CLINICAL PHARMACOLOGY REVIEW

NDA #:	207695/S-010
Submission Date:	09/13/2019 (SDN 495)
Brand Name:	EUCRISA® ointment
Generic Name:	Crisaborole (b) (4) 2%
Dosage Form:	Topical ointment
Dosage Strength:	2 %
Reviewer:	Luke Oh, Ph.D.
Pharmacometrics Reviewer:	Da Zhang, Ph.D.
Team Leader:	Chinmay Shukla, Ph.D.
OCP Division:	Division of Inflammation and Immune Pharmacology
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Pfizer, Inc
Submission Type:	Efficacy supplement
Indication:	Atopic dermatitis in adult patients and pediatric patients 3 months of age and older

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1. EXECUTIVE SUMMARY

Crisaborole is a benzoxaborole agent approved as a topical treatment for atopic dermatitis (12/14/2016). This supplemental New Drug Application (sNDA) contains the completed study (C3291002) report in response to a Written Request issued on 03/16/2017 and additionally this application is also aimed to fulfill postmarking requirement (PMR) 3142-1 issued on 12/14/2016 (see below).

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

The primary focus of this review would be on the Phase 4 study C3291002 in pediatric subjects (3 months - < 24 months of age) with atopic dermatitis and two population modeling analysis reports.

- Non-linear regression analysis of crisaborole systemic exposures
- Regression analysis of crisaborole and propylene glycol (PG) systemic exposure associated with crisaborole ointment 2% twice daily (BID)

1.1 Recommendation

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

1.2 Post-Marketing Requirements/Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics (PK): The Applicant conducted study C3291002 to evaluate the safety and PK of crisaborole in pediatric subjects (3 months - < 24 months of age). There were 21 subjects in the PK cohort who received topical application of crisaborole twice a day (BID) for 8 days under maximal use conditions and, following PK assessment these subjects continued to receive twice a day (BID) topical treatment till Day 28 (End of Treatment) identical to the non-PK cohort. The final number of subjects in the PK cohort was 13 as 3 subjects were not compliant, and the Applicant identified 5 subjects were outliers due to a possible cross-contamination. The Applicant submitted errata providing information on probable cross contamination to support the exclusion of 5 subjects and this is deemed reasonable from Clinical Pharmacology perspective. (see Section 2.1.2 for

further details). As a result, the youngest subject in the PK cohort was 4 months of age; however, a 3 month old subject is included in the safety assessment but not PK.

Table 1. Summary of PK parameters of crisaborole products

	n = 18		n = 13*	
Crisaborole	Mean	SD	Mean	SD
AUC_{tau} (h.ng/mL)	25080	66381	1163.5	549.6
C_{max} (ng/mL)	3320	8749.7	188	99.6
AN7602				
AUC_{tau} (h.ng/mL)	609.1	630.1	333.1	250.1
C_{max} (ng/mL)	80	73.7	53.1	46.1
AN8323				
AUC_{tau} (h.ng/mL)	76670	47751	81292	51805
C_{max} (ng/mL)	8468	5548.5	9064	6071

* 5 subjects were excluded based on information provided in the errata submitted by the Applicant.

Reviewer comments:

The Applicant's PK results exhibited a wide range of variability due to cross contamination of PK samples as described under Section ABC. The Applicant initially identified 2 subjects with high systemic exposure and excluded as outliers; two subjects (3 months of age and 4 months of age) presented Cmax of 236000 ng/mL and 160000 ng/mL, respectively, whereas the rest of subjects had Cmax ranged from 45 ng/mL to 1030 ng/mL. The Applicant later identified that there were 5 subjects from one clinic site (Site 1009) where potential cross-contamination was found as described in the submitted errata. Below is description from the errata:

> *Per Appendix 16.1.1, Protocol Section 6.11.3, prior to obtaining blood samples for PK analysis, the phlebotomy site was to be thoroughly cleansed with mild soap and water prior to being cleaned with isopropyl alcohol. The principal investigator at Site 1009 confirmed that the site did not cleanse the phlebotomy sites with soap and water prior to blood sample collection on Day 8. The site followed their standard procedure of cleaning the phlebotomy site with isopropyl alcohol wipes.*
> *Furthermore, the 5 participants had treated atopic dermatitis lesions on their arms. The principal investigator confirmed that the phlebotomy site for all participants was the antecubital vein.*

The Applicant stated the deviation did not have any impact on the safety nor withdrawal from the study. Based on the errata provided by the Applicant, this reviewer concluded

that it was reasonable to exclude the 5 subjects and re-analyzed the PK data (n = 13) and the summary of PK assessment is shown in Table 1. The mean systemic exposure of crisaborole in young pediatric subjects appear to be numerically higher to the systemic exposure of crisaborole in older pediatric subjects (2 to 17 years of age). Definitive conclusions could not be made due to high variability in the PK data and fewer number of subjects. It should be noted that all 18 subjects were included in safety assessments.

Drug formulation: The Applicant used the currently approved formulation for the treatment of AD in subjects 2 years of age and older.

Drug interaction assessment: As the current supplement does not require drug interaction assessment, the Applicant did not conduct any drug-drug interaction (DDI) studies.

2. QUESTION BASED REVIEW

2.1 General Clinical Pharmacology

2.1.1 What are the clinical trials conducted to support this application?

The Applicant conducted Phase 4 study and submitted pediatric study report as efficacy supplement to fulfill PMR and support approval of twice daily topical doing of EUCRISA in subjects 3 months to 2 years with atopic dermatitis.

2.1.2 What are the design features of the clinical pharmacology studies and what were the pharmacokinetic (PK) results?

As a subgroup of Phase 4 study, the Applicant conducted PK assessment under maximal use conditions in subjects from 4 - <24 months of age with atopic dermatitis.

Phase 4 study (C3291002): This was a multicenter, open-label, safety study of crisaborole ointment 2% in pediatric subjects with mild to moderate atopic dermatitis involving at least 5% treatable body surface area (BSA). In addition, pharmacokinetic (PK) assessment was conducted in a sub-group of subjects with at least 35% BSA under maximal use conditions.

Number of subjects: A total of 137 subjects 3 months to less than 24 months of age with atopic dermatitis were enrolled. The PK cohort had 21 subjects enrolled and 13 subjects were evaluated. The PK subgroup had 4 subjects who were less than 9 months of age enrolled.

