitted data from an extensive nonclinical program. The following paragraphs contain excerpts from the review of nonclinical pharmacology/toxicology reviewer, Dr. Kumar D. Mainigi:

In vitro assays for safety pharmacology revealed that crisaborole did not affect the common receptors, ion channels, and monoamine transporters; the drug also tested as a low-potency HERG-channel blocker.

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In animal safety pharmacology studies, drug did not damage the functioning of cardiovascular system in rats and mice at an oral dose of 1000mg/kg [40 and 81 maximum recommended human dose (MRHD)].

In single-dose (30,100,300mg/kg) male dog study, one high-dose animal died from hypertensive shock, however, at the same dose level, EKG, QTc intervals, and locomotor activity were not affected. Absolutely, no adverse cardiovascular effects were observed at the mid-dose level (27 MRHD).

Cardiovascular functions in minipigs treated with crisaborole, 5% ointment for three months remained normal. In 9-month minipig dermal study, two daily applications of 7% crisaborole ointment did not cause any changes in ECGs during the entire treatment and 1-month recovery period.

In single dose dog oral study, the bioavailability at 300mg/kg (81 MRHD) was only 0.8%. In single dose rat intravenous study, the elimination half-life in the abdominal fat was 1.2 hours; no drug retention was observed in major organs. In 90-day minipig dermal study (0%, 0.5%, 2%, 5% crisaborole ointment), the approximate drug accumulation did not exceed 2-4x; a concentration below the threshold level for minimum systemic toxicity.

In a set of in vitro assays using freshly isolated human hepatocytes from three healthy volunteers, drug did not induce any critical drug metabolizing CYP enzymes, especially CYP3A4, the most prominent CYP in humans induced by a broad spectrum of drugs. These findings suggest minimal (if any) drug-drug interactions.

In assays with human hepatic microsomes, drug did not exhibit any significant inhibition of CYP450 isoenzymes of C subfamily involved in drug metabolism. Together, these isoforms are estimated to account for metabolism of 20% of the prescribed drugs.

In mouse local lymph node assay, crisaborole at 1, 5, and 10% (w/v) levels did not produce any skin sensitization. In primary ocular and skin irritation assays in rabbits, 2% AN2728 ointment was tested as a mild to moderate irritant.

During 6-month of oral treatment, crisaborole at the highest dose level of 450mg/kg/day (NOAEL) did not cause any local or systemic toxicity in rats. Pharmacokinetic data at the end of treatment period did not indicate any accumulation of parent drug or its two major toxicologically/pharmacologically inert metabolites, deboronated crisaborole (AN7602) and carboxy-AN7602.

In 3-month minipig dermal study (vehicle, 0.5%, 2%, and 5% crisaborole ointment B) with one-month recovery period, two daily applications did not produce any systemic toxicity at NOAEL of 5 percent. On day-90, AUC (0-24 hr) values for 2% crisaborole ointment (the recommended human dose) and 5% crisaborole ointment in males were 1,080 ng hr/ml and 1,450 ng hr/ml, respectively. The corresponding AUC0-24 hr values in females were 851 ng·hr/ml and 1,330 ng·hr/ml, respectively. Taking into account, the pediatric mean AUC0-24 hr of 1,320 ng hr/ml, the safety margin at the NOAEL of 5% crisaborole ointment is approximately equivalent to the maximum recommended human dose (MRHD) based on AUC comparisons.

Following two daily applications of crisaborole ointment at the maximum feasible strength of 7% (w/v) for 9 months, absolutely no systemic toxicity was exhibited by minipigs. Sporadically distributed dermal lesions (e.g. hyperkeratosis/parakeratosis) among groups including controls, were due to slight traumatic dermal abrasion developed during handling of large animals. A minimal systemic absorption of crisaborole did not provide enough meaningful toxicokinetic data to determine systemic bioavailability of drug. However, the available data definitely supported an absolute lack of systemic toxicity during nine months of drug treatment and one month of recovery periods. The highest test concentration of 7% crisaborole (3.5 times the applied human concentration) was established as NOAEL for drug. Irrespective of the concentration level and the gender, AUC(0-24 hr) in males on day 168 and 252 ranged from lowest of 639 ng hr/ml to highest of 1,130 ng·hr/ml, expressing a relatively low systemic margin of safety compared to the human pediatric mean AUC0-24 hr of 1,320 ng·hr/ml (see table 2 in this review).

