

ORIGINAL ARTICLE

Phase 1 study of crisaborole in Japanese healthy volunteers and patients with atopic dermatitis

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ABSTRACT

Crisaborole ointment, 2%, is a non-steroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate atopic dermatitis (AD). This parallel-cohort, phase 1 study was conducted to investigate skin irritation potential and safety of crisaborole in healthy Japanese adults (cohort 1) and the safety and pharmacokinetic profile of crisaborole and metabolites AN7602 and AN8323 in Japanese adults with mild to moderate AD (cohort 2). In cohort 1, 20 healthy volunteers received single applications of crisaborole and vehicle simultaneously on separate locations under 48-h occlusion. In cohort 2, 12 patients with mild to moderate AD received crisaborole ($n = 10$) or vehicle ($n = 2$) twice daily for 8 days. Skin irritation and safety were assessed in cohort 1. Pharmacokinetics and safety were assessed in cohort 2. Skin irritation index (scale 0–400) was 40.0 for crisaborole and 5.0 for vehicle. No treatment-emergent adverse events (TEAE) were reported in cohort 1. The most common TEAE in the crisaborole group in cohort 2 were application site irritation ($n = 7$) and application site pain ($n = 4$). Crisaborole was rapidly absorbed, with limited systemic exposure between days 1 and 8 that was comparable with that seen in US-based participants in previous trials. Crisaborole had higher skin irritation than vehicle under occlusion in healthy Japanese adults and had an acceptable safety profile in Japanese adults with mild to moderate AD.

Key words: atopic dermatitis, crisaborole, Japanese patients, pharmacokinetics, phosphodiesterase 4 inhibitors.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition; global prevalence is approximately 15–30% in children and 2–10% in adults.¹ Initial pharmacological therapy typically consists of topical treatments such as topical corticosteroids and topical calcineurin inhibitors.^{2–4} Limitations of these agents prompt the need for other non-steroidal topical treatments.

Crisaborole ointment, 2%, is a non-steroidal phosphodiesterase 4 (PDE4) inhibitor for the treatment of mild to moderate AD.^{5,6} Crisaborole is a small, boron-based molecule with low molecular weight (251 Da), which allows for easier penetration into the skin.⁷ Crisaborole has particular affinity for PDE4 isoforms PDE4A, PDE4B and PDE4D, and is quickly metabolized to the oxidative metabolites AN7602 and AN8323; however, neither metabolite has been shown to have activity against PDE4.^{7–9}

Regulatory approvals of crisaborole in Australia, Canada, Israel and the USA have been based on the results of two pivotal phase 3 clinical studies (AD-301, ClinicalTrials.gov, NCT02118766; AD-302, NCT02118792) and a long-term safety study (AD-303).^{10,11} In these studies, which were conducted in the USA in patients at least 2 years of age with mild to moderate AD, crisaborole showed improvement in Investigator's Static Global Assessment (ISGA) score and an acceptable safety profile.^{10,11} The most common treatment-emergent adverse event (TEAE) in crisaborole-treated patients during the pivotal studies was application site pain (4.4%).¹⁰

The objectives of the current study were to investigate skin irritation potential, safety and tolerability of single topical applications under occlusion of crisaborole and vehicle in healthy Japanese adult volunteers; to investigate the safety and tolerability of crisaborole compared with vehicle after multiple twice-daily (8 days) topical applications of crisaborole; and to

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characterize the plasma pharmacokinetic (PK) profile of crisaborole, AN7602 and AN8323 in Japanese adults with mild to moderate AD.

METHODS

Study design

This was a randomized, single-center, vehicle-controlled, parallel-cohort, phase 1 study conducted in Japan. In cohort 1, using an intraindividual design, skin irritation potential, safety and tolerability of crisaborole and vehicle were assessed in healthy men aged 20–55 years. In cohort 2, the safety and tolerability of crisaborole and the PK profile of crisaborole and its main oxidative metabolites (AN7602 and AN8323) were to be assessed in men and women aged 20–55 years with a diagnosis of AD per Hanifin and Rajka criteria,¹² mild or moderate disease per ISGA, and percentage of treatable body surface area (%BSA) of 25 or more. The final protocol, any amendments and informed consent documentation were reviewed and approved by the institutional review board at the clinical research unit participating in the study. The study was conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects and ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed and all participants provided written informed consent.