Reviewer comments: As a part of Phase 4 study C3291002, the Applicant enrolled 21 subjects (3 - < 24 months of age) to evaluate the systemic exposure of crisaborole

following topical applications under maximal use conditions. However, 3 out of 21 subjects did not comply and were excluded. This resulted in a total number of 18 subjects in the PK cohort. The Applicant found later that additional 5 subjects from a single clinical site (site 1009) exhibited markedly high exposures due to possible cross-contamination between the phlebotomy site and treatment site on these subjects. The plasma sampling procedure was to wash the arm with soap and water and then clean the site with alcohol wipe prior to obtaining the PK sample. Site1009 was non-compliant and the arms were not wasted with soap and water, rather the phlebotomy area was only cleaned with an alcohol wipe prior to obtaining the PK sample. The 5 subjects identified as outliers had areas in the arm affected by AD and these subjects were excluded due to the possibility of cross contamination of the PK samples. This reviewer concurs with the exclusion of these 5 subjects.

The clinical pharmacology's recommendation in the written request was to target at least 16 completers in the PK cohort. The final evaluable subjects in the PK cohort were 13 subjects. The lower number of subjects are considered acceptable because the purpose of maximal use study is to assess systemic safety and all 18 subjects are included in the safety assessment and there are no systemic safety signals were identified. Based on totality of evidence, PK data from 13 subjects is considered reasonable.

Study period: 28 days of treatment. PK assessments were conducted on 8-day and these subjects continued in the study will 28 days.

Study design: This study had non-PK cohort and PK cohort who received treatment as described below:

- Non-PK cohort subjects: A thin layer of crisaborole ointment 2% was applied BID to all treatable AD lesions (excluding the scalp) with at least 5% BSA.
- PK cohort subjects: A thin layer of crisaborole ointment 2% was applied BID to all treatable AD lesions (excluding the scalp) with at least 35% BSA involved. Subjects with moderate AD were included in the PK subgroup. The amount of crisaborole ointment 2% to be topically applied was calculated individually for each subject by study staff, based upon the treatable %BSA as determined at Baseline/Day 1.

Plasma samples were collected at 3 sampling time points (i.e. pre-dose, 3 and 12 hours post-dose) on Day 8 to assess PK of crisaborole and its metabolites. In addition to this, systemic levels of propylene glycol (PG) were also assessed to address PG toxicity in infants by obtaining plasma samples at screening and Day 28 (end of treatment, EOT) in all the subjects and an additional pre-dose sample on Day 8 was obtained from subjects in the PK cohort.

PK results: Plasma concentrations of crisaborole and its metabolites in Table 2 are reported from all 18 subjects. Plasma concentrations shown in Table 3 are from n = 13 subjects excluding data from 5 subjects who were considered as outliers.

Plasma crisaborole concentrations

N = 18: Mean ± SD AUC_{tau} and C_{max} plasma crisaborole levels were 25080 ± 66381 h.ng/mL and 3320 ± 5849.7 ng/mL, respectively. Systemic exposures appear notably variable; AUC_{tau} ranged from 463 h.ng/mL to 236000 h.ng/mL and Cmax ranged from 45 ng/mL to 28000 ng/mL (Table 2).

N = 13: Mean ± SD AUC_{tau} and C_{max} plasma crisaborole levels were 1163.5 ± 549.6 h.ng/mL and 188 ± 99.6 ng/mL, respectively. Systemic exposures appear variable but less marked compared to all subjects (N = 18); AUC_{tau} ranged from 463 h.ng/mL to 2230 h.ng/mL and Cmax ranged from 45 ng/mL to 395 ng/mL (Table 3).

Metabolite PK in plasma

AN7602

N = 18: Mean ± SD AUC_{tau} and C_{max} were 609.1 ± 630.1 h.ng/mL and 80 ± 73.7 ng/mL, respectively (Table 2).

N = 13: Mean ± SD AUC_{tau} and C_{max} were 333.1 ± 250.1 h.ng/mL and 53.1 ± 46.1 ng/mL, respectively (Table 3).

AN8323

N = 18: Mean ± SD AUC_{tau} and C_{max} were 76670 ± 47751 h.ng/mL and 8468 ± 5548.5 ng/mL, respectively (Table 2).

N = 13: Mean ± SD AUC_{tau} and C_{max} were 81292 ± 51805 h.ng/mL and 9064 ± 6071 ng/mL, respectively (Table 3).

Table 2. Descriptive summary of plasma crisaborole PK parameters (n = 18) *(Source: Tables 14.4.4.2.1, 14.4.4.2.3, and 14.4.4.2.5 of Study report C3291002)*

	Plasma crisaborole		
	Mean	SD	(min, max)
AUC_{tau} (h.ng/mL)	25080	66381	463, 236000
C_{max} (ng/mL)	3320	8749.7	45, 28000
T_{max} (h)	4.3	2.7	11.7

	AN7602 (Oxidative metabolite)		
	Mean	SD	(min, max)
AUC_{tau} (h.ng/mL)	609.1	630.1	98.7, 2520
C_{max} (ng/mL)	80	73.7	10, 285
T_{max} (h)	4.6	3.7	0, 11.7

	AN8323 (Oxidative metabolite)		
	Mean	SD	(min, max)
AUC_{tau} (h.ng/mL)	76670	47751	6710, 191000
C_{max} (ng/mL)	8468	5548.5	648, 19800
T_{max} (h)	2.4	1.1	0, 3.1

Table 3. Summary of PK parameters of crisaborole product *(Source: Reviewer's analysis)*

	n = 13*		
Crisaborole	Mean	SD	(min, max)
AUC_{tau} (h.ng/mL)	1163.5	549.6	(462, 2230)
C_{max} (ng/mL)	188	99.6	(45, 398)
AN7602			
AUC_{tau} (h.ng/mL)	333.1	250.1	(99, 967)
C_{max} (ng/mL)	53.1	46.1	(10, 190)
AN8323			
AUC_{tau} (h.ng/mL)	81292	51805	(25800, 191000)
C_{max} (ng/mL)	9064	6071	(2470, 19800)

* 5 subjects were excluded based on information provided in the errata submitted by the Applicant.

Reviewer comments:

The Applicant stated the deviation (i.e. exclusion of 5 subjects) did not have any impact on the safety nor withdrawal from the study. Based on the errata provided by the Applicant, this reviewer re-analyzed the PK data (n = 13) and the summary of PK assessment is shown in Table 1. The mean systemic exposure of crisaborole in young pediatric subjects appear to be numerically higher to the systemic exposure of crisaborole in older pediatric subjects (2 to 17 years of age). Definitive conclusions could not be made due to high variability in the PK data and small number of subjects. Specifically, the mean ± SD Cmax and AUC_{0-12} of plasma crisaborole concentrations in pediatric subjects 4 - < 24 months of age were 188 ± 99.6 ng/mL and 1164 ± 549.6 h.ng/mL; while the mean ± SD Cmax and AUC_{0-12} of plasma crisaborole concentrations in older pediatric subjects (2 to 17 years of age) with AD were 127 ± 196 ng/mL and 949 ± 1240 h.ng/mL, respectively (*Data source: USPI of Eucrisa*).

