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GENERIC DRUG NAME: Crisaborole

PROTOCOL NO.: C3291029

PROTOCOL TITLE:

A Phase 1, Single-Center, Randomized, Vehicle-Controlled, Parallel-Cohort Study of Crisaborole Ointment 2% to Evaluate the Skin Irritation Potential in Adult Japanese Healthy Subjects, and to Evaluate the Safety, Tolerability and Pharmacokinetics in Adult Japanese Subjects with Mild to Moderate Atopic Dermatitis

Study Center:

The study was conducted at a single center in Japan

Study Initiation and Final Completion Dates:

13 September 2017 and 27 November 2017

Phase of Development:

Phase 1

Study Objectives:

Primary Objective for Cohort 1:

- To investigate the skin irritation potential of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects.

Secondary Objective for Cohort 1:

- To investigate the safety and tolerability of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects.

Primary Objective for Cohort 2:

- To investigate the safety and tolerability of multiple topical doses of crisaborole ointment 2% twice daily (BID) in adult Japanese subjects with mild to moderate atopic dermatitis (AD).

Secondary Objective for Cohort 2:

- To characterize the plasma pharmacokinetic (PK) profile of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment 2% BID in adult Japanese subjects with mild to moderate AD.

METHODS

Study Design:

This was a Phase 1, single-center, randomized, vehicle-controlled, parallel-cohort study of crisaborole ointment 2% conducted in 2 cohorts evaluating the skin irritation potential in adult Japanese healthy subjects in Cohort 1, and safety, tolerability and PK in adult Japanese subjects with mild to moderate AD in Cohort 2. Both cohorts could be run in parallel such that completion of Cohort 1 was not required in order to proceed with Cohort 2 (Table 1).

Table 1. Description of Cohorts

Cohort		N	Investigational Product
Cohort 1	Skin irritation cohort in healthy subjects	20	Crisaborole ointment 2% and vehicle
Cohort 2	Safety, tolerability and PK cohort in subjects with mild to moderate AD	12	Crisaborole ointment 2% (n=10) Vehicle (n=2)

Abbreviations: AD=atopic dermatitis; N=number of subjects; n=number of subjects with prespecified criteria; PK=pharmacokinetic.

Cohort 1:

This was a randomized, observer and subject-blind, vehicle-controlled cohort, of the investigational products (crisaborole ointment 2% and vehicle) under occlusive patch conditions to evaluate skin irritation potential and safety in Japanese healthy male subjects aged 20 to 55 years, inclusive. Approximately 20 subjects could be enrolled into the cohort. All subjects were to have skin area fields designated for investigational product patches at 2 randomly assigned, adjacent sites, for the purpose of determining irritation potential.

The investigational products were to be applied topically once on Day 1 and remain under occlusion for 48 hours. The skin irritancy was to be evaluated approximately 30 minutes after removal of the patches (Day 3, around 48 hours after investigational product patch application) and 24 hours after removal of the patches (Day 4, approximately 72 hours after the investigational product application). A follow-up telephone call (end of study) was scheduled by study site staff to the subjects on Day 29 (+7 days) to assess adverse events (AEs).

All applications of investigational products were to be conducted by the study site staff. The observer and subjects were blinded to minimize evaluation bias for skin irritation.

Cohort 2:

This was a randomized, double-blind cohort of crisaborole ointment 2% BID to evaluate the safety, tolerability and PK in adult Japanese subjects with mild to moderate AD. The cohort enrolled male and female subjects with AD aged 20 to 55 years, inclusive, at the time of

screening. Approximately 12 subjects having at least 25% treatable percent body surface area (%BSA) were to be enrolled into the study. The treatable %BSA was calculated at Screening and Day 1. The investigational product was to be applied BID to the treatable %BSA areas identified on Day 1 for a duration of 8 days; on Days 1 and 8, investigational product was to be administered once daily in the morning. All investigational product doses were to be dispensed and applied by study site staff.

Subjects were to be screened within 28 days prior to application of investigational product on Day 1 to confirm that they met the subject eligibility criteria for the study. Subjects were admitted to the Clinical Research Unit (CRU) on Day -1 and were to remain confined in the CRU until completion of all assessments on Day 9. A follow-up telephone call (end of study) was planned by study site staff to the subjects on Day 36 (+7 days) to assess AEs.

Refer to Table 2 and Table 3 for a complete list of assessments performed during the study for Cohort 1 and Cohort 2, respectively.