Crisaborole tested non-mutagenic in Ames assays conducted using four Salmonella and one E. coli strains in presence/absence of Aroclor- induced rat liver S9 fraction. Drug also did not induce any structural/numerical chromosomal aberrations in activated/non-activated (Aroclor-S9) human peripheral blood lymphocytes. In rat micronucleus assay, crisaborole at dose levels up to 2,000mg/kg did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes.

In 104-week rat oral carcinogenicity study (0, 30, 100, and 300mg/kg/day), no treatment related non neoplastic lesions were found. A drug related increased incidence of benign granular cell tumors in uterus with cervix or vagina combined was noted in high-dose females (control 6/65; low-dose 7/65; mid-dose 4/65; high-dose 20/65). Relevance of this finding in humans is unknown.

No drug-related neoplastic findings were noted at topical doses up to 7% crisaborole ointment in a dermal carcinogenicity study conducted in CD-1 mice.

Oral rat and rabbit embryofetal development studies 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

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administered to pregnant rabbits during organogenesis. No drug related fetal malformations were noted in the rat or rabbit embryofetal development studies. 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 68 non-clinical in vitro assays and whole animal studies in multiple species have projected a safety profile with a comfortable margin for human users.

The reader is referred to the comprehensive review by Kumar D. Mainigi, MSc., M.P.H., Ph.D., dated August 15, 2016.

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer Kumar D. Mainigi, MSc., M.P.H., Ph.D., recommended *Approval* of this application from nonclinical pharmacology/toxicology perspective (review dated August 15, 2016).

5. Clinical Pharmacology

Crisaborole is a topical phosphodiesterase-4 (PDE-4) inhibitor. PDE-4 is a cyclic adenosine monophosphate cAMP-specific PDE, a dominant PDE in inflammatory cells. PDE-4 inhibition elevates intracellular cAMP levels, which in turn activates protein kinase A and other downstream effectors, resulting in inhibition of pro-inflammatory cytokines' transcription and other cellular responses such as neutrophil degranulation, chemotaxis, and adhesion to endothelial cells. Nonclinical in-vitro and in-vivo studies performed to evaluate the potential for pharmacologic activity of the crisaborole metabolites AN7602 and AN8323 revealed the lack of PDE-4 inhibitory activity.

Pharmacokinetics (PK)

Absorption

The pharmacokinetics of crisaborole (AN2728), its metabolite AN7602 and downstream metabolite AN8323 were evaluated in a maximal use PK trial AN2728-AD-102. This was an open-label trial that enrolled 33 male and female subjects with mild to moderate AD, 2 to 17 years of age. Subjects below 12 years of age had $\geq 35\%$ of body surface area (BSA) involvement and subjects older than 12 years had $\geq 25\%$ BSA involvement. Subjects were divided in 3 cohorts:

- Cohort 1: 12 to 17 years
- Cohort 2: 6 to 11 years
- Cohort 3: 2 to 5 years

Approximately $3\text{mg}/\text{cm}^2$ of crisaborole ointment, 2% was applied to affected area of skin twice daily, for 8 consecutive days. The mean $\pm$ 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 $127 \pm 196 \text{ ng/mL}$ and $949 \pm 1240 \text{ ng}\cdot\text{h/mL}$, respectively. The mean $\pm$ SD C_{max} and AUC_{0-12} for AN7602 and AN8323 were $40.8 \pm 48.6 \text{ ng/mL}$, $290 \pm 313 \text{ ng}\cdot\text{h/mL}$ and $6150 \pm 4790 \text{ ng/mL}$, $63,400 \pm 49,000 \text{ ng}\cdot\text{h/mL}$, respectively, on Day 8. The mean accumulation factor based on the ratio of AUC_{0-12} between Day 8 and Day 1, were 1.87, 1.71 and 6.28 for crisaborole, AN7602 and AN8323, respectively.