Propylene glycol concentrations:

Mean ± SD plasma PG levels at baseline (i.e., at screening), Days 8, and 28 (or EOT) were (b) (4) ng/mL, (b) (4) ng/mL, and (b) (4) ng/mL, respectively (Table 4).

Table 4. Summary of propylene glycol concentration (ng/mL) *(Source: Table 14.4.4.1.3 of Study report C3291002)*

	Crisaborole 2% BID									
Analysis Visit	**N**	**NALQ**	**Mean**	**Std Dev**	**SE**	**Min**	**Q1**	**Median**	**Q3**	**Max**
BASELINE	135	[redacted]								(b) (4)
DAY 8	19									
END_OF_TREATMENT	119									

Baseline (n = 135) and end of treatment (n = 119) include subjects in non-PK cohort.

The plasma levels of PG were variable from (b) (4) (below the lower limit of quantitation, LLOQ) to (b) (4) ng/mL (or (b) (4) mg/dL) in subjects (Table 4). High systemic levels of propylene glycol are reported to cause cardiac and neurologic toxicity in infants and neonates. It should be noted that for the purpose of safety assessment of propylene glycol, none of the subject were excluded in the assessment of propylene glycol systemic concentrations. A potential toxicity of plasma PG level was investigated further in literature and available from foreign Agencies. There was no clear threshold level identified to define the safety of plasma PG level by FDA. Clinical reviewer provided information from the European Medicines Agency (EMA) indicating that PG is used as an excipient. Additionally, following literatures were in the Section 4.4.2 of EMA's "PG used as an excipient"

> *Similarly, Allegaert et al. [3] demonstrated that no short term biochemical impact was detected during or following a median propylene glycol exposure of 34 mg/kg/24 h (range 14–252). Exposure to propylene glycol seemed well tolerated and did not affect normal postnatal maturational changes in renal, metabolic and hepatic functions. De Cock et al. [19] built a pharmacokinetic model that showed that for these commonly used dosing regimens, the population mean of propylene glycol peak concentrations range between 2.8–21.8 mg /dL depending on birth weight and age of the neonates.*

[3] Allegaert, K., Vanhaesebrouck, S., Kulo, A., Cosaert, K., Verbesselt, R., Debeer, A. and Hoon, J. De (2010). Prospective assessment of short-term propylene glycol tolerance in neonates. *Archives of disease in childhood* 95, 1054–1058.

[19] De Cock, R. F. W., Allegaert, K., Vanhaesebrouck, S. and Al., E. (2013). Low but inducible contribution of renal elimination to clearance of propylene glycol in preterm and term neonates. *Submitted to Ther Drug Monitor*.

The information from the literature suggests that plasma PG level up to 21.8 mg/dL appears safe. The highest plasma PG concentration measured in Phase 4 study C3291002 was (b) (4) ng/mL ((b) (4) mg/dL), which is about (b) (4) fold lower than the literature reported PG level (21.8 mg/dL). While the available information suggests that the highest plasma

PG level in this study appears acceptable, and furthermore there was no safety signal indicating PG toxicity in this study.

2.1.3 What is the summary of efficacy?

Since this was an open label study, efficacy was assessed as an exploratory endpoint. The primary efficacy endpoint was the proportion of subjects with Investigator's Static Global Assessment (ISGA) score of clear or almost clear with at least a 2-grade improvement from baseline at Day 29 following 28 days of BID treatment.
The Applicant indicated that ISGA success was achieved in 20.0% of subjects by Day 8 and had increased to 30.2% by Day 29 after topical crisaborole treatment. Eczema Area and Severity Index (EASI) scores improved by 49.56% at Day 15 and by 57.53% by Day 29 compared with baseline after topical crisaborole treatment.

Reviewer comments: *See Clinical and Biostatics reviews for further details.*

2.1.4 What is the summary of safety?

For the purpose of systemic safety assessment, none of the subjects were excluded. There were no deaths or unexpected adverse events (AEs). One subject (not in the maximal use cohort) experienced a serious AE (seizure associated with fever and assessed as not related) and no subjects withdrew from the study due to AEs. For 7 subjects, investigators reduced the dose or withdrew the study product due to treatment emergent AE (TEAE). Four subjects discontinued the study product permanently [febrile convulsion (subject not in the maximal use cohort), dermatitis infected, application site pain and application site discomfort]; three subjects reduced the dose (application site erythema) or temporarily withdrew the study product (dermatitis atopic, application site reaction/contact dermatitis).
Overall, 88 subjects (88/137, 64%) experienced a total of 192 TEAEs. The most common system organ classes were Infections and Infestations (43/137, 31%), Skin and Subcutaneous Tissue Disorders (37/137, 27%), General Disorders and Administration Site Conditions (26/137, 19%) and Gastrointestinal Disorders (15/137, 11%). The most common preferred terms (PT) were pyrexia (13/137, 10%), upper respiratory tract infection (10/137, 7%) and diarrhea (10/137, 7%). A total of 43 subjects (31%) experienced 59 adverse events localized to the application site. One subject (1%) experienced a severe TEAE (dermatitis allergic) and 4 subjects (3%) experienced contact dermatitis at the application site.