Table 2. Schedule of Activities - Cohort 1

Day[a]	-28 to -2 Screening	-1	1	2	3	4/ET	29 (+7 Days) FU Contact[b] (EOS)
Informed consent	X						
CRU confinement		X[c]	→	→	→	X[d]	
Inclusion/exclusion criteria	X	X	X				
Medical history	X	X					
Physical examination	X	X				X	
Safety laboratory	X	X[e]					
Demographics	X						
Height and weight	X						
Vital signs[f]	X						
ECG[g]	X						
HIV, HepBsAg, HepBcAb, HCVAb and syphilis testing	X						
Urine drug testing	X	X[h]					
Visual assessment of application field	X		X				
Treatments/patch application			X[i]	→[i]	→[i]		
Patch removal					X		
Skin irritation assessment					X[j]	X[j]	
Review and record prior and concomitant medications	X[k]	X	X	X	X	X	
Assess for AEs and SAEs[l]	X	X	X	X	X	X	X

Abbreviations: →=ongoing/continuous event; AE=adverse event; CRU=clinical research unit; ECG=electrocardiogram; EOS=end of study; ET=early termination; FU=follow-up; HIV=human immunodeficiency virus; HepBsAg=hepatitis B surface antigen; HepBcAb=hepatitis B core antibody; HCVAb=hepatitis C antibody; labs=laboratory evaluations; SAE=serious adverse event.

a. Day relative to start of study treatment (Day 1).
b. Follow-up contact was completed on Day 29 (28+7 calendar days after the application of the investigational product patches on Day 1) to capture any potential AEs.
c. Subjects were admitted to the CRU on Day -1.
d. Subjects were discharged from CRU on Day 4 after completion of all assessment on Day 4.
e. Day -1 clinical labs did not have to be repeated if clinical labs were completed within 7 days prior to Day -1.
f. Vital signs (pulse rate and blood pressure) taken supine position after subject had been calmly lying for 5 minutes.
g. Single ECG was collected.
h. Day -1 urine drug testing did not have to be repeated if urine drug testing was completed within 7 days prior to Day -1.
i. Day 1 patches remained in place through Day 3.
j. Skin irritation assessment of the patch sites were conducted on Day 3 (approximately 30 minutes after removal of the patches) and Day 4 (approximately

Table 2. Schedule of Activities - Cohort 1

24 hours after removal of the patches).

k. All medications and non-medication therapies used within 28 days prior to the planned first dose.

l. If AEs/SAEs occurred at a patch site, the patch site location was recorded.

Table 3. Schedule of Activities - Cohort 2

Day[a]	-28 to -2 Screening	–1	1	2	3	4	5	6	7	8/ET	9	36 (+7 Days) FU Contact[b] (EOS)
Informed consent	X											
CRU confinement		X[c]	→	→	→	→	→	→	→	→	X[d]	
Inclusion/exclusion criteria	X	X	X									
Medical history	X	X										
Confirmation of diagnosis of AD	X											
Physical examination	X	X								X[e]	X	
Physical examination[f] (skin examination)	X		X								X	
Assess ISGA	X		X									
Record treatable AD areas			X									
Calculate and record treatable %BSA[g]	X		X									
Safety laboratory	X	X								X		
Demographics	X											
Height and weight	X		X[h]									
Vital signs[i]	X		X							X		
ECG	X[j]		X[j]							X[j]		
Urine pregnancy test	X	X										
Contraception check	X	X									X	X
FSH[k]	X											
HIV, HepBsAg, HepBcAb, HCVAb and syphilis testing	X											
Urine drug testing	X	X[l]										
AM dosing: weigh dose and apply			X	X	X	X	X	X	X	X		
PM dosing: weigh dose and apply				X	X	X	X	X	X			
Obtain PK samples			X[m]	X[n]					X[n]	X[m]	X[n]	
Review and record prior and concomitant medications	X[o]	X	X	X	X	X	X	X	X	X	X	
Assess for AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X

Table 3. Schedule of Activities - Cohort 2

Abbreviations: →=ongoing/continuous event; %BSA=percent body surface area; AE=adverse event; AD=atopic dermatitis; AM=ante meridiem; CRU=clinical research unit; ECG=electrocardiogram; EOS=end of study; ET=early termination; FSH=follicle-stimulating hormone; FU=follow-up; HIV=human immunodeficiency virus; HepBsAg=hepatitis B surface antigen; HepBcAb=hepatitis B core antibody; HCVAb=hepatitis C antibody; ISGA=investigator's static global assessment; PK=pharmacokinetic; Prep D1=dipotassium edetic acid; PM=post meridiem; SAE=serious adverse event.