Treatment

In cohort 1, treatment was observer and participant blinded and consisted of participants receiving one-time application of crisaborole and vehicle under 48-h occlusion on separate locations (upper and lower) on one side of the infrascapular area of the back. Participants were randomly assigned to one of two treatment placement sequences (i.e. crisaborole on the upper location with vehicle on the lower location or vehicle on the upper location and crisaborole on the lower location). Study treatments were applied and removed by study site staff. Participants were confined to the Clinical Research Unit (CRU) during assessment, and no bathing was permitted during this time. In cohort 2, patients were randomly assigned 5:1 to receive crisaborole ointment, 2%, or vehicle (to blind the study) without occlusion twice daily for 8 days. Patients were admitted to the CRU on day –1 and were to remain confined in the CRU until completion of all assessments on day 9. The intended dose of product applied to treatable AD-involved areas (defined as skin that was AD involved and was not on the scalp or in venous access areas, leaving an untreated margin of at least 5 cm radius around the venipuncture site) was approximately 3 mg/cm² and was measured and applied to designated areas by study site staff. Bathing was not permitted for at least 4 h after each application. For both cohorts, vehicle ointment was identical to the crisaborole ointment except for the exclusion of crisaborole. Cohort 2 included a washout period for AD treatments which prohibited use of weak potency topical corticosteroids within 3 days, medium potency topical

corticosteroids within 7 days, strong potency topical corticosteroids or calcineurin inhibitors within 14 days, and systemic (oral/injectable) corticosteroids 28 days prior to the first investigational product application.

End-points and assessments

In cohort 1, the primary end-point was skin irritation index, which was calculated as the sum of the individual maximum irritation scores divided by the number of evaluable participants who had the skin irritation assessment and multiplied by 100 for a range of scores from 0 to 400.¹³ Definitions of the scores used in assessing skin irritation in individuals can be found in Table 1. Skin irritation was assessed 30 min after removal of the occlusive patches (day 3; i.e. 48 h after application) and 24 h after removal of the patches (day 4; i.e. 72 h after application). The secondary end-point for cohort 1 was the incidence of TEAE, assessed on days 1–4 at the clinic and at the end of study follow-up telephone call on day 29.

The primary end-point for cohort 2 was the incidence of TEAE, assessed on days 1–9 at the clinic and at the end of study follow-up telephone call on day 36 to capture any potential TEAE that occurred after treatment cessation. PK parameters were secondary end-points for cohort 2 and included the area under concentration-time curve from time 0 to 12 h (AUC_{0–12}), AUC from time 0 to last measurable concentration (AUC_{last}), AUC from time 0 to 24 h (AUC₂₄), maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), accumulation ratio for C_{max} (R_{ac} C_{max}) and accumulation ratio for AUC_{0–12} (R_{ac} AUC_{0–12}). Plots were included showing mean plasma concentration-time profiles for crisaborole and its metabolites (AN7602 and AN8323) after the first and multiple twice-daily administrations as well as relationship between crisaborole dose and exposure, and %BSA-normalized exposure to crisaborole, from the current study compared with crisaborole data from two previous phase 1/2 studies.^{8,9}

Statistical analysis

The safety analysis population for each cohort was defined as all participants who received at least one dose of study treatment. Demographics and safety data were summarized for the safety analysis population descriptively. TEAE were summarized using Medical Dictionary for Regulatory Activities (version 20.1) system organ class and preferred terms.