Table 2: Summary of Mean PK Parameters

PK Parameter	AN2728			AN7602			AN8323		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
<i>Day 1</i>									
T _{max} , h ^a	34	3.00	3–12	34	3.00	3–12	34	12.0	3–24
C _{max} , ng/mL	34	111	113	34	37.8	35.0	34	2270	2640
AUC ₍₀₋₁₂₎ , ng·h/mL	32	759	730	32	247	224	32	16,800	16,900
AUC _(0-T) , ng·h/mL	34	863	759	34	288	237	34	30,800	30,500
AUC ₍₀₋₂₄₎ , ng·h/mL	29	833	694	29	274	207	29	32,500	32,500
<i>Day 8</i>									
T _{max} , h ^a	33	3.00	3–24	33	3.00	0–12	33	3.00	0–24
C _{max} , ng/mL	33	127	196	33	40.8	48.6	33	6150	4790
AUC ₍₀₋₁₂₎ , ng·h/mL	32	949	1240	32	290	313	32	63,400	49,000
AUC _(0-T) , ng·h/mL	33	1320	1310	33	398	347	33	119,000	87,600
AUC ₍₀₋₂₄₎ , ng·h/mL	32	1320	1330	32	391	351	32	116,000	86,700
AUC ₍₀₋₁₂₎ , area under the plasma concentration-time curve from time zero to 12 hours post dosing; AUC ₍₀₋₂₄₎ , area under the plasma concentration-time curve from time zero to 24 hours post dosing; AUC _(0-T) , area under the plasma concentration-time curve from time zero to the last measurable concentration; C _{max} , observed maximum plasma concentration after dosing; h, hour(s); PK, pharmacokinetic; SD, standard deviation; T _{max} , time to reach C _{max} .									
Note: Cohort 1, Ages 12–17 years, inclusive, with ≥25% Treatable BSA; Cohort 2, Ages 6–11 years, inclusive, with ≥35% Treatable BSA; Cohort 3, Ages 2–5 years, inclusive, with ≥35% Treatable BSA.									
^a For T _{max} , the median and range, rather than the mean and SD, are displayed									
Source: Clinical Pharmacology review; by Chinmay Shukla, Ph.D.; Table 2, page 7									

The summaries of mean PK data for crisaborole and its metabolites by age cohorts are presented below.

Table 3: Mean PK data of crisaborole (AN2728) by age cohort

PK Parameter	Cohort 1			Cohort 2			Cohort 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Day 1									
T _{max} , h	12	3.00	3 - 12	12	3.00	3 - 12	10	3.00	3 - 3
C _{max} , ng/mL	12	88.5	128	12	161	126	10	78.4	42.9
AUC ₍₀₋₁₂₎ , ng·h/mL	12	599	818	11	1,120	799	9	536	275
AUC _(0-T) , ng·h/mL	12	738	893	12	1,180	816	10	633	332
AUC ₍₀₋₂₄₎ , ng·h/mL	12	738	893	9	1,070	637	8	707	318
Day 8									
T _{max} , h	12	3.00	3 - 3	12	3.00	3 - 12	9	3.00	3 - 24
C _{max} , ng/mL	12	81.4	55.3	12	205	312	9	83.3	36.2
AUC ₍₀₋₁₂₎ , ng·h/mL	12	642	392	11	1,490	2,020	9	702	272
AUC _(0-T) , ng·h/mL	12	916	510	12	1,840	2,010	9	1,150	507
AUC ₍₀₋₂₄₎ , ng·h/mL	12	916	510	11	1,890	2,100	9	1,150	507

^aExpressed as median and range;

Source: Clinical Pharmacology review; by Chinmay Shukla, Ph.D.; Table 6, page 16

Table 4: Mean PK data of AN7602 (metabolite) by age cohort

PK Parameter	Cohort 1			Cohort 2			Cohort 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Day 1									
T _{max} , h ^a	12	3.00	3 - 12	12	3.00	3 - 12	10	3.00	3 - 3
C _{max} , ng/mL	12	27.4	31.0	12	57.0	44.0	10	27.3	14.0
AUC ₍₀₋₁₂₎ , ng·h/mL	12	185	201	11	366	285	9	185	89.0
AUC ₍₀₋₇₎ , ng·h/mL	12	230	228	12	397	290	10	225	120
AUC ₍₀₋₂₄₎ , ng·h/mL	12	230	228	9	351	237	8	253	117
Day 8									
T _{max} , h ^a	12	3.00	0 - 3	12	3.00	3 - 12	9	3.00	3 - 12
C _{max} , ng/mL	12	26.8	18.4	12	62.6	73.9	9	30.3	18.9
AUC ₍₀₋₁₂₎ , ng·h/mL	12	203	128	11	426	486	9	241	146
AUC ₍₀₋₇₎ , ng·h/mL	12	274	159	12	545	494	9	366	236
AUC ₍₀₋₂₄₎ , ng·h/mL	12	274	159	11	540	517	9	366	236