a. Day relative to start of study treatment (Day 1).
b. Follow-up contact was completed on Day 36 (28+7 calendar days after the last application of the investigational product) to capture any potential AEs and to confirm appropriate contraception usage.
c. Subjects were admitted to the CRU on Day -1.
d. Subjects were discharged from CRU on Day 9 after completion of all assessment on Day 9.
e. A physical examination was conducted at ET.
f. A skin examination was conducted by dermatologist.
g. Treatable % BSA is defined as the percent of a subject's total body surface area that is AD-involved, excluding the scalp and venous access areas.
h. Only weight was measured on Day 1.
i. Vital signs (pulse rate and blood pressure) taken supine position after subject had been calmly lying face up for 5 minutes.
j. ECG was collected in single.
k. Any female subject who had been amenorrheic for at least 12 consecutive months.
l. Day -1 urine drug testing did not have to be repeated if urine drug testing was completed within 7 days prior to Day -1.
m. Obtained PK samples at predose, 3 hours and 12 hours post Day 1 and Day 8 AM dose.
n. Obtained PK samples prior to AM dose on Day 2 and Day 7 (at 24 hours post Day 1 and Day 6 AM dose). Obtained PK samples on Day 9 at 24 hours post Day 8 AM dose.
o. All medications and non-medication therapies used within 28 days prior to Screening.

Number of Subjects (Planned and Analyzed):

A total of approximately 32 subjects were planned in this study. For Cohort 1, a sample size of approximately 20 subjects were selected empirically, for Cohort 2, a sample size of approximately 12 subjects (10 subjects for crisaborole ointment 2% and 2 subjects for vehicle) were selected empirically. In Cohort 1, a total of 39 subjects were screened, out of which 20 subjects were assigned to study treatment. In Cohort 2, a total of 19 subjects were screened, out of which 12 subjects were assigned to study treatment; 10 subjects to crisaborole ointment 2% and 2 subjects to vehicle.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Cohort 1

Main Inclusion Criteria: Healthy male Japanese subjects who, at the time of screening, were between the ages of 20 and 55 years, inclusive.

Main Exclusion Criteria: Subjects who had any visible skin disease at the application site which, in the opinion of the investigative personnel, could have interfered with the evaluation of the test site reaction, who had psoriasis and/or active AD/eczema, and who had a history of AD

Cohort 2

Main Inclusion Criteria: Male or female Japanese subjects aged 20 years to 55 years (inclusive) at the time of screening, and in generally good health except for AD. Good health is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including blood pressure and pulse rate measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests. Diagnosis of AD based on the criteria of Hanifin and Rajka (1980). Subjects had at least 25% treatable %BSA on Day 1 (excluding the scalp and designated venous access areas) and an investigator's static global assessment (ISGA) score of mild (2) or moderate (3) on Day 1.

Main Exclusion Criteria: Subject who had any clinically significant medical disorder, condition, disease (including active or potentially recurrent dermatological conditions other than AD), significant physical examination or laboratory findings that may have interfered with study objectives, in the investigator's opinion.

Study Treatment:

The investigational products were crisaborole ointment 2% and matching vehicle.

Crisaborole ointment 2%, was formulated to contain PF-06930164 (2% wt/wt), white petrolatum, propylene glycol, mono- and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

Vehicle (no active drug in the formulation) contained white petrolatum, propylene glycol, mono- and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

Crisaborole ointment 2% and vehicle were provided in 60 g tubes by the sponsor. The tubes were labeled according to local regulatory requirements. Subjects received the investigational product once on Day 1 to the designated areas of the back according to the randomization sequence and remained under occlusion for 48 hours in accordance with a skin irritation manual.

Safety and Pharmacokinetic Endpoints:

Primary Endpoint for Cohort 1:

- Skin irritation index.

Secondary Endpoint for Cohort 1:

- Assessment of AEs.

Primary Endpoint for Cohort 2:

- Assessment of AEs, clinical laboratory tests, vital signs, and 12-lead ECG.