The PK concentration population was defined as all randomly assigned patients who received at least one dose of study treatment and had at least one concentration value. The

Table 1. Skin irritation assessment grades and scores

Definition	Grade	Score
No reaction	–	0
Mild erythema	±	0.5
Erythema	+	1
Erythema + edema + papule	++	2
Erythema + edema + papule + small water blister	+++	3
Large water blister	++++	4

PK parameter analysis population was defined as all randomly assigned patients who received at least one dose of study treatment and had a value for at least one of the PK parameters of primary interest. PK data were descriptively summarized by study day and analytes for crisaborole and its main metabolites. Comparison between study days was performed by descriptive analysis of the within-patient ratio of day 8/day 1 PK parameters. Samples were assayed for crisaborole, AN7602 and AN8323 using a validated, sensitive and specific high-performance liquid chromatography–tandem mass spectrometric method. The lower limits of quantification (LLOQ) for crisaborole, AN7602 and AN8323 were 0.200, 0.200 and 10.0 ng/mL, respectively. Summary statistics of PK parameters were calculated by setting concentration values below the LLOQ to 0.

RESULTS

Participants

In cohort 1, 20 participants were randomly assigned to either of two treatment placement sequences (i.e. upper vs lower infrascapular area), and all received both study treatments. In cohort 2, 12 patients were randomly assigned to study treatment: 10 patients received crisaborole and two patients received vehicle. For both cohorts, all participants were adult males and most were aged 18–44 years (Table 2). In cohort 2, most patients had a moderate ISGA score (83.3% overall) and the mean %BSA was 63.9 (range, 35.0–87.0). All participants completed the study in cohort 1. In cohort 2, 10 patients completed the study; one patient in the crisaborole arm and one patient in the vehicle arm discontinued, both because of TEAE (see Safety section for more detail). Nine of the 10 participants who received crisaborole (90%) and both participants who received vehicle in cohort 2 had received a topical corticosteroid and/or topical calcineurin inhibitor prior to study drug application.

Skin irritation: Cohort 1

In the skin irritation analysis, one participant each had an irritation score of 0.5 at day 3 and day 4, with vehicle. The maximum irritation score was 0 or 0.5 for all participants with vehicle, and the overall skin irritation index was 5.0 (Table 3).

With crisaborole, one participant had an irritation score of 2 at day 3 and three participants had irritation scores of 2 at day 4; the other 17 participants had maximum irritation scores of 0 or 0.5 with crisaborole. Four participants had irritation scores of 0.5 at day 4. The overall skin irritation index in crisaborole-treated participants was 40.0 (Table 3).

Safety

No TEAE were reported in cohort 1. In cohort 2, nine (90%) patients in the crisaborole group and two (100%) patients in the vehicle group experienced TEAE. No serious or severe TEAE were reported, and no TEAE resulted in dose reduction or temporary discontinuation of investigational product in either treatment group. However, one patient in each treatment group in cohort 2 permanently discontinued the

investigational product and discontinued the study because of a TEAE. The patient receiving crisaborole discontinued on day 2 because of treatment-related mild application site pain on the face, neck and back on day 1, which resolved without treatment. The patient receiving vehicle discontinued on day 2 because of treatment-related moderate dermatitis atopic, which the investigator described as dermatitis atopic aggravated; this also resolved without treatment. In total, 13 TEAE were reported for nine patients in the crisaborole group (Table 4). The most frequently reported TEAE were application site irritation ($n = 7$) and application site pain ($n = 4$) in the crisaborole group. Application site irritation differed from application site pain in that the application site irritation was a milder sensation than pain as reported by the patient. All TEAE in the crisaborole group were mild. In the vehicle group, six TEAE were reported for two patients, including one event each of application site coldness, application site irritation, application site pain and application site pruritus (which were all mild), and nasopharyngitis and atopic dermatitis (which were both moderate). There were no clinically significant laboratory abnormalities, changes in vital signs or change in electrocardiographic data in either cohort, and no deaths were reported.

Pharmacokinetics

Ten patients treated with crisaborole in cohort 2 were included in the PK concentration analysis set. Of these, nine were included in the PK parameter analysis set (one patient discontinued after the morning application on day 1, and only the 0- and 3-h time points were collected; this was considered an incomplete profile and no PK parameters were calculated). Mean plasma concentration-time profiles of crisaborole and its AN7602 and AN8323 metabolites on days 1 and 8 after multiple twice-daily topical administrations are presented in Figure 1. PK parameters for days 1 and 8 are also summarized descriptively in Table 5.