^aExpressed as median and range

Source: Clinical Pharmacology review by Chinmay Shukla, Ph.D.; Table 7, page 16

Table 5: Mean PK data of AN8323 (downstream metabolite) by age cohort

PK Parameter	Cohort 1			Cohort 2			Cohort 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Day 1									
T _{max} , h ^a	12	12.0	3 - 24	12	3.00	3 - 24	10	7.50	3 - 24
C _{max} , ng/mL	12	1,090	938	12	3,410	3,690	10	2,300	2,040
AUC ₍₀₋₁₂₎ , ng·h/mL	12	9,640	9,670	11	23,700	20,200	9	18,100	17,900
AUC _(0-T) , ng·h/mL	12	21,200	19,100	12	40,700	38,200	10.0	30,400	30,300
AUC ₍₀₋₂₄₎ , ng·h/mL	12	21,200	19,100	9	45,500	43,400	8.00	34,700	32,600
Day 8									
T _{max} , h ^a	12	3.00	0 - 12	12	3.00	0 - 24	9	0.00	0 - 12
C _{max} , ng/mL	12	4,100	3,550	12	7,750	5,900	9	6,750	3,980
AUC ₍₀₋₁₂₎ , ng·h/mL	12	44,400	37,200	11	76,200	62,500	9	73,200	40,900
AUC _(0-T) , ng·h/mL	12	82,200	63,300	12	146,000	110,000	9	132,000	71,400
AUC ₍₀₋₂₄₎ , ng·h/mL	12	82,200	63,300	11	139,000	113,000	9	132,000	71,400

^aExpressed as median and range

Clinical pharmacology reviewer, Dr. Chinmay Schukla concluded the following: “....the C_{max} and AUC₀₋₁₂ on Day 8 in Cohort 2 (ages 6-11 years) appear to be numerically higher than Cohort 1 and Cohort 3. However, definitive conclusions cannot be made regarding the effect of age because of the difference in the dose due to difference in BSA between younger and older subjects.”

Distribution

Based on in-vitro studies, crisaborole was 97% bound to human plasma proteins and the downstream metabolite AN8323 was 99% bound to human plasma proteins.

Metabolism

Crisaborole is extensively metabolized. The major metabolite was 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol (AN7602), which was formed by oxidative deboronation and hydrolysis. AN7602 was further metabolized to produce several downstream metabolites, among which 5-(4-cyanophenoxy)-2-hydroxyl benzoic acid (AN8323) (produced by oxidation) and AN7602-sulfate (produced by sulfation) were major circulating components accounting for ~70% and ~30% of the total radioactivity in the plasma, respectively, from 1 to 24 hours post-dose.

CYP3A4 and 1A1/2 seem to play a major role in the formation of AN7602. CYP2B6 and 2E1 also seem to contribute to the formation of AN7602.

Excretion

Renal excretion is the major route of excretion. The Absorption Distribution Metabolism and Excretion (ADME) study (AN2728-PSR-105) conducted in 6 healthy male subjects following a single topical dose of [14C]-AN2728 ointment E, 2% revealed median Tmax values of 8 hours and t1/2 values of 20.0 hours in plasma. Approximately 25% of the applied dose was absorbed percutaneously and 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 for [14C]-AN2728-derived radioactivity in humans after a topical dose.

Extrinsic Factors

To determine the inhibition and induction potential of crisaborole and its major metabolites on the activities of cytochrome P450 isoforms, the applicant conducted several in vitro studies.

I. CYP inhibition

In-vitro studies were conducted in human liver microsomes to determine whether crisaborole and its metabolites were an inhibitors or inducers of CYP enzymes (CYP450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5).

- **Crisaborole** did not inhibit (direct or metabolism-dependent) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 at concentrations up to 15 µM. However, crisaborole was found to competitively inhibit CYP2C19 with a Ki of 8.96 µM and it also showed a metabolism-based inactivation of CYP2C19 with a Ki of 22.3 µM.