Secondary Endpoint for Cohort 2:

- PK parameters: Maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from 0 time until the last measurable concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 to the 24 hours postdose (AUC_{24}), area under the plasma concentration-time curve from time 0 to time tau (τ), the dosing interval, where τ=12 hours for BID dosing (AUC_{tau}) on Day 1 and Day 8, and accumulation ratio for C_{max} (R_{ac} [C_{max}]) and accumulation ratio for AUC_{tau} (R_{ac} [AUC_{tau}]) on Day 8.

Efficacy evaluations were not performed for this study.

Safety Evaluations:

Safety evaluations included skin irritation assessment (Cohort 1), AEs, safety laboratory tests, vital signs (heart rate, blood pressure), and 12-lead ECGs. Vital signs and 12-lead ECGs were observed at Screening in Cohort 1 and at Screening, on Day 1 and Day 8 in Cohort 2.

Statistical Methods:

The PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration. The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest. PK analysis was based on the PK analysis set.

PK data was descriptively summarized by study day and analyte for crisaborole and its metabolites respectively. Comparison between study days was performed by descriptive analysis of the within-subject ratio of Day 8/Day 1 PK parameters.

The safety analysis population was defined as all subjects who received at least 1 dose of study medication. All subjects who received at least 1 dose of study medication were classified according to the actual study treatment received. The safety analysis set was the

primary population for treatment administration/compliance and safety. The safety analysis was conducted for Cohort 1 and Cohort 2, separately.

The analysis of AEs was based on the safety analysis population. Descriptive summaries and listing of the AE/serious adverse event (SAE) data was provided by treatment. In addition, AEs that occurred in the treatment area were separately summarized by treatment. AEs were reported in accordance with the sponsor data standards. The analysis of laboratory data was based on the safety analysis population. Laboratory data was descriptively summarized and listed by treatment in accordance with the sponsor data standards. Baseline was the last predose measurement. For each subject in Cohort 1, the maximum irritation score of the skin irritation assessment through all visits (ie, Day 3 and Day 4) was calculated. The skin irritation index was calculated as the sum of the individual maximum irritation scores divided by the number of evaluable subjects who had the skin irritation assessment and multiplied by 100.

RESULTS

Subject Disposition and Demography:

Subject disposition is summarized in Table 4 and Table 5 for Cohort 1 and Cohort 2, respectively. In Cohort 1, a total of 39 subjects were screened out of which 20 subjects were assigned to study treatment. All subjects assigned to study treatment received study drug. No subjects discontinued from Cohort 1. All subjects who received study medication were analysed for safety.

In Cohort 2, a total of 19 subjects were screened, out of which 12 subjects were assigned to study treatment; 10 subjects to crisaborole ointment 2% and 2 subjects to vehicle. All subjects assigned to study treatment received at least 1 dose of study drug. Overall 10 subjects completed the study (9 in the crisaborole ointment 2% group, 1 in the vehicle group). Overall 2 subjects discontinued in the treatment phase, 1 subject in the crisaborole ointment 2% group and 1 subject in the vehicle group; both due to AEs. Of the subjects assigned to crisaborole ointment 2%, all were included in the PK concentration analysis set and 9 subjects were included in the PK parameter analysis set. All 12 subjects who received at least 1 study drug were analysed for safety.

Table 4. Subject Disposition (Cohort 1)

Parameters	Crisaborole Ointment 2% and Vehicle (N=20) n%
Screened: 39	
Screen failure: 11	
Not assigned: 8	
Conflicting work schedule: 2	
Exceeded enrollment limit: 6	
Assigned to treatment	20 (100.0)
Treated	20 (100.0)
Not treated	0
Discontinued (treatment phase)	0
Discontinued (follow-up phase)	0
Safety analysis set	20 (100.0)

Abbreviations: N=number of subjects; n=number of subjects with specified criteria.

Table 5. Subject Disposition (Cohort 2)

Parameters	Crisaborole Ointment 2% (N=10) n%	Vehicle (N=2) n%	Total (N=12) n%
Screened: 19			
Screen failure: 4			
Not assigned: 3			
Exceeded enrollment limit: 3			
Assigned to treatment	10 (100.0)	2 (100.0)	12 (100.0)
Treated	10 (100.0)	2 (100.0)	12 (100.0)
Not treated	0	0	0
Discontinued (treatment phase)	1 (10.0)[a]	1 (50.0)[a]	2 (16.7)[a]
Completed (treatment phase)	9 (90.0)	1 (50.0)	10 (83.3)
Discontinued (follow-up phase)	0	0	0
PK concentration analysis set	10 (100.0)	0	0
PK parameter analysis set	9 (90.0)	0	0
Safety analysis set	10 (100.0)	2 (100.0)	12 (100.0)

Abbreviations: N=number of subjects; n=number of subjects with specified criteria; PK=pharmacokinetics.
a. Discontinued due to adverse events.

