Title Page

A PHASE 3, MULTICENTER, OPEN-LABEL STUDY OF THE LONG-TERM SAFETY OF CRISABOROLE OINTMENT, 2% IN JAPANESE PEDIATRIC AND ADULT PARTICIPANTS WITH MILD TO MODERATE ATOPIC DERMATITIS

Study Intervention Number:	PF-06930164
Study Intervention Name:	Crisaborole
US IND Number:	N/A
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Protocol Number:	C3291027
Phase:	3

Short Title: A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants with Mild to Moderate Atopic Dermatitis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	20 May 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants with Mild to Moderate Atopic Dermatitis

Rationale

Crisaborole development as a topical therapy for patients with mild to moderate AD is based on its mechanism of action and the results obtained from 11 AD clinical studies conducted in Japan and foreign countries to date.

In Japan, a phase 2 study (C3291028) in pediatric and adult participants with mild to moderate AD was completed and it showed superiority of crisaborole ointment, 2% relative to the corresponding vehicle in both regimens (QD and BID) for both age groups of 12 years and older and 2 to under 12 years old. In addition, in the descriptive comparison of BID and QD regimens, crisaborole ointment, 2% BID was more effective than crisaborole ointment, 2% QD for both age groups, and both regimens were well-tolerated.

An Asia regional phase 3 study (C3291032) is planned to support the registration of crisaborole in China, Japan and other Asian countries/region. In this study, the efficacy and safety of crisaborole ointment, 2% BID will be investigated in Asian pediatric and adult participants (ages 2 years and older) with mild to moderate AD.

In addition, a global phase 3 study (C3291031) is also planned to assess the efficacy, safety, and local tolerability of crisaborole ointment, 2%, applied twice a day in participants who are 1 month to less than 24 months of age with mild to moderate AD.

The purpose of this long-term extension study (C3291027) is to assess the one-year long-term safety of crisaborole ointment, 2% BID in Japanese AD pediatric and adult participants who completed study intervention period in the studies C3291032 or C3291031.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To study the safety of crisaborole ointment, 2% applied BID in Japanese pediatric and adult participants with mild to moderate AD	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	• The incidence of treatment emergent adverse events and serious adverse events

Overall Design

This study is a Phase 3, multicenter, open-label, long-term safety extension study of Studies C3291032 and C3291031 in Japanese pediatric and adult participants with mild to moderate AD to support the registration of crisaborole in Japan. After completion of the study intervention period in Study C3291032 or Study C3291031 and confirmed Study C3291027 eligibility, participants will be offered participation in the study from investigator sites in Japan. Scheduled study visits will occur every 4 weeks (1 cycle) with On-Treatment or Off-Treatment cycles to be decided by the investigator based on the ISGA score. PK blood sampling will be conducted at the selected study sites for the participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032.

When the investigator assessment of ISGA is Almost Clear (1) or greater, an On-Treatment Cycle will be initiated. When the investigator assessment of ISGA is Clear (0), crisaborole ointment, 2% treatment will not be initiated and the participant will enter an Off-Treatment Cycle. Based on the ISGA score throughout the study, a participant may be administered a variable number of cycles of crisaborole ointment, 2% treatment (On-Treatment Cycle) during their up to 52 weeks of study participation.

On Week 56 (EOS), a follow-up telephone call will be made by site staff to assess for AEs that may have occurred since the last visit.

Number of Participants

Sample size will be determined by the number of participants who enroll from the qualifying parent studies. It is estimated that at least 150 participants (ie, 20 participants for under 2 years old and 130 participants for 2 years and older) are expected to join from the currently planned qualifying parent studies. Analyses performed, including interim evaluations, if any, will primarily be for safety though some measures of efficacy may be analyzed.

Intervention Groups and Duration

All participants will receive crisaborole ointment, 2% BID for up to 52 weeks.

The expected total duration of participation in the study is 56 weeks, including an open label intervention period of 52 weeks and a follow up period of 4 weeks after EOT.

Data Monitoring Committee or Other Independent Oversight Committee: Yes

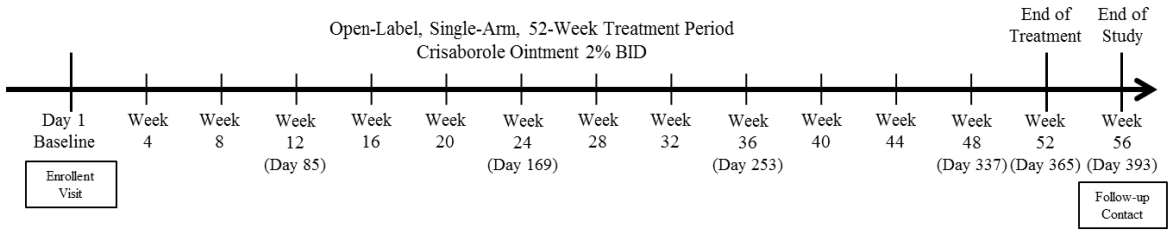
Statistical Methods

The primary endpoint of incidence of safety events will be analyzed using descriptive measures such as percentages and exposure-adjusted incidence rates along with confidence intervals. No statistical hypotheses will be tested.