Reviewer comments: *Seizure and febrile convulsions were reported in subjects not in the maximal use cohort. For further information, see Clinical review.*

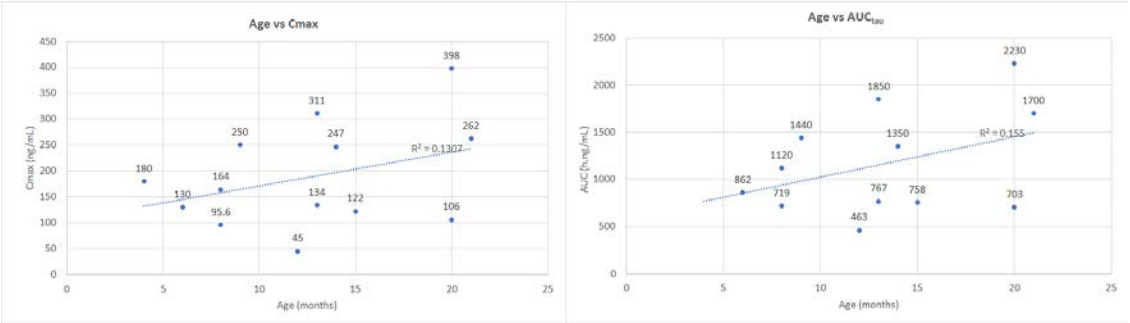
2.2 Intrinsic Factors

2.2.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.2.1.1 Effect of age and body surface area (BSA) on PK

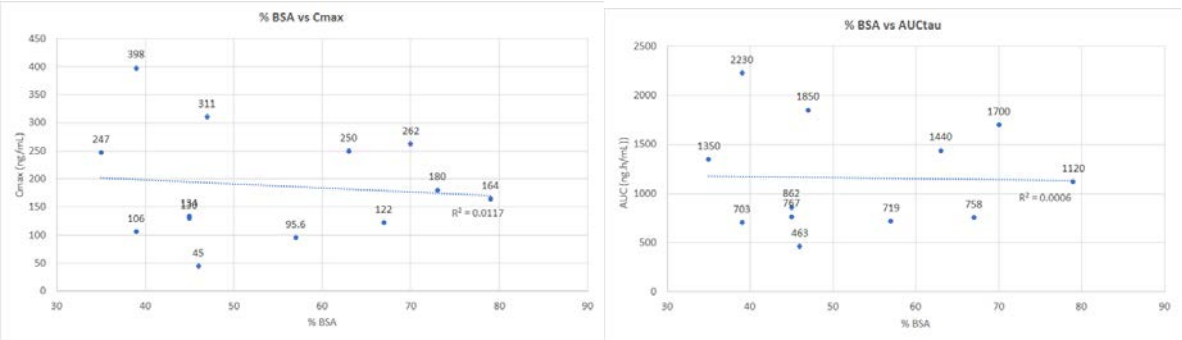
This reviewer's exploratory analysis on a potential effect of age and BSA treated on the systemic exposure of crisaborole. The results suggest increase of systemic exposure of crisaborole following topical application with increase in age (Figure 1). The Applicant conducted the study with 3 mg/cm^2 of the study product applied to the treatable BSA. The mean ± SD of % BSA of subjects in the PK cohort was 54.2 ± 14.1%. Systemic exposure of crisaborole exhibited no correlation with % BSA (Figure 2). Definitive conclusions could not be made due to small number of subjects.

Figure 1. Effects of age (4 - < 24 months) on C_{max} or AUC_{tau} in Study C3291002 (n = 13) *(Source: Reviewer's analysis)*



Note: Data in Figure 1 is excluding 5 subjects with suspected cross contamination.

Figure 2. Effects of % BSA on C_{max} or AUC_{tau} in Study C3291002 (n = 13) *(Source: Reviewer's analysis)*

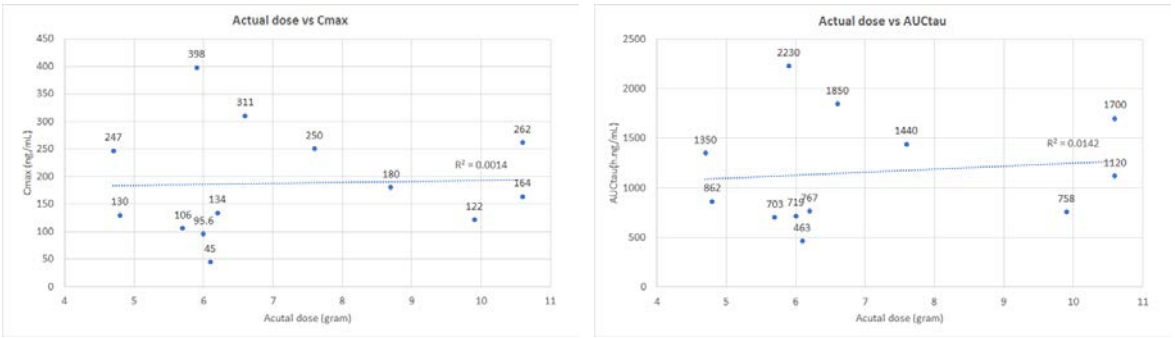


Note: Data in Figure 2 is excluding 5 subjects with suspected cross contamination.

2.2.1.2 Effect of actual dose on PK

This reviewer's exploratory analysis on a potential effect of actual dose applied on the systemic exposure of crisaborole suggest there is little correlation between actual dose applied per day and systemic exposure of crisaborole (Figure 3). Mean ± SD of actual dose applied per day was 7.2 ± 2.0 gram.

Figure 3. Effects of actual dose per day on C_{max} or AUC_{tau} in Study C3291002 (n = 13) *(Source: Reviewer's analysis)*



Note: Data in Figure 3 is excluding 5 subjects with suspected cross contamination.

2.3 Analytical Section

2.3.1 How are the active moieties identified, and measured in the clinical trials?

Crisaborole and metabolites concentrations in the plasma samples collected from Phase 4 study C3291002 were analyzed using high performance liquid chromatography and

tandem mass spectrometry (HPLC-MS/MS). Although not the active moiety, the Applicant measured the systemic levels of propylene glycol (PG) in enrolled subjects.

2.3.2 Which metabolites have been selected for analysis and why?

The Applicant assessed the systemic exposure of two metabolites (AN7602 and AN8323) following topical application of the study product under maximal use conditions. The metabolites selected are the same ones that were studied in subjects 2 years of age and older.

2.3.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured.

2.3.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of standard curve was:

- Crisaborole: 0.2 – 100 ng/mL
- AN7602: 0.2 – 100 ng/mL
- AN8323: 10 – 5000 ng/mL
- PG: 100 – 10,000 ng/mL

Plasma concentrations of crisaborole, metabolites and PG in the Phase 4 study C3291002 were mostly within the range of the assay.

2.3.5 What are the accuracy and precision at LLOQ?

Table 5. Summary of accuracy and precision of bioanalysis method

Analyte	Inter-Assay	
	Accuracy (%)	*Precision (% CV)*
Crisaborole	1.33 to 1.75	≤ 5.03
AN7602	-3.67 to 0.533	≤ 5.35
AN8323	-4.75 to 5.07	≤ 4.00
PG	-3.6 to 3.3	≤ 7.8

2.3.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Table 6. Summary of stability analysis

Parameter	Crisaborole	AN7602, AN8323	PG
Freeze/Thaw cycle stability	4 cycles at -70 ºC/on ice	4 cycles at -70 ºC/on ice	5 cycles at - 80 ºC
Room temperature stability	N/D	N/D	N/D
Long term stability	185 days at -70 ºC	185 days at -70 ºC	213 days at -20 ºC and - 80 ºC

N/A: Not determined

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for Phase 4 study C3291002.*

2.3.7 What are the results of incurred sample reanalysis (ISR)?

Crisaborole, AN7602, and AN8323

The ISR was performed on 19 samples from 7 subjects. Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of within ± 20.0% for HPLC-MS/MS assays.