For both cohorts, all subjects were male and the majority of subjects were aged 20 to 44 years. In Cohort 2, the majority of subjects had a moderate ISGA score (83.3% overall) and the mean treatable %BSA was 63.92% overall (range: 35.0% to 87.0%).

Pharmacokinetic Results:

Plasma Crisaborole: Following a single application of crisaborole ointment 2% in adult Japanese subjects with mild to moderate AD, maximum crisaborole plasma concentrations were observed 3 hours postdose. Based on the trough plasma concentrations on Days 7, 8, and 9, steady state seems to have been achieved by Day 7.

Exposures based on geometric mean AUC_{tau} and C_{max} values were 928.9 ng•h/mL and 163.7 ng/mL respectively, on Day 1 following a single dose and 1123 ng•h/mL and 164.9 ng/mL on Day 8 following multiple BID dose administration (Table 6). Overall there was minimal accumulation of crisaborole on Day 8 following multiple BID administration with geometric mean accumulation ratios based on AUC_{tau} (R_{ac} AUC_{tau}) and C_{max} (R_{ac} C_{max}) of 1.209 and 1.007 respectively.

Between-subject variability in plasma crisaborole exposure on Day 1 and Day 8 was moderate to high based on geometric %CV, ranging between 56% to 71% for C_{max} and 51% to 65% for AUC_{tau}.

Table 6. Summary of Plasma Crisaborole Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 8) BID Administration

Parameter, Units	Parameter Summary Statistics[a] for Crisaborole by Dosing Day	
	Day 1	Day 8
N	9	9
AUC_{tau} (ng•h/mL)	928.9 (65)	1123 (51)
AUC_{last} (ng•h/mL)	1171 (60)	1527 (48)
AUC_{24} (ng•h/mL)	1171 (60)	1527 (48)
C_{max} (ng/mL)	163.7 (71)	164.9 (56)
T_{max} (h)	3.00 (3.00-3.00)	3.00 (3.00-3.00)
R_{ac} C_{max}	NA	1.007 (32)
R_{ac} AUC_{tau}	NA	1.209 (25)

Abbreviations: %CV=percent coefficient of variation; AUC_{24}=area under the plasma concentration-time curve from time 0 to the 24 hours postdose; AUC_{last}=area under the plasma concentration-time curve from 0 time until the last measurable concentration (C_{last}); AUC_{tau}=area under the plasma concentration-time curve from time 0 to time tau (τ), the dosing interval, where τ=12 hours for BID dosing; BID=twice daily; C_{max}=maximum observed plasma concentration; h=hour; N=number of subjects in the PK parameter analysis population as outlined in the SAP contributing to the summary statistics; NA=not applicable; PK=pharmacokinetic; R_{ac} C_{max}=accumulation ratio for C_{max}; R_{ac} AUC_{tau}=accumulation ratio for AUC_{tau}; SAP=statistical analysis plan; T_{max}=time to reach maximum observed plasma concentration.

a. Geometric mean (Geometric %CV) for all except: median (range) for T_{max}.

Plasma AN7602 (Metabolite): Following a single application of crisaborole ointment 2%, C_{max} for the AN7602 metabolite were observed 3 hours postdose. Based on the trough plasma concentrations on Days 7, 8, and 9, steady state seems to have been achieved by Day 7.

Exposures based on geometric mean AUC_{tau} and C_{max} values were 500.4 ng•h/mL and 94.97 ng/mL respectively on Day 1 and 434.9 ng•h/mL and 68.83 ng/mL on Day 8 following multiple BID dose administration of crisaborole ointment 2% (Table 7). Overall there was no accumulation of AN7602 metabolite on Day 8 with both of the R_{ac} AUC_{tau} and R_{ac} C_{max} <1.

Between-subject variability in plasma AN7602 exposure on Day 1 and Day 8 was moderate to high based on geometric percent coefficient of variation (%CV), ranging between 59% to 75% for C_{max} and 50% to 66% for AUC_{tau}.