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.

Efficacy analyses will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 6.	**Enrollment Visit**	**Intervention Period**				**Follow-up Contact**[b]
	Visit 1	**Visit 2-13**		**Unplanned Visit to initiate study intervention during Off-Treatment Cycle**	**Visit 14**	**Visit 15**
	Day 1[c]	**Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48**			**Week 52/ EOT/ET**	**Week 56/EOS**
		Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337			**Day 365/ EOT/ET**	**Day 393/EOS** At least 28 days after last study dose
		Start Day of On-Treatment Cycle[c]	**Start Day of Off-Treatment Cycle**[c]			
Visit Window		**±7 days based on Day 1**			**±7 days based on Day 1**	**+7 days based on Week 52/EOT/ET**
Informed consent, including assent	X[d]					
Registration	X					
Demographics and medical history including AD history/prior AD treatment (including reasons of stop)	X[e]					
Current/prior treatments for current/prior medical history other than AD	X[e]					
Inclusion/exclusion criteria	X					
Physical examination	X[e]	X (Week 24 only)	X (Week 24 only)		X	
Weight (age ≥18)	X				X	
Height and Weight (age <18)	X[e]	X (Weeks 12, 24, 36, 48 only)	X (Weeks 12, 24, 36, 48 only)		X	
Laboratory						
Pregnancy test[f]	X[e]	X	X		X	

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		Start Day of On-Treatment Cycle[c]	**Start Day of Off-Treatment Cycle**[c]			
Visit Window		**±7 days based on Day 1**			**±7 days based on Day 1**	**+7 days based on Week 52/EOT/ET**
Contraception check[g]	X	X	X		X	X
Study intervention						
Body Site Checklist of AD lesions	X	X		X	X	
Record treatable AD areas	X	X		X		
Study Intervention Dispensing[h]	X[i]	X		X		
Instruction for dosing and dispense dosing diary	X[i]	X		X		
Weigh the investigational product tube(s) and dispense	X[i]	X		X		
Study intervention administration	X[i]	BID, throughout On-Treatment Cycle[j,k]		BID, for the remainder of a treatment cycle[j,k]		
Review dosing diary; assess compliance		X[l]	X[l]		X[l]	
Collect and weigh returned investigational product tubes, including empty, partially used and unused tubes		X[l]	X[l]		X[l]	
Assessments						
Calculate and record treatable %BSA	X[e]	X	X	X	X	
ISGA[m]	X[e]	X	X	X	X	
Regional ISGA-face[m,o]	X[e]	X	X		X	
EASI[m]	X[e]	X	X		X	

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 6.	**Enrollment Visit**	**Intervention Period**				**Follow-up Contact**[b]
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	Day 1[c]	**Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48**			**Week 52/ EOT/ET**	**Week 56/EOS**
		Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337			**Day 365/ EOT/ET**	**Day 393/EOS** At least 28 days after last study dose
		Start Day of On-Treatment Cycle[c]	**Start Day of Off-Treatment Cycle**[c]			
Visit Window		**±7 days based on Day 1**			**±7 days based on Day 1**	**+7 days based on Week 52/EOT/ET**
Peak Pruritus NRS/Patient Reported Itch Severity Scale/ Observer Reported Itch Severity Scale[n]	X[e]	X	X		X	
Concomitant treatment(s)	X[e]	→	→	→	→	X
Serious and nonserious adverse event monitoring	X[e]	→	→	→	→	→
Review lifestyle considerations	X	X	X		X	X
Schedule/reconfirm next study visit or contact	X	X	X		X	
Remind to bring all investigational product tubes and the dosing diary to the next visit	X[i]	X	X[p]	X		
Blood sampling to obtain plasma for crisaborole and metabolites PK	X[q]					

a. Day relative to start of study intervention (Day 1).
b. Contact may occur via telephone contact and must occur 28 to 35 days from Week 52/EOT/ET Visit.
c. Day 1 will be the same day as EOT visit of Study C3291032 or C3291031. Procedure done at Day 1 Visit of next treatment cycle. Depending upon ISGA score and investigator's judgment, participant will initiate an "On-treatment Cycle" or "Off-treatment Cycle".
d. Obtain written informed consent (from adult participant or parent/legal guardian of pediatric participant) and assent (from pediatric participant, as applicable) before any study procedures are performed.
e. Procedure done at Day 29 (concomitant treatment, physical examination, %BSA, ISGA, Regional ISGA-face, EASI, Peak Pruritus NRS/Patient Reported Itch Severity Scale/ Observer Reported Itch Severity Scale, urine pregnancy test and AE/SAE) and Screening (medical history including AD history/prior AD treatment) of Study C3291032 or procedure done at Week 24 (concomitant medications/therapies, physical examination, height/length and