Propylene glycol

The ISR was performed on 29 study samples, composed of 2 samples from 14 subjects, 1 sample from 1 subject. Samples were reanalyzed using the identical analytical method and same dilution factors as used for the original reported results. Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of within ± 20.0% for HPLC-MS/MS assays. The results are presented in Table 7.

Table 7. Incurred Sample Reanalysis (ISR) assessment *(Source: Section 4 Assay performance summery in 16.2.5.10.1 C3291002 analytical report)*

Crisaborole, AN7602, and AN8323

Total number of ISR samples reanalyzed:	PF-06930614 (AN2728): 19 PF-06932648 (AN7602): 19 PF-06947370 (AN8323): 19
Total number of ISR samples reanalyzed ≤20% difference:	PF-06930614 (AN2728): 19 PF-06932648 (AN7602): 16 PF-06947370 (AN8323): 19
Percentage within ±20.0%:	PF-06930614 (AN2728): 100% PF-06932648 (AN7602): 84.2% PF-06947370 (AN8323): 100%
Comments: Statistical results were reported in a manner consistent with MicroConstants LIMS systems. Concentrations are reported to 3 significant figures and all percentages are reported to 1 decimal place. The following terminology is considered equivalent: %CV = RSD = Precision (%), % Bias = Accuracy (%).	

Propylene glycol

Total number of ISR samples reanalyzed:	29
Total number of ISR samples reanalyzed ≤ 20.0% difference:	29
Percentage within ± 20.0%:	100.0%
Comments: Statistical results were reported in a manner consistent with WuXi AppTec LIMS systems. Concentrations are reported to 3 significant figures and all percentages are reported to 1 decimal place. The following terminology is considered equivalent: %CV = Precision (%), % Bias =%RE	

Reviewer comments: *The ISR data for plasma crisaborole, metabolites, and PG were within the acceptable limit.*

3. DETAILED LABELING RECOMMENDATIONS

The following changes are recommended in the Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer, and the ~~strikethrough~~ text indicates recommended deletion. A complete revision of Section 12.3 Pharmacokinetics is recommended.

Proposed labeling by the Applicant	Labeling recommendation
	12.2 Pharmacodynamics **Cardiac Electrophysiology** **At therapeutic doses, EUCRISA ointment is not expected to prolong QTc to any clinically relevant extent.**
12.3 Pharmacokinetics	**12.3 Pharmacokinetics**

Absorption The pharmacokinetics (PK) of EUCRISA were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and 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 factor for crisaborole was 1.9.	Absorption The pharmacokinetics (PK) of EUCRISA were investigated in 33 pediatric subjects 2 to 17 years of age with mild to moderate atopic dermatitis and 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 factor for crisaborole was 1.9. **The PK of EUCRISA were investigated in 13 subjects 4 months to less than 24 months of age, the mean ± SD C_{max} and AUC_{0-12} for crisaborole were 188 ± 100 ng/mL and 1164 ± 550 ng·h/mL, respectively.**

4. APPENDIX

Phase 4 Study C3291002

Section 2.1.2 describes detailed results and overall conclusion. This section will have individual information as summarized in Table A1.

Reviewer's analysis: *PK values of each individual in Table A1 shows the variability in plasma concentrations in pediatric population as anticipated. Overall, systemic exposure of crisaborole between younger subjects (4 months - < 2 years of age) after excluding the 5 outliers were numerically higher than the older subjects (2 years of age - < 17 years of age).*

In subjects 4 months - < 2 years, the mean ± SD Cmax and AUCtau of plasma crisaborole concentrations were 188 ± 99.6 ng/mL and 1163.5 ± 549.6 h.ng/mL, respectively. While the mean ± SD Cmax and AUCtau of plasma crisaborole concentrations in older pediatric subjects (2 to 17 years of age) with AD were 127 ± 196 ng/mL and 949 ± 1240 h.ng/mL, respectively (data obtained from the approved label).

Table A1. Summary of PK values of individual subjects in PK cohort (*Source: Reviewer's analysis)*

count	Subject ID		Age (months)	gender	AUCtau (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	Treatable %BSA	Actual dose (gm)	PG at screening (ng/mL)	PG at Day 8	PG at EOT
1	1007	(b) (6)	12	f	463	45	3	46	6.1	30000	1030	39500
2	1008		6	m	862	130	2.95	45	4.8	4140	2470	4720
3	1008		13	m	767	134	2.83	45	6.2	324	553	472
4	1009		23	m	4650	640	2.83	48	7.9	367	559	137
5	1009		20	m	2230	398	11.7	39	5.9	250	872	3980
6	1009		13	m	1850	311	2.68	47	6.6	6340	8130	2020
7	1009		21	f	1700	262	2.72	70	10.6	1370	713	6710
8	1009		19	f	5390	1030	2.72	43	6.7	1320	1650	2110
9	1009		9	m	1440	250	3.1	63	7.6	<100	138	393
10	1009		4	f	160000	26700	11.1	56	5.3	348	916	NA
11	1009		14	m	6310	937	2.98	56	7.8	1110	469	10000
12	1009		3	m	236000	28000	11.1	59	6.3	399	799	9350
13	1028		15	m	758	122	3	67	9.9	21300	1390	NA
14	1029		14	f	1350	247	2.9	35	4.7	2140	997	4840
15	1036		20	f	703	106	3.08	39	5.7	6100	1470	1540
16	1036		8	m	719	95.6	3	57	6	<100	364	504
17	1036		8	f	1120	164	3.08	79	10.6	415	1250	1920
18	1036		4	m	NA	180	2.93	73	8.7	250	475	2650
Mean					25077.2	3319.5	4.3	53.7	7.1	4760.8	1346.9	5677.9
SD					66480.9	8749.7	3.2	12.8		8547.3	1781.2	9524.3
Mean	w/o outliers				1163.5	188.0				6602.6	1527.1	5770.8
SD	w/o outliers				549.6	99.6				9877.0	2072.5	10808.2

Yellow indicates outlier.