Table 7. Summary of Plasma AN7602 Metabolite Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 8) Administration of Crisaborole Ointment 2% (BID)

Parameter, Units	Parameter Summary Statistics[a] for AN7602 by Dosing Day	
	Day 1	Day 8
N	9	9
AUC_{tau} (ng•h/mL)	500.4 (66)	434.9 (50)
AUC_{last} (ng•h/mL)	601.9 (60)	565.5 (44)
AUC_{24} (ng•h/mL)	601.9 (60)	565.5 (44)
C_{max} (ng/mL)	94.97 (75)	68.83 (59)
T_{max} (h)	3.00 (3.00-3.00)	3.00 (3.00-3.00)
R_{ac} C_{max}	NA	0.7247 (24)
R_{ac} AUC_{tau}	NA	0.8688 (19)

Abbreviations: %CV=percent coefficient of variation; AUC_{24}=area under the plasma concentration-time curve from time 0 to the 24 hours postdose; BID=twice daily; AUC_{last}=area under the plasma concentration-time curve from 0 time until the last measurable concentration (C_{last}); AUC_{tau}=area under the plasma concentration-time curve from time 0 to time tau (τ), the dosing interval, where τ=12 hours for BID dosing; C_{max}=maximum observed plasma concentration; h=hour; N=number of subjects in the PK parameter analysis population as outlined in the SAP contributing to the summary statistics; NA=not applicable; PK=pharmacokinetic; R_{ac} C_{max}=accumulation ratio for C_{max}; R_{ac} AUC_{tau}=accumulation ratio for AUC_{tau}; SAP=statistical analysis plan; T_{max}=time to reach maximum observed plasma concentration.
a. Geometric mean (Geometric %CV) for all except: median (range) for T_{max}.

Plasma AN8323 (Metabolite): Following a single application of crisaborole ointment 2%, C_{max} for the AN8323 metabolite was observed between 3 and 12 hours postdose. Based on the trough plasma concentrations on Days 7, 8, and 9, steady state was achieved by Day 7.

Plasma exposures based on geometric mean AUC_{tau} and C_{max} values for the AN8323 metabolite were higher than those observed for crisaborole and the AN7602 metabolite with mean values of 29360 ng•h/mL and 3064 ng/mL respectively on Day 1 following a single administration of crisaborole ointment 2% and 90360 ng•h/mL and 8080 ng/mL on Day 8 following multiple BID administration of crisaborole ointment 2% (Table 8). Unlike crisaborole and AN7602 metabolite, there was some accumulation observed for the AN8323 metabolite on Day 8 with geometric mean R_{ac} AUC_{tau} and R_{ac} C_{max} of 3.080 and 2.638 respectively.

Between-subject variability in plasma AN8323 exposure on Day 1 and Day 8 was moderate to high based on geometric %CV, ranging between 71% to 97% for C_{max} and 68% to 92% for AUC_{tau}.

Table 8. Summary of Plasma AN8323 Metabolite Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 8) Dosing of Crisaborole Ointment 2% (BID)

Parameter, Units	Parameter Summary Statistics[a] for AN8323 by Dosing Day	
	Day 1	Day 8
N	9	9
AUC_{tau} (ng•h/mL)	29360 (92)	90360 (68)
AUC_{last} (ng•h/mL)	57560 (84)	169100 (68)
AUC_{24} (ng•h/mL)	57560 (84)	169100 (68)
C_{max} (ng/mL)	3064 (97)	8080 (71)
T_{max} (h)	3.00 (3.00-12.0)	3.00 (3.00-12.0)
R_{ac} C_{max}	NA	2.638 (52)
R_{ac} AUC_{tau}	NA	3.080 (48)

Abbreviations: %CV=percent coefficient of variation; AUC_{24}=area under the plasma concentration-time curve from time 0 to the 24 hours postdose; AUC_{last}=area under the plasma concentration-time curve from 0 time until the last measurable concentration (C_{last}); AUC_{tau}=area under the plasma concentration-time curve from time 0 to time tau (τ), the dosing interval, where τ=12 hours for BID dosing; BID=twice daily; C_{max}=maximum observed plasma concentration; h=hour; N=number of subjects in the PK parameter analysis population as outlined in the SAP contributing to the summary statistics; NA=not applicable; PK=pharmacokinetic; R_{ac} C_{max}=accumulation ratio for C_{max}; R_{ac} AUC_{tau}=accumulation ratio for AUC_{tau}; SAP=statistical analysis plan; T_{max}=time to reach maximum observed plasma concentration.

a. Geometric mean (Geometric %CV) for all except: median (range) for T_{max}.