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 6.	Enrollment Visit	Intervention Period			Follow-up Contact[b]
	Visit 1	Visit 2-13	Unplanned Visit to initiate study intervention during Off-Treatment Cycle	Visit 14	Visit 15
	Day 1[c]	Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48		Week 52/ EOT/ET	Week 56/EOS
		Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337		Day 365/ EOT/ET	Day 393/EOS At least 28 days after last study dose
		Start Day of On-Treatment Cycle[c] / Start Day of Off-Treatment Cycle[c]			
Visit Window		±7 days based on Day 1		±7 days based on Day 1	+7 days based on Week 52/EOT/ET

weight, %BSA, EASI, ISGA, Observer Reported Itch Severity Scale, and AE/SAE) and Screening (medical history including AD history/prior AD treatment) of Study C3291031 will serve as Enrollment Visit data for Study C3291027.

f. For all female participants biologically capable of having children (refer to Section 10.4.2 for definition of a female of childbearing potential). The participant and his/her parent/legal guardian will be instructed regarding the contraception method requirement and informed of the requirement to conduct a urine pregnancy test. Pediatric female participant who has not experienced menarche is not required to perform pregnancy testing. If the pediatric female participant starts menarche during the study, pregnancy testing will be performed.
g. For studies enrolling pediatric participants, it is the opportunity to assess changing potential to father/bear children and allows for implementing contraception and pregnancy testing as children mature physically and behaviorally during conduct of the study.
h. Study coordinator or specified designee will contact IRT to register the visit and, if applicable, obtain the next investigational product tube(s) assignment.
i. Participant who will start "On-treatment Cycle" from Enrollment Visit.
j. At home dosing by participant or his/her parent/legal guardian. Investigational product application BID through the evening before the day of visit. After the procedure/assessment of the visit, the participant or his/her parent/legal guardian can apply the investigational product, if applicable.
k. In the event the scheduled Start Day of the next treatment cycle visit does not fall exactly on the scheduled date, the participant or his/her parent/legal guardian will be instructed to continue investigational product application BID through the evening before the actual visit date.
l. Performed only for those participants completing a previous On-Treatment Cycle (e.g., Previous "On-treatment" and continue "On-treatment", or previous "On-treatment" and initiate "Off-treatment").
m. The ISGA should be completed prior to Regional ISGA-face and EASI assessments, whenever possible.
n. Peak Pruritus NRS will be completed by participants ≥12 years of age at the time of signing the ICD in the prior study, Patient Reported Itch Severity Scale will be completed by participants ≥6 years and <12 years at the time of signing the ICD in the prior study, and Observer Reported Itch Severity Scale will be completed by the observers (caregivers of participants) for participants <6 years of age at the time of signing the ICD in the prior study.
o. Only for participants who completed study intervention for Study C3291032 and had AD in face at Day 1 Visit of Study C3291032.
p. Performed to remind the participants initiating "Off-treatment Cycle" to bring back dosing diary which records concomitant medication usage.
q. PK blood sampling will be conducted at the selected study sites in participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032. The date and time for most recent dose (last dose in C3291032 study) will be collected.

2. INTRODUCTION

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory PDE-4 inhibitor that penetrates the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate levels, which suppresses inflammation and secretion of certain cytokines, such as TNF-α, IL-2, IL-4, IL-5, and IFN-γ, implicated in the pathogenesis of AD. Crisaborole applied to human skin ex vivo or on AD lesions of patients reduces expression of key drivers of atopic inflammation, including T-cell derived cytokines IL-13, IL-31, and IFN-γ as well as innate markers of inflammation such as MMP-12. The specific mechanism(s) by which crisaborole exerts its therapeutic action for AD is not well defined.[1]

Crisaborole ointment, 2% (20 mg/g) (referred to as crisaborole hereafter), is an approved therapy in the US and Canada (EUCRISA®), and EU, Israel and Australia (STAQUIS®) as a topical treatment in patients 2 years of age and older with mild to moderate AD.[1] In 2020, crisaborole also obtained supplemental approval for treatment in patients as young as 3 months of age in US.[2] It is currently being developed worldwide as a topical therapy for patients with mild to moderate AD.

2.1. Study Rationale

Crisaborole development as a topical therapy for patients with mild to moderate AD is based on its mechanism of action and the results obtained from 11 AD clinical studies conducted in Japan and foreign countries to date.

In Japan, a phase 2 study (C3291028) in pediatric and adult participants with mild to moderate AD was completed and it showed superiority of crisaborole ointment, 2% relative to the corresponding vehicle in both regimens (QD and BID) for both age groups of 12 years and older and 2 to under 12 years old. In addition, in the descriptive comparison of BID and QD regimens, crisaborole ointment, 2% BID was more effective than crisaborole ointment, 2% QD for both age groups, and both regimens were well-tolerated.

An Asia regional phase 3 study (C3291032) is planned to support the registration of crisaborole in China, Japan and other Asian countries/region. In this study, the efficacy and safety