After first application, crisaborole was absorbed quickly with maximum plasma concentrations observed 3 h after dosing for crisaborole and AN7602, and between 3 and 12 h after dosing for AN8323. Based on trough plasma concentrations for days 7, 8 and 9, steady state was achieved for crisaborole and both metabolites by day 7.

Exposures based on geometric mean AUC_{0-12} and C_{max} values for crisaborole were 928.9 ng·h/mL and 163.7 ng/mL, respectively, on day 1 after the first application, and 1123 ng·h/mL and 164.9 ng/mL, respectively, on day 8 after multiple twice-daily applications. Overall, there was minimal accumulation of crisaborole by day 8 after multiple twice-daily applications; geometric mean accumulation ratios for AUC_{0-12} ($R_{ac} AUC_{0-12}$) and C_{max} ($R_{ac} C_{max}$) were 1.209 and 1.007, respectively.

Exposures based on geometric mean AUC_{0-12} and C_{max} values for the AN7602 metabolite 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. Overall, there was no accumulation of AN7602 metabolite on day 8; both $R_{ac} AUC_{0-12}$ and $R_{ac} C_{max}$ were less than 1.

Table 2. Demographic characteristics

Parameters	Cohort 1		Cohort 2	
	Crisaborole and vehicle (<i>n</i> = 20)	Crisaborole (<i>n</i> = 10)	Vehicle (<i>n</i> = 2)	Total (<i>n</i> = 12)
Age, years				
Mean	26.2	35.0	23.5	33.1
SD	5.66	11.28	4.95	11.24
Sex, <i>n</i> (%)				
Male	20 (100)	10 (100)	2 (100)	12 (100)
Race, <i>n</i> (%)				
Asian	20 (100)	10 (100)	2 (100)	12 (100)
Weight, kg				
Mean	61.77	71.99	66.25	71.03
SD	8.105	10.067	4.031	9.454
Height, cm				
Mean	171.35	171.58	169.55	171.24
SD	5.297	5.975	5.728	5.729
BMI, kg/m ²				
Mean	21.00	24.47	23.10	24.24
SD	2.323	3.484	2.970	3.319
ISGA score, <i>n</i> (%)				
0: Clear	NA	0	0	0
1: Almost clear	NA	0	0	0
2: Mild	NA	2 (20.0)	0	2 (16.7)
3: Moderate	NA	8 (80.0)	2 (100)	10 (83.3)
4: Severe	NA	0	0	0
%BSA				
Mean	NA	68.60	40.50	63.92
SD	NA	17.790	6.364	19.552

%BSA, percentage of treatable body surface area; BMI, body mass index; ISGA, Investigator's Static Global Assessment; NA, not applicable; SD, standard deviation.

Table 3. Summary of skin irritation response in cohort 1

Assessment scores	Day 3 (<i>n</i> = 20)	Day 4 (<i>n</i> = 20)	Maximum irritation score (<i>N</i> = 20)
Crisaborole			
Assessment score, <i>n</i> (%)			
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)
Skin irritation index	–	–	40.0
Vehicle			
Assessment score, <i>n</i> (%)			
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)
Skin irritation index	–	–	5.0

Skin irritation index = (sum of individual maximum irritation scores / number of evaluable participants) × 100. The range of the index is 0–400.

Table 4. Incidence of all-cause treatment-emergent adverse events by treatment group in cohort 2[†]

	Crisaborole (<i>n</i> = 10)	Vehicle (<i>n</i> = 2)
With any AE, <i>n</i> (%)	9 (90.0)	2 (100)
TEAE by system organ class and preferred term, <i>n</i> (%)		
Eye disorders	1 (10.0)	0
Eyelid edema	1 (10.0)	0
General disorders and administration site conditions	9 (90.0)	2 (100)
Application site coldness	1 (10.0)	1 (50.0)
Application site irritation	7 (70.0)	1 (50.0)
Application site pain	4 (40.0)	1 (50.0)
Application site pruritus	0	1 (50.0)
Infections and infestations	0	1 (50.0)
Nasopharyngitis	0	1 (50.0)
Skin and subcutaneous tissue disorders	0	1 (50.0)
Dermatitis atopic	0	1 (50.0)
Total preferred term events, <i>n</i>	13	6

AE, adverse event; TEAE, treatment-emergent adverse event.