Additional analysis to investigate the ratios of metabolite/parent suggest that cross-contamination is likely a factor causing a high crisaborole level in plasma samples and this further justifies the exclusion of the 5 subjects (Table A2).

Crisaborole was found to be extensively metabolized. The major metabolite was 5-(4-cyanophenoxy)-2-hydroxyl benzyl alcohol (AN7602). CYP3A4 and 1A1/2 seem to play a major role in the formation of AN7602. AN7602 is further metabolized into AN8323. Since AN8323 is downstream metabolite, it's metabolite/parent ratio will not be considered for this discussion.

The expression of CYP3A4, the major enzyme involved in producing metabolite AN7602, in young pediatric subjects (3 – < 24 months of age) appears to approach the expression of CYP3A4 in the older subjects as reported by Hakkola et al. (1998) and Gregory Kearns (2000). Hence the metabolite to parent ratio of the exposure of AN7602 and crisaborole should be fairly comparable between all subjects aged 3 months and older.

In the event there is contamination of the phlebotomy site due to crisaborole left on the skin, the ratio of metabolite and parent should be smaller.

In subjects 4 months to < 2 years, the mean ratio of AUC and Cmax AN7602/crisaborole not including outliers were 0.27 for both, while mean values of the same ratio for the 5 subjects that were outliers were 0.09 and 0.07, respectively (Table A2). Based on clinical pharmacology review of the original NDA, the mean ratios of AUC and Cmax of AN7602/crisaborole in adult subjects were 0.31 and 0.32 while those values in subjects 2 year to 12 year old were 0.31 and 0.28 (calculated based on PK data reported in the review by Dr. Chinmay Shukla, see review in DARRTS dated 08/30/2016). This further justifies the exclusion of 5 subjects as the low value of AN7602/crisaborole ratios in outliers indicates that there are high levels of crisaborole in the plasma sample suggesting that cross-contamination could be a likely factor.

The low ratios in outliers indicated that there are high levels of crisaborole suggesting that cross-contamination could be a likely factor.

<u>References:</u>

- *Hakkola, J., Tanaka, E., and Pelkonen, O. (1998). Developmental expression of cytochrome P450 enzymes in human liver. Pharmacology & toxicology Vol.82(5), p209-217*
- *Gregory L. Kearns (Sept 2000). Impact of developmental pharmacology on pediatric study design: Overcoming the challenges. J Allergy Clin Immunology Vol. 106(3), p S128-S138*

Table A2. Ratio of plasma levels of metabolite (AN7602)/parent (*Reviewer's analysis*)

				Ratio AN7602/parent	
count	Subject ID	(b) (6)	Age (months)	AUC	Cmax
1	1007		12	0.21	0.22
2	1008		6	0.36	0.39
3	1008		13	0.13	0.12
4	1009		23	0.14	0.12
5	1009		20	0.43	0.48
6	1009		13	0.26	0.22
7	1009		21	0.35	0.26
8	1009		19	0.10	0.07
9	1009		9	0.21	0.15
10	1009		4	0.01	0.01
11	1009		14	0.17	0.12
12	1009		3	0.01	0.01
13	1028		15	0.30	0.29
14	1029		14	0.20	0.19
15	1036		20	0.23	0.20
16	1036		8	0.19	0.20
17	1036		8	0.32	0.35
18	1036		4		0.40
Mean				0.21	0.21
SD				0.12	0.13
Mean (excluding outliers)				0.27	0.27
SD (excluding outliers)				0.09	0.11
Mean of outliers				0.09	0.07

Population PK Modeling Analysis Review

Non-linear Regression Analysis of Crisaborole Systemic Exposures

The Sponsor conducted non-linear regression analysis of crisaborole systemic exposures (Report PMAR-EQDD-C329a-DP4-774) based on data from 3 Phase 1 HV, 2 Phase 1b in AD subjects and 1 Phase 1b in psoriasis subjects utilizing crisaborole topical ointment 2% with the objectives to characterize the correlation of systemic exposure parameters of crisaborole and ointment dose in HV, AD and psoriasis subjects, and to identify covariates that impact the PK and systemic exposure parameters of crisaborole in HV, AD and psoriasis subjects.

Data for Analysis:

Crisaborole plasma concentration were collected and PK parameters were calculated in all studies listed in **Table A3**. In total, there were 244 subjects with measured steady state AUC or Cmax. There were 239 and 241 subjects with measured steady state AUC and Cmax respectively.

Table A3. Description of the Clinical Studies Included in the Pharmacometric Analysis

Anacor Study ID	Pfizer Study ID	Design	Formulation	Number of Subjects and Age Range (years)	Treatment Duration
AN2728-PSR-104	C3291010	Single-center, randomized, double-blind, vehicle-controlled, multiple cohort, ascending dose	Crisaborole topical ointment 2%	16 Males 19–31 years	Crisaborole Ointment, 2% Ointment vehicle Applied to 10% or 35% BSA QD on Days 1 and 7; BID on Days 2-6
AN2728-TQT-108	C3291019	Single-center, randomized, parallel cohort with nested crossover QT/QTc interval study.	Crisaborole topical ointment 2%	98 Males, 82 Females 8-45 years Crisaborole: Supratherapeutic dosing, 60 subjects; therapeutic dosing, 60 subjects Moxifloxacin control, 60 subjects	Crisaborole Topical Ointment, 2%, therapeutic dose (15 g BID applied to ~30% treatable BSA) or supratherapeutic dose (45 g applied to ~60% treatable BSA) Ointment Vehicle QD Days 1, 2, and 9 and BID Days 3–8 Moxifloxacin tablets, single dose Moxifloxacin-matching placebo tablets, single dose
AN2728-PK-101	C3291009	Open label, 3 period, fixed-sequence DDI study	Crisaborole topical ointment 2%	15 Males, 9 Females 21-55 years	Treatment A (Period 1): Single total oral dose of 25 mg warfarin sodium 25 mg at Hour 0 on Day 1 following an overnight fast of at least 8 hours. Treatment B (Period 2): Multiple topical administrations of Crisaborole Topical Ointment, 2%, applied in the amount of 45 g to designated treatment areas which represent approximately 60% of BSA, BID (approximately every 12 hours) on Days 1