Safety Results:

There were no deaths, SAEs or AEs of severe intensity reported in this study. There were no discontinuations due to AEs in Cohort 1. There were no treatment-emergent AEs (TEAEs) in Cohort 1. There were 2 subjects that discontinued treatment due to AEs in Cohort 2. An overview of subjects that discontinued treatment due to an AE in Cohort 2 is summarized in Table 9.

Table 9. Overview of Subjects That Discontinued Treatment due to an Adverse Event; All-Causalities (Cohort 2)

Number (%) of Subjects	Crisaborole Ointment 2% n (%)	Vehicle n (%)
Subjects discontinued from study due to AEs	1 (10.0)[a]	1 (50.0)[b]

Abbreviations: AEs=adverse events; n=number of subjects; TEAE=treatment-emergent adverse event.

a. Permanent discontinuation due to mild TEAE of application site pain.

b. Permanent discontinuation due to moderate TEAE of atopic dermatitis.

The incidence of TEAEs (all-causalities and treatment-related) by treatment group for Cohort 2 are summarized in Table 10. A total of 13 TEAEs were reported in 9 subjects in the crisaborole ointment 2% group; all of which were of mild intensity. The most frequently reported all-causalities TEAEs by preferred term were application site irritation (7 subjects) and application site pain (4 subjects) in the crisaborole ointment 2% group. Except for eyelid oedema, all TEAEs in the crisaborole ointment 2% group were considered treatment-related. In the vehicle group, 6 TEAEs were reported in all subjects.

Table 10. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (Cohort 2)

Number of Subjects Evaluable for AEs	Crisaborole Ointment 2% (N=10)			Vehicle (N=2)			Total (N=12)		
Number (%) of Subjects or Occurrences: by System Organ Class and Preferred Term	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
With AEs	9 (90.0)			2 (100.0)			11 (91.7)		
Eye disorders	1 (10.0)	1	0	0	0	0	1 (8.3)	1	0
Eyelid oedema	1 (10.0)	1	0	0	0	0	1 (8.3)	1	0
General disorders and administration site conditions	9 (90.0)	24	24	2 (100.0)	6	6	11 (91.7)	30	30
Application site coldness	1 (10.0)	1	1	1 (50.0)	1	1	2 (16.7)	2	2
Application site irritation	7 (70.0)	15	15	1 (50.0)	1	1	8 (66.7)	16	16
Application site pain	4 (40.0)	8	8	1 (50.0)	2	2	5 (41.7)	10	10
Application site pruritus	0	0	0	1 (50.0)	2	2	1 (8.3)	2	2
Infections and infestations	0	0	0	1 (50.0)	1	0	1 (8.3)	1	0
Nasopharyngitis	0	0	0	1 (50.0)	1	0	1 (8.3)	1	0
Skin and subcutaneous tissue disorders	0	0	0	1 (50.0)	1	1	1 (8.3)	1	1
Dermatitis atopic	0	0	0	1 (50.0)	1	1	1 (8.3)	1	1

Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject might report ≥2 different AEs within the higher level category.
Includes data up to lag days after last dose of study drug.
Except for n1 and n2 subjects were only counted once per treatment for each row.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA Version 20.1 coding dictionary applied.
Abbreviations: AEs=adverse events; MedDRA=Medical Dictionary of Regulatory Activities; N=number of subjects; n1=the number of occurrences of treatment-emergent all causalities AEs; n2=the number of occurrences of treatment-emergent causally related to treatment AEs; n=the number of subjects in this reporting group affected by any occurrence of this AE, all causalities.

Skin irritation assessment of the patch sites were conducted on Day 3 and Day 4 by a blinded observer who was a dermatologist for Cohort 1. The maximum irritation score was 0 or 0.5 for all subjects with the vehicle patch (Table 11). Also, the maximum irritation score was 0 or 0.5 for all subjects of the crisaborole ointment 2% except for the 3 subjects with a maximum irritation score of 2. The skin irritation indexes were 5.0 with a safety category of safe for the vehicle patch and 40.0 with a safety category of risky for the crisaborole ointment 2% patch.