[†]Includes data up to lag days after last dose of study treatment.

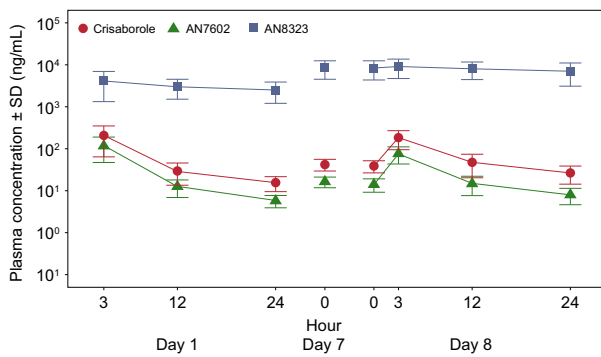


Figure 1. Mean plasma concentration-time profiles for crisaborole, AN7602 and AN8323 after the first and multiple twice-daily administrations. SD, standard deviation.

Exposures based on geometric mean AUC_{0-12} and C_{max} values for the AN8323 metabolite were higher than those observed for crisaborole and the AN7602 metabolite; AUC_{0-12} and C_{max} geometric mean values were 29 360 ng·h/mL and 3064 ng/mL, respectively, on day 1, and 90 360 ng·h/mL and 8080 ng/mL, respectively, on day 8. Unlike crisaborole and AN7602, some accumulation was observed for the AN8323

metabolite on day 8; geometric means for R_{ac} AUC_{0-12} and R_{ac} C_{max} were 3.080 and 2.638, respectively.

The dose-exposure relationship of crisaborole and %BSA-normalized exposure to crisaborole are presented in Figures 2 and 3, respectively. Exposure to crisaborole (based on AUC_{0-12} and C_{max}) appeared to increase linearly with increasing dose.

DISCUSSION

In this parallel-cohort study, patients who received crisaborole had higher skin irritation than those who received vehicle under occlusion in healthy Japanese adults in cohort 1. In cohort 2, crisaborole was found to be well tolerated and had an acceptable safety profile in Japanese adult patients with mild to moderate AD. Overall, there were no TEAE in cohort 1, and all TEAE in the crisaborole group in cohort 2 were mild. There were no clinically significant changes in laboratory values, vital signs or electrocardiography, and no deaths or serious TEAE were reported in this study. Two patients in cohort 2 discontinued: one in the crisaborole arm because of treatment-related application site pain and one in the vehicle arm because of treatment-related dermatitis atopic (described by the investigator as dermatitis atopic aggravated). TEAE in both patients resolved without treatment. Overall, multiple twice-daily

Table 5. Summary of plasma crisaborole pharmacokinetic parameters after single (day 1) and multiple (day 8) twice-daily administration