To address the potential for crisaborole to inhibit CYP2C19 following clinical application of crisaborole ointment, 2%, the exposure of crisaborole, as determined in the maximal use PK trial (AN2728-AD-102) conducted in pediatric subjects with AD, was considered for the calculation of I/K_i. The results indicated that there is a low probability that the crisaborole is going to inhibit CYP2C19 under conditions of clinical use.

- **AN7602** did not inhibit any of the CYP enzymes tested.
- **AN8323** was a weak direct inhibitor of CYP1A2 and CYP2B6 and a moderate direct inhibitor of CYP2C8 and CYP2C9.

To address the potential for inhibition of CYP2C9 and CYP2C8 following clinical application of crisaborole topical ointment, 2%, the [I]/K_i ratio was calculated using plasma AN8323 results from the maximal use PK trial conducted in pediatric subjects with AD (AN2728-AD-102). The results indicated that [I]/K_i ratio for both CYP2C8 and CYP2C9 was more than 0.1 and therefore the clinical DDI studies investigating these two CYP subtypes were warranted. Because CYP2C9 was the most sensitive of CYP enzymes in-vitro, a clinical DDI study of co-administration of crisaborole ointment, 2% and 25 mg oral dose of warfarin (a CYP2C9 substrate) was conducted (AN2728-PK-101). The results of this study showed lack of drug interaction between crisaborole and warfarin.

II. CYP induction

- **Crisaborole:** In an in-vitro study using human hepatocytes with mRNA levels as endpoint, crisaborole did not induce CYP1A2, CYP2C9, CYP2C19, and CYP3A4/5. Crisaborole showed weak induction of CYP2B6 in 1 of 3 donors at a concentration of 10 µM. This interaction is not expected to occur under the conditions of clinical use.
- **AN7602:** A study was conducted to characterize the in-vitro induction potential of 0.1, 1, and 10 µM AN7602 on the activities of the CYP450 isoforms CYP1A2, CYP2B6, and CYP3A4, in human hepatocytes using mRNA levels as the end point. AN7602 did not induce any of the CYP enzymes tested.
- **AN8323:** An in-vitro study in human hepatocytes was conducted to characterize the in-vitro induction potential of AN8323 (at concentrations of 0.1 to 50 µM) on the activities of the CYP450 isoforms CYP1A2, CYP2B6 and CYP3A4/5. AN8323 appears to be a weak inducer of CYP1A2 but not CYP2B6 or CYP3A. However under conditions of clinical use, AN8323 is not expected to induce any of the CYP enzymes.

QT study

In order to evaluate the effects of crisaborole ointment, 2% (to-be-marketed formulation) on QT/QTc interval in comparison with vehicle and moxifloxacin positive control, the applicant conducted a TQT trial (AN2728-TQT-108) in healthy subjects. A total of 175

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subjects completed this study and this included 78 females and 97 males. Subjects were randomized in a 1:1:1 ratio of one of the 3 cohorts.

- Cohort 1: Vehicle and positive control (moxifloxacin) cohort
- Cohort 2: Therapeutic dose of crisaborole ointment, 2% for 8 days on 30% BSA
- Cohort 3: Supra-therapeutic dose of crisaborole ointment, 2% for 8 days on 60% BSA

Because the trial enrolled healthy adult volunteers, the systemic concentrations of crisaborole achieved in this trial were approximately 30% lower than that obtained in the maximal use PK trial (AN2728-AD-102). Due to the systemic concentration of crisaborole being lower in the TQT trial compared to maximal use PK trial, the applicant was advised to include standard cardiac safety monitoring in the Phase 3 trials. The results of the cardiac safety monitoring during Phase 3 trials did not show the signal for QT prolongation. Based on this information, the clinical pharmacology reviewer Chinmay Shukla, Ph.D., concluded the following: *“This reviewer concurs with the assessment of the QT-IRT reviewer and opines that clinically significant effects on QT prolongation are unlikely to occur under the conditions of clinical use of crisaborole ointment, 2%.”*

Post marketing Requirement:

Conduct a maximal use pharmacokinetic trial in 16 subjects 3 months to 1 year and 11 months with moderate atopic dermatitis with a body surface area involved of $\geq 35\%$.