					Treatment C (Period 3): Multiple topical administrations of Crisaborole Topical Ointment, 2%, applied in the amount of 45 g to designated treatment areas which represent approximately 60% of BSA, BID (approximately every 12 hours) on Day 1 to Day 7 with a single total oral dose of 25 mg warfarin sodium at Hour 0 on Day 1, 30 minutes following Crisaborole Topical Ointment, 2% application, and following
AN2728-AD-203	C3291007	Multicenter, open-label, nonrandomized, safety/ tolerability, PK study	Crisaborole topical ointment 2%	4 Males, 19 Females 12–17 years	PK Phase: QD (Days 1 and 8); BID (Days 2–7)
AN2728-AD-102	C3291006	Multicenter, open-label, MUSE study to assess safety and PK in 2 years – 17 years old AD subjects	Crisaborole topical ointment 2%	15 Males, 19 Females 2.1–17.7 years	PK Phase: QD (Days 1 and 8); BID (Days 2–7)
AN2728-PSR-106	C3291012	Multicenter, open-label, MUSE study to assess safety and PK in adult Psoriasis subjects.	Crisaborole topical ointment 2%	29 Males, 4 Females 25–70 years	PK Phase: QD (Days 1 and 8); BID (Days 2–7)

AD = atopic dermatitis; BID = twice a day; BSA = body surface area; DDI = drug-drug interaction; MUSE = maximal use systemic exposure; PK = pharmacokinetics; QD = once daily.
Source: Table S1 in Population Modeling Analysis Report (PMAR-EQDD-C329a-DP4-774)

Methods:

Non-linear regression analysis correlating the steady state PK parameters (AUCss and Cmax,ss) to the ointment dose was conducted. The regression model for AUCss or Cmaxss as dependent variable and ointment dose as the independent variable was defined with an estimated Slope and intercept fixed to 0. Weight was included as a covariate on Slope as multiplicative term, using the allometric function with exponent *ex1*. Covariate parameters for race (categorical), gender (categorical), disease (categorical, HV or AD or psoriasis subject), baseline disease severity (categorical, based on Investigator's Static

Global Assessment (ISGA) for AD and Physicians Global Assessment (PGA) for psorasis) and Age (continuous) were added to the base model to estimate their influence on the Slope parameter. Multi-category covariates such as race were converted to binary (White Vs Non- white subjects) due to insufficient number of subjects in each category. Disease severity had only 2 categories as the dataset comprised of only moderate and severe AD or psoriasis subjects. The potential for additional non-linearity was evaluated by estimating an exponent on ointment dose. Adjustments were made to the full model and covariates with high correlation/collinearity or which caused ill-conditioning of the model were eliminated. Non- parametric bootstrap was used to create 95% confidence interval (CI) for the final model parameters.

Results:

The final model describing the relationship between AUCss or Cmaxss and ointment dose is provided below as Equation 1 and Equation 2.

Equation 1:

$$\text{AUC}_{ss} = (\beta_0 \times (\frac{Wt_i}{70})^{-0.75} \times \text{GE}^{SEX-1} \times \text{RC}^{RACE1} \times (\text{DISad}^{POPad} \times \text{ADms}^{ADSE3}) \times (\text{DISps}^{POPps} \times \text{PSOse}^{\text{PSOSEse}})) \times \text{Oint Dose} \quad (1)$$

Equation 2:

$$\text{AUC}_{ss} = (\beta_0 \times (\frac{Wt_i}{70})^{-0.75} \times \text{GE}^{SEX-1} \times \text{RC}^{RACE1} \times (\text{DISad}^{POPad} \times \text{ADms}^{ADSE3}) \times (\text{DISps}^{POPps} \times \text{PSOse}^{\text{PSOSEse}})) \times \text{Oint Dose} \quad (1)$$

Where, GE, RC, DISad, ADms, DISps and PSOse represent parameters for gender, race, subject with AD, AD subject with severe disease, subject with psoriasis and psoriasis subject with severe disease respectively. The disease severity parameters were included as nested parameters with respective disease parameter. POPad, ADSE3, POPps and PSOSEse are dichotomized indicator variables which take a value of 1 if the relevant condition is true and zero otherwise. RACE1 is an indicator variable for race and takes a value of zero for white and 1 for other (Black+Asian+Other). SEX is an indicator variable for gender and takes value of 1 for male and 2 for female.

Subject with AD or Psoriasis have ~2.5 fold higher Slope relative to healthy reference subject. Hence, for every milligram increase in ointment dose, subjects with AD or Psoriasis will have ~2.5 fold higher unit increase in AUCss or Cmaxss compared to a HV. Severity of disease also has an impact on Slope. Subjects with severe AD have a marginally lower Slope compared to subjects with moderate disease while the converse relationship applies to psoriasis subjects with varying severity for AUCss. For Cmaxss

disease severity in subjects with AD was not identified to have a significant impact on Slope. However, subjects with severe psoriasis had a marginally higher Slope compared to subject with moderate disease for Cmaxss. The marginal impact of disease severity on Slope is unlikely to result in clinically significant differences in AUCss or Cmaxss. Race and gender also appear to have marginal impact on Slope for AUCss or Cmaxss, which is unlikely to have clinically significant impact on systemic exposures.

Conclusion:

- The relationship between ointment dose and crisaborole AUCss and Cmaxss was described by a non-linear regression models with weight included as an allometric function.
- Disease status had a significant impact on Slope ($ß_0$) for AUCss and Cmaxss with a ~2.5 fold higher Slope for AD or psoriasis subjects relative to healthy volunteers.
- Race, gender and disease severity were identified as significant covariates on the Slope ($ß_0$) parameter; however, the impact of these covariates (race, gender, disease severity) is marginal and not likely to lead to clinically significant differences in systemic exposure.
- At similar % treated BSA, crisaborole systemic exposures across age groups are expected to be in a similar range.

Reviewer's Comments: *The relationship between crisaborole ointment dose and crisaborole AUC_{ss} and $Cmax_{ss}$ was adequately described by a non-linear regression model with weight included as an allometric function. Disease status had a significant impact on Slope ($ß_0$) for AUC_{ss} and $Cmax_{ss}$. Hence, subjects with AD will have higher (~2.5 fold) crisaborole AUC_{ss} and $Cmax_{ss}$ at a given ointment dose relative to healthy volunteers. At similar % treated BSA, crisaborole systemic exposures across age groups are expected to be in a similar range.*

Regression Analysis of Crisaborole and Propylene Glycol Systemic Exposure Associated with Crisaborole Ointment 2% BID

The Sponsor further developed the non-linear regression model described in report PMAR-EQDD-C329a-DP4-956 based on the original 6 clinical studies combined with data from 2 additional studies C3291029 and C3291002 with the objectives to characterize the relationship between systemic PK parameters and ointment dose, to

identify covariates that impact the systemic PK parameters of crisaborole and to explore the relationship between ointment dose and propylene glycol concentrations in plasma.