Parameter	Day 1 N = 9	Day 8 N = 9
Crisaborole		
AUC_{0-12} , geometric mean (geometric %CV), ng·h/mL	928.9 (65)	1123 (51)
AUC_{last} , geometric mean (geometric %CV), ng·h/mL	1171 (60)	1527 (48)
AUC_{24} , geometric mean (geometric %CV), ng·h/mL	1171 (60)	1527 (48)
C_{max} , geometric mean (geometric %CV), ng/mL	163.7 (71)	164.9 (56)
T_{max} , median (range), h	3.00 (3.00–3.00)	3.00 (3.00–3.00)
R_{ac} C_{max} , geometric mean (geometric %CV)	NA	1.007 (32)
R_{ac} AUC_{0-12} , geometric mean (geometric %CV)	NA	1.209 (25)
AN7602 metabolite		
AUC_{0-12} , geometric mean (geometric %CV), ng·h/mL	500.4 (66)	434.9 (50)
AUC_{last} , geometric mean (geometric %CV), ng·h/mL	601.9 (60)	565.5 (44)
AUC_{24} , geometric mean (geometric %CV), ng·h/mL	601.9 (60)	565.5 (44)
C_{max} , geometric mean (geometric %CV), ng/mL	94.97 (75)	68.83 (59)
T_{max} , median (range), h	3.00 (3.00–3.00)	3.00 (3.00–3.00)
R_{ac} C_{max} , geometric mean (geometric %CV)	NA	0.7247 (24)
R_{ac} AUC_{0-12} , geometric mean (geometric %CV)	NA	0.8688 (19)
AN8323 metabolite		
AUC_{0-12} , geometric mean (geometric %CV), ng·h/mL	29 360 (92)	90 360 (68)
AUC_{last} , geometric mean (geometric %CV), ng·h/mL	57 560 (84)	169 100 (68)
AUC_{24} , geometric mean (geometric %CV), ng·h/mL	57 560 (84)	169 100 (68)
C_{max} , geometric mean (geometric %CV), ng/mL	3064 (97)	8080 (71)
T_{max} , median (range), h	3.00 (3.00–12.0)	3.00 (3.00–12.0)
R_{ac} C_{max} , geometric mean (geometric %CV)	NA	2.638 (52)
R_{ac} AUC_{0-12} , geometric mean (geometric %CV)	NA	3.080 (48)

%CV, coefficient of variation; AUC_{0-12} , area under concentration-time curve from time 0 to 12 h; AUC_{24} , AUC from time 0 to 24 h; AUC_{last} , AUC from time 0 to last measurable concentration; C_{max} , maximum observed plasma concentration; NA, not applicable; R_{ac} AUC_{0-12} , accumulation ratio for AUC_{0-12} ; R_{ac} C_{max} , accumulation ratio for C_{max} ; T_{max} , time to reach C_{max} .

administrations of crisaborole ointment resulted in minimal systemic crisaborole exposure on day 8; geometric means for R_{ac} AUC_{0-12} and R_{ac} C_{max} were 1.209 and 1.007, respectively. There was no accumulation of the AN7602 metabolite on day 8; both R_{ac} AUC_{0-12} and R_{ac} C_{max} were less than 1. However, accumulation was observed for the AN8323 metabolite on day 8; geometric means for R_{ac} AUC_{0-12} and R_{ac} C_{max} were 3.080 and 2.638, respectively. Ultimately, based on trough concentrations for days 7, 8 and 9, steady state was achieved by day 7 for crisaborole and its metabolites AN7602 and AN8323.

To contextualize these results, comparisons can be made with two previous studies of crisaborole conducted in the USA.^{8,9} One study was a phase 1b maximal use trial that evaluated crisaborole in 31 children aged 2–17 years.⁸ The other was a phase 2a open-label study evaluating standard twice-daily dosing of crisaborole in adolescents aged 12–17 years.⁹ Compared with the current study which recruited Japanese adults, both previous US studies recruited children, most of