The clinical pharmacology reviewer, Dr. Chinmay Shukla, recommended that the application is acceptable.

The reader is referred to the comprehensive review by, Chinmay Shukla, PhD., for a full discussion of the clinical pharmacology data (dated August 30, 2016).

I concur with the conclusions and recommendations reached by the clinical pharmacology review team.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two identically-designed, pivotal trials, AN2728-AD-301 and AN2728-AD-302, to establish the effectiveness of their product in the treatment of mild to moderate AD. Trials were randomized, double-blind, multicenter, vehicle-controlled, parallel-group, Phase 3 trials conducted in 1522 subjects 2 years of age and older. Subjects had mild to moderate AD defined by body surface area (BSA) involvement of $\geq 5\%$ and an Investigator's Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate).

Table 6: Clinical Study Overview for the Pivotal Trials

Trial	Trial Sites	Study Population	Treatment Arms	N	Dates
AN2728-AD-301	U.S. (47 centers)	Aged 2 years and older, BSA ≥ 5%, and ISGA score of 2 (mild) or 3(moderate)	Crisaborole ointment, 2%	503	3/26/2014 – 4/29/2015
			Vehicle ointment	256	
AN2728-AD-302	U.S. (42 centers)		Crisaborole ointment, 2%	513	3/26/2014 – 4/27/2015
			Vehicle ointment	250	

Source: Review by Dr. Matthew Guerra ; Table 2; page 5;

The trials enrolled similar population: subjects 2 years of age and older with mild to moderate AD. Trial AN2728-AD-301 enrolled and randomized a total 763 subjects (507 to crisaborole ointment, 2% and 256 to vehicle) from 47 centers in the United States. Four of the 507 subjects randomized to crisaborole ointment, 2% were not dispensed study drug and are not included in the ITT population. Trial 302 enrolled and randomized a total of 764 subjects (514 to crisaborole ointment, 2% and 250 to vehicle) from 42 centers in the United States. One of the 514 subjects randomized to crisaborole ointment, 2% was not dispensed study drug and was not included in the ITT population. In both trials, the discontinuation rate was higher in the vehicle arm compared to crisaborole ointment, 2% arm.

The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between each trial. Approximately 38% and 39% of subjects had an ISGA score of 2 (mild) at baseline in Trials AN2728-AD-301 and Trial AN2728-AD-302, respectively. The majority of study subjects were female (56%) and Caucasians (61%).

Table 7: Subject Disposition (ITT)

	Trial 301		Trial 302	
	EUCRISA (N=503)	Vehicle (N=256)	EUCRISA (N=513)	Vehicle (N=250)
Discontinued	30 (6%)	31 (12%)	31 (6%)	37 (15%)
<i>Adverse Event</i>	7 (1%)	2 (1%)	5 (1%)	4 (2%)
<i>Lost to Follow-Up</i>	5 (1%)	4 (2%)	4 (1%)	4 (2%)
<i>Other</i>	3 (1%)	1 (<1%)	2 (<1%)	6 (2%)
<i>Withdrawal by Parent/Guardian</i>	12 (2%)	18 (7%)	14 (3%)	20 (8%)
<i>Withdrawal by Subject</i>	3 (1%)	6 (2%)	6 (1%)	3 (1%)

Source: Review by Dr. Matthew Guerra; Table 6; page 9.

The protocol-specified primary efficacy endpoint was the proportion of subjects achieving success on ISGA at Day 29, where 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 protocol specified the following two secondary efficacy endpoints: the proportion of subjects with an ISGA score of 0 (clear) or 1 (almost clear) at Day 29; and the time to success on ISGA (i.e., score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline)

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP). The PP population was defined as all subjects in the ITT population who complete the Day 29 evaluation without any major protocol deviations.

Table 8 presents the results for the primary efficacy endpoint at Day 29 for both trials in the ITT population. Crisaborole ointment, 2% was statistically superior (p-values ≤ 0.038) to vehicle ointment on the primary efficacy endpoint in both trials. The proportions of subjects who achieved success in the crisaborole arms were similar between the two trials (i.e., 32.8% for Trial AN2728-AD-301 and

31.4% for Trial AN2728-AD- 302). The proportions of subjects who achieved success in the vehicle arms was higher in Trial AN2728-AD-301 compared to Trial AN2728-AD-302 (i.e., 25.4% vs. 18.0%).