Table 11. Summary of Skin Irritation Response (Cohort 1)

Assessment Scores	Day 3 N=20 n (%)	Day 4 N=20 n (%)	Maximum Irritation Score N=20 n (%)
Investigational Product: Crisaborole Ointment 2% Patch			
0	19 (95.0)	13 (65.0)	13 (65.0)
0.5	0 (0.0)	4 (20.0)	4 (20.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	1 (5.0)	3 (15.0)	3 (15.0)
3	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)
Median	0.00	0.00	0.00
Mean	0.10	0.40	0.40
SD	0.447	0.718	0.718
Range (min, max)	(0.0, 2.0)	(0.0, 2.0)	(0.0, 2.0)
Skin irritation index	0	0	40.0
Safety category of skin irritation index	0	0	Risky
Investigational Product: Vehicle Patch			
0	19 (95.0)	19 (95.0)	18 (90.0)
0.5	1 (5.0)	1 (5.0)	2 (10.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)
Median	0.00	0.00	0.00
Mean	0.03	0.03	0.05
SD	0.112	0.112	0.154
Range (min, max)	(0.0, 0.5)	(0.0, 0.5)	(0.0, 0.5)
Skin irritation index	0	0	5.0
Safety category of skin irritation index	0	0	Safe

Categorized as 'Safe' (0≤ - ≤5), 'Acceptable' (5 <-≤15), 'Improvable' (15< -≤30) or 'Risky' (30 < -≤400).
Skin Irritation Index=(Sum of individual maximum irritation scores/number of evaluable subjects) × 100.
Abbreviations: max=maximum; min=minimum; N=number of subjects; SD=standard deviation.

Laboratory test abnormalities were >1.2 × upper limit of normal (ULN) eosinophils (%) (7 subjects in the crisaborole ointment 2% group), <0.8 × lower limit of normal lymphocytes (%) (4 subjects in the crisaborole ointment 2% group and 1 subject in the vehicle group), and >1.5 × ULN leukocytes (10^9/L) (1 subject in the vehicle group). Of note, there were no AEs related to hematology reported in this study. No clinically significant changes were observed in the laboratory data. No clinically significant changes were observed in vital signs data. None of the ECG values meeting predefined criteria were considered clinically significant nor reported as AEs.

CONCLUSIONS:

- Crisaborole plasma exposure based on geometric mean AUC_{tau} and C_{max} values were 928.9 ng•h/mL and 163.7 ng/mL respectively on Day 1 following a single administration and 1123 ng•h/mL and 164.9 ng/mL on Day 8 following multiple BID administration of crisaborole ointment 2%. Overall there was minimal accumulation of crisaborole on Day 8 following multiple BID administration with geometric mean R_{ac} AUC_{tau} and R_{ac} C_{max} of 1.209 and 1.007 respectively.

- Plasma exposure for the AN7602 metabolite of crisaborole based on geometric mean AUC_{tau} and C_{max} values were 500.4 ng•h/mL and 94.97 ng/mL respectively on Day 1 and 434.9 ng•h/mL and 68.83 ng/mL respectively on Day 8 following multiple dose administration of crisaborole ointment 2% BID. Overall there was no accumulation of AN7602 metabolite on Day 8 with both of the R_{ac} AUC_{tau} and R_{ac} C_{max} <1.

- Plasma exposures based on geometric mean AUC_{tau} and C_{max} values for the AN8323 metabolite were much higher than those observed for crisaborole and the AN7602 metabolite with mean values of 29360 ng•h/mL and 3064 ng/mL respectively on Day 1 following a single BID administration of crisaborole ointment 2% and 90360 ng•h/mL and 8080 ng/mL on Day 8 following multiple BID administration of crisaborole ointment 2%. Unlike crisaborole and AN7602 metabolite, there was some accumulation observed for the AN8323 metabolite on Day 8 with geometric mean R_{ac} AUC_{tau} and R_{ac} C_{max} of 3.080 and 2.638 respectively.

- Based on the trough concentrations on Days 7, 8, and 9, steady state was achieved by Day 7 for crisaborole and its metabolites.

- Crisaborole ointment 2% BID was found to be well tolerated and have a favorable safety profile in Japanese subjects with mild to moderate AD. There were no TEAEs in Cohort 1 and all TEAEs in the crisaborole ointment 2% group in Cohort 2 were mild in severity, though the skin irritation index for crisaborole ointment 2% patch was 40.0 and was categorized as risky. No deaths or SAEs were reported in this study. There were no clinically significant changes for laboratory values, vital signs or ECG.