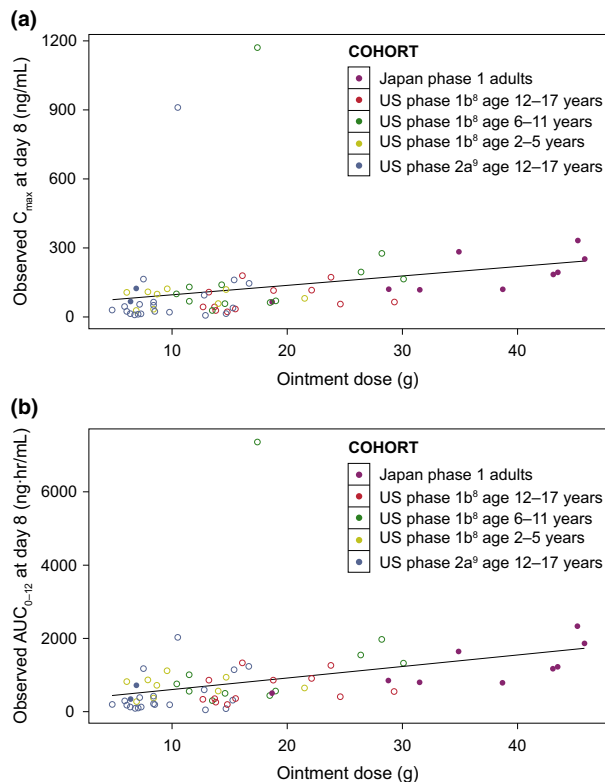


Figure 2. Observed (a) C_{max} and (b) AUC_{0-12} of plasma crisaborole at day 8 by crisaborole dose in the current study and two previous crisaborole studies.^{8,9} Ointment dose (g) represents the amount of ointment applied for a single application. The solid line represents the naive-pooled linear regression fit of the data; filled dots represent race “Asian”; empty dots represent other races, including “White”, “Black or African American”, “Native Hawaiian or other Pacific Islander” and “Other”. %BSA, percentage of treatable body surface area; AUC_{0-12} , area under concentration-time curve from time 0 to 12 h; C_{max} , maximum observed plasma concentration; y, years.

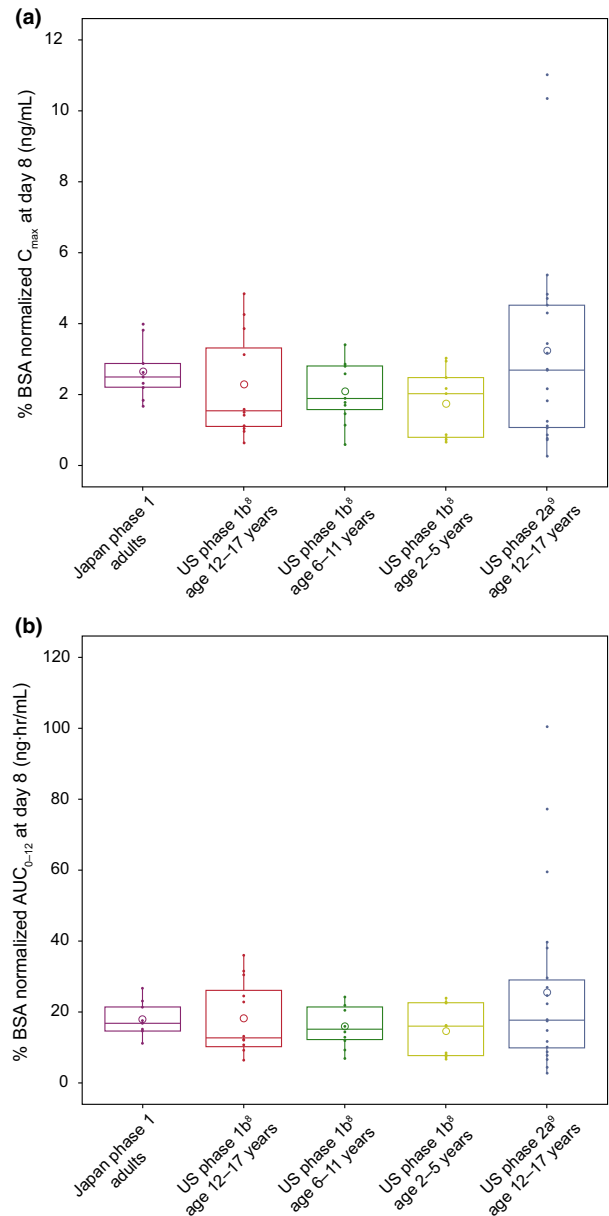


Figure 3. %BSA-normalized (a) C_{max} and (b) AUC_{0-12} of plasma crisaborole at day 8 in current study and two previous crisaborole studies.^{8,9} The solid dark line in the box represents the median; the bottom and top of the box represent the 1st (25th percentile) and 3rd (75th percentile) quartiles, respectively; the whiskers represent the highest and the lowest datum within the $\times 1.5$ interquartile range; dots represent individual patient data; the open circle represents the mean. Three points from two patients included in Figure 2 were excluded from Figure 3 box plots as being outliers: this includes one patient (aged 6–10 years) from the phase 1b study with AUC_{0-12} 7360 ng·h/mL and C_{max} 1170 ng/mL, and one patient (aged 12–17 years) from the phase 2a study with C_{max} 910 ng/mL. % BSA, percentage of treatable body surface area; AUC_{0-12} , area under concentration-time curve from time 0 to 12 h; C_{max} , maximum observed plasma concentration; y, years.