Table 8: Results for the Primary Efficacy Endpoint at Day 29 (ITT, MI⁽¹⁾)
Trial AN2728-AD 301 Trial AN2728-AD 302

	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: Review by Dr. Matthew Guerra; Table 8; page 10.

Table 9 presents the results for the secondary efficacy endpoints in both trials. In both trials, crisaborole ointment, 2% was statistically superior (p-values ≤ 0.005) to vehicle ointment on both secondary efficacy endpoints. However, that the median time to success on 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 on ISGA.

Table 9: Results for the Secondary Efficacy Endpoints at Day 29 (ITT, MI⁽¹⁾)
Trial AN2728-AD 301 Trial AN2728-AD 302

Endpoint	Trial 301			Trial 302		
	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: Review by Dr. Matthew Guerra; Table 12; page 12.

Because an ISGA score of clear (0) or almost clear (1) with a 1-grade or greater improvement from baseline is not considered clinically meaningful improvement, this secondary endpoint was not considered for labeling.

The reader is referred to the reviews of Matthew Guerra, Ph.D. and Melinda McCord, M.D. for further information and additional analyses. Both Dr. Guerra and Dr. McCord concluded that the data support a determination of efficacy (reviews dated August 19, 2016 and November 11, 2016). I conclude that the applicant provided substantial evidence of effectiveness of crisaborole ointment, 2% for the indication of treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. In each of two adequate and well-controlled trials, a significantly greater proportion of subjects who were treated with crisaborole ointment, 2% demonstrated success on the primary endpoint of the proportion of subjects achieving score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline on ISGA at Day 29, compared to subjects treated with vehicle ointment.

8. Safety

The applicant conducted two identical randomized, vehicle controlled, Phase 3 trials (AN2728- AD-301 and AN2728-AD-302) in subjects 2 years of age and older, with mild to moderate atopic dermatitis. Pooled data from trials AN2728-AD-301 and AN2728-AD-302 comprised the primary safety database. In addition, 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 study product.

In addition, the applicant included findings from Trial AN2728-TQT-108 and Trial AN2728-RIPT-101 which investigated the effect of the crisaborole 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.

The primary safety population was comprised of subjects who took part in two pivotal Phase 3 trials including a total of 1012 subjects who were treated with crisaborole ointment, 2% and 499 subjects treated with vehicle ointment. 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.

In the primary safety population, the majority of subjects were White and female. The mean age of subjects in the pooled crisaborole group (12.3 years) was similar to the mean age of subjects in the vehicle group (12.1 years) and, approximately 60% of subjects in both treatment groups were 2 to 11 years of age. The majority of subjects in both treatment groups had AD of moderate severity and reported moderate pruritus. The mean treatable BSA in both treatment groups was 18%.

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. The number of subjects participating in the trial for 6 months or greater was 395 and the number of subjects participating for 12 months was 271.

Similar proportion of subjects in both treatment groups discontinued treatment due to AEs; 12 (1.2%) subjects in crisaborole group and 6 (1.2%) in vehicle group.

There were no deaths in crisaborole development program.

During the two pivotal Phase 3 trials a total of 8 subjects (0.8%) in the crisaborole treatment group and 1 subject (0.2%) in vehicle group reported serious adverse events (SAEs). None of reported SAEs occurred in more than one subject in the crisaborole group. The following SAEs were reported in the crisaborole group: Kawasaki’s disease; pneumonia; asthma; appendicitis; suicide attempt; application site infection; laceration; and suicidal ideation.

During the conduct of pivotal Phase 3 trials, the only adverse reaction reported at frequency of $\geq 1\%$ was the application site pain. In the crisaborole group, 4.4% of subjects reported application site pain compared to 1.2% of subjects in vehicle group.