Data for Analysis:
Crisaborole plasma concentration were collected and PK parameters were calculated in all studies listed in **Table A4**. In total there were 271 subjects with measured steady state AUC or Cmax for crisaborole. There were 264 and 267 subjects with measured steady state AUC and Cmax respectively. For propylene glycol data was available from 135 subjects from study C3291002.

Table A4. Description of the Additional Clinical Studies Included in the Pharmacometric Analysis

Anacor Study ID	Pfizer Study ID*	Design	Number of Subjects and Age Range (years)	Treatment Duration
	C3291029	A single center, randomized, vehicle-controlled study to evaluate skin irritation potential in adult Japanese healthy subjects and safety, local tolerability and pharmacokinetics in adult Japanese subjects with mild to moderate AD	12 Male 20 – 52 y	PK Phase: BID dosing for 8 days in AD subjects with at least 25% treatable BSA, with serial PK samples obtained on Days 1 and 8 in Cohort 2.
	C3291002	A multicenter, open- label safety study in children aged 3 months to less than 24 months with mild to moderate atopic dermatitis	13 Male and 8 Female 3 – 23 months	PK cohort of 16 subjects with minimum treatable BSA of 35% with serial PK samples obtained on Day 8 following BID dosing.

Source: Table S1 in Population Modeling Analysis Report (PMAR-EQDD-C329a-DP4-956)

Methods:
Crisaborole
Non-linear regression analysis correlating the steady state PK parameters (AUCss and Cmax,ss) to the ointment dose was conducted. The regression model for AUCss or Cmaxss as dependent variable and ointment dose as the independent variable was defined with an estimated Slope and intercept fixed to 0. Weight was included as a covariate on Slope as multiplicative term, using the allometric function with exponent *ex1* fixed to a value of -0.75 for both AUCss and Cmaxss. Covariate parameters for race (categorical), gender (categorical), disease (categorical, HV or AD or psoriasis subject), baseline

disease severity (categorical, based on Investigator's Static Global Assessment (ISGA) for AD and Physicians Global Assessment (PGA) for psorasis) were added to the base model to estimate their influence on the Slope parameter. Multi-category covariates such as race were converted to binary (White Vs Non-white subjects) due to insufficient number of subjects in each category. Disease severity had only 2 categories as the dataset comprised of only mild and moderate for AD or moderate and severe for psoriasis subjects. Non-parametric bootstrap was used to create 95% confidence interval (CI) for the final model parameters.

Propylene Glycol

The changes in propylene glycol systemic concentrations were examined visually in plots for screening visits and on treatment visits. The change in propylene glycol concentrations from screening visit was analyzed using regression analysis to identify any relationship with
%treated BSA. The %treated BSA was used as a surrogate for dose as actual ointment dose was not collected in all subjects except for the PK cohort.

Results:

Crisaborole

The final model describing the relationship between AUCss or Cmaxss and ointment dose is provided below as Equation 1 and Equation 2.

Equation 1:

$$\mathrm{AUC}_{ss} = (\beta_0 \times (\frac{Wt_i}{70})^{-0.75} \times \mathrm{GE}^{SEX-1} \times \mathrm{RC}^{RACE1} \times (\mathrm{DISad}^{POPad} \times \mathrm{ADms}^{ADSE3}) \times (\mathrm{DISps}^{POPps} \times \mathrm{PSOse}^{\mathrm{PSOSEse}})) \times \mathrm{Oint\ Dose}\ (1)$$

Equation 2:

$$Cmax_{ss,i} = (\beta_0 \times (\frac{Wt_i}{70})^{-ex_1} \times \mathrm{GE}^{SEX-1} \times \mathrm{RC}^{RACE1} \times (\mathrm{DISad}^{POPad} \times \mathrm{PE}^{PROT}) \times (\mathrm{DISps}^{POPps} \times \mathrm{PSOse}^{\mathrm{PSOSEse}})) \times Oint\ Dose_i\ \ (2)$$

Where, GE, RC, DISad, ADms, DISps and PSOse represent parameters for gender, race, subject with AD, AD subject with severe disease, subject with psoriasis and psoriasis subject with severe disease respectively. The disease severity parameters were included as nested parameters with respective disease parameter. POPad, ADSE3, POPps and PSOSEse are dichotomized indicator variables which take a value of 1 if the relevant condition is true and zero otherwise. RACE1 is an indicator variable for race and takes a value of zero for white and 1 for other (Black+Asian+Other). SEX is an indicator variable for gender and takes value of 1 for male and 2 for female.

Propylene Glycol

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

Conclusions:

- The relationship between ointment dose and crisaborole AUCss and Cmaxss was described by a non-linear regression models with weight included as an allometric function.
    - Disease status had a significant impact on Slope ($ß_0$) for AUCss and Cmaxss with a ~2.3 fold higher Slope for AD or psoriasis subjects relative to healthy volunteers.
    - Race, gender and disease severity were identified as significant covariates on the Slope ($ß_0$) parameter; however, the impact of these covariates (race, gender, disease severity) is marginal and not likely to lead to clinically significant differences in systemic exposure.
    - At similar % treated BSA, crisaborole systemic exposures across age groups are expected to be in a similar range.
  - At similar % treated BSA, AUCss across age groups are expected to be in a similar range.
    - At similar %treated BSA, Cmaxss is expected to be slightly higher (~1.25 fold) in subjects 3 months to less than 24 months relative to ≥2 years old subjects. (Note: The ~1.25 fold higher Cmax in subjects 3 months to less than 24 months subjects is sensitive to the data from Site 1009.)
- Crisaborole ointment dose does not statistically correlate to the change of propylene glycol systemic concentrations.

Reviewer's Comments: *The relationship between crisaborole ointment dose and crisaborole AUC_{ss} and $Cmax_{ss}$ was adequately described by the non-linear regression model. Disease status had a significant impact on Slope ($ß_0$) for AUC_{ss} and $Cmax_{ss}$. Hence, subjects with AD will have higher (~2.3 fold) crisaborole AUC_{ss} and $Cmax_{ss}$ at a given ointment dose relative to healthy volunteers. At similar % treated BSA, crisaborole systemic exposures across age groups are expected to be in a similar range. Crisaborole*

systemic exposures in children (> 3 months of age) at maximum possible dose are unlikely to exceed the systemic exposures at the maximum possible dose in adults. Crisaborole ointment dose does not statistically correlate to the change of propylene glycol systemic concentrations.

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