whom were white or black.^{8,9} The inclusion criteria for the maximal use study required patients aged 12–17 years to have %BSA of 25 or more, and patients aged 2–11 years to have %BSA of 35 or more.⁸ In the phase 2a study, patients were included if they had %BSA between 10 and 35.⁹ Similar to the patients with AD in the current study, all patients in both US studies had to have mild or moderate disease per ISGA at baseline.^{8,9} Crisaborole was applied twice daily at a dose of 3 mg/cm² for 28 days in both US studies with PK assessments performed at day 1 and day 8.^{8,9} A safety profile comparable with that of the current study was observed in both US studies: most TEAE were mild or moderate.^{8,9} Similar to the current study, one patient in each study discontinued treatment with crisaborole because of a TEAE of application site pain or application site dermatitis.^{8,9} PK parameters for crisaborole and its metabolites AN7602 and AN8323 were also evaluated and results were comparable with those observed for the Japanese adult patients in the current study.^{8,9} Systemic exposures increased in a linear manner across all three studies (Fig. 2). Based on %BSA-normalized systemic exposure of crisaborole (AUC_{0–12} and C_{max}), results between Japanese and US participants were similar, even when examined by age group (Fig. 3). PK parameters in Japanese participants did not exceed the higher range of exposures seen in the maximal use study in US patients.

The skin irritation index for crisaborole under occlusion was 40.0 (on a scale of 0–400). However, because of the methods used in the current study, it is difficult to compare with data from non-Japanese healthy volunteers, especially because skin irritation is generally scored differently outside of Japan. A phase 1, vehicle-controlled study in the USA was conducted to evaluate crisaborole applied twice daily to sensitive skin areas for 21 days without occlusion in healthy white adults aged 18–55 years.¹⁴ Local tolerability was graded on a 4-point scale ranging from 0 (none) to severe (3).¹⁴ Most participants (98.8%) reported a tolerability grade of 0 (no irritation), whereas 0.85% reported a tolerability grade of 1 (mild irritation) and 0.1% reported a tolerability grade of more than 1.¹⁴ In the current study, some skin irritation was observed, though skin irritation was tested under occlusion in healthy volunteers only. However, the skin irritation did not result in the reporting of a TEAE. Patients with AD are already likely to have a higher potential for skin irritation than healthy volunteers because of barrier dysfunction and increased skin permeability to irritants, allergens and pathogens,¹⁵ but, as shown in data from cohort 2, crisaborole was generally well tolerated. However, there was a limited number of patients in cohort 2 and treatments were only applied for 8 days. Occlusion typically increases local absorption of topically applied pharmaceuticals.¹⁶ The results from skin irritation testing that had been performed using occlusion may not be as applicable to normal application scenarios (i.e. without occlusion) because of the potential for increased local drug exposure for a prolonged period of time (48-h occlusion).

For the purposes of this phase 1 study, patient's severity of AD in cohort 2 was determined by the baseline ISGA alone and patients were only eligible to participate with baseline severity of mild or moderate disease per ISGA. The safety and

tolerability of crisaborole in Japanese patients with severe baseline ISGA remains to be studied.

Crisaborole ointment, 2%, was found to be well tolerated in Japanese patients who had mild to moderate AD, with application site pain and application site irritation being the most common TEAE. In healthy volunteers, no TEAE were reported; however, greater skin irritation was observed in participants receiving crisaborole compared with vehicle under occlusion. Additional studies are necessary to evaluate the safety and efficacy of crisaborole for longer periods of treatment in Japanese pediatric and adult patients with AD.

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