In the two Phase 3 trials, 2 subjects in crisaborole treatment group and 3 subjects in vehicle group have reported application site urticaria. All five AEs of urticaria were deemed by the investigator as possibly related or related to the study drug administration. Two ingredients contained in the current formulation of crisaborole ointment, 2%, propylene glycol and butylated hydroxytoluene (BHT), have been described in medical literature^{1,2,3} to be associated with allergic contact dermatitis therefore, it is reasonable to conclude that the vehicle may be responsible for application site urticaria AEs. This reviewer recommends that the information regarding urticarial reactions be included in product labeling under **4 CONTRAINDICATIONS** section; **5 WARNINGS AND PRECAUTIONS** section, **5.1 Hypersensitivity Reactions** subsection and **6 ADVERSE REACTIONS** section.

In the Phase 3 trials, four cases of suicidal ideation and behavior (SIB) were reported in crisaborole treatment group compared to none in vehicle group. A consult was obtained from Jean Kim, MD., from the Division of Psychiatric Products. In her review, Dr. Kim stated the following: “Causality assessments from the case narratives for the SIB events only seemed possible for two of the four cases reviewed based on temporality and hypothetical mania induction in one case” and “The overall rates of psychiatric AEs appear extremely low in these Phase 3 studies, although there was also no formal psychiatric monitoring.”

During the open-label Trial AN2728-AD-303, 7 subjects reported SAEs: application site infection; upper respiratory tract infection; CNS ventriculitis; asthma; suicide attempt; depression; and anaphylactic reaction.

The applicant conducted two provocative dermal safety studies in a population of healthy subjects to evaluate the cumulative skin irritation and sensitization potential of crisaborole ointment, 2%. No subject had reaction suggestive of sensitization. Crisaborole was less irritating than negative control (0.9% saline solution) and positive control (0.5% sodium lauryl sulfate).

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

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The Phase 3 trials enrolled subjects age 2 years and older. On April 24, 2014 the applicant submitted an initial Pediatric Study Plan (iPSP) which included a request for a partial waiver for assessments of pediatric population from birth to less than 3 months old. The reason for this request was as follow: “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 conducting studies in pediatric subjects age 3 months to 2 years of age.

In the Agreed initial Pediatric Study Plan (iPSP) (dated October 6, 2014), the applicant proposed to conduct an open-label, 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). 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 (b) (4) and complete the trial by the (b) (4)

Current NDA submission included a request to defer the requirement to conduct clinical studies with crisaborole 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 $\geq$ 2 years (b) (4) .”

The Division presented the Pediatric Study Plan to the Pediatric Review Committee (PeRC) on August 10, 2016.

Per the Pediatric Study Plan, the applicant agreed to conduct the following pediatric assessment: 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 following timeline for pediatric study includes:

- Protocol Submission: 11/2016
- Date of Initiation: 12/2017
- Study Completion: 04/2019
- Study Submission: 09/2019

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted. The following is the conclusion reached by OSI reviewer Roy Blay, Ph.D.: “Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.” For detailed information refer to review by Dr. Roy Blay dated October 6, 2016.

12. Labeling

The package insert conforms to the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

All components of labeling were reviewed.

The proposed proprietary name, EUCRISA, was found acceptable from a safety and misbranding perspective.

The carton and container labels were acceptable.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Postmarketing Requirements (PMRs) under Food and Drug Administration Amendments Act (FDAAA):

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 following are PMR Schedule Milestones:

- Protocol Submission: 11/2016

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- Date of Initiation: 12/2017
- Study Completion: 04/2019
- Study Submission: 09/2019

14. Recommended Comments to the Applicant

None.

References:

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 2. North American Contact Dermatitis Group patch test results for 2007-2008. Fransway AF, Zug KA, Belsito DV, DeLeo VA, Fowler JF Jr, Maibach HI, Marks JG, Mathias CG, Pratt MD, Rietschel RL, Sasseville D, Storrs FJ, Taylor JS, Warshaw EM, Dekoven J, Wirwas M. Dermatol, 2013, Jan-Feb; 24(1); 10-21.
 3. Positive patch-test reactions to propylene glycol: a retrospective cross-sectional analysis from the North American Contact Dermatitis Group, 1996 to 2006. Warshaw EM, Botto NC, Maibach HI, Fowler JF Jr, Rietschel RL, Zug KA, Belsito DV, Taylor JS, DeLeo BA, Pratt MD, Sasseville D, Storrs FJ, Marks JG, Mathias CG. Dermatol 2009 Jan-Feb; 20(1):14-20.
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/s/

SNEZANA TRAJKOVIC
12/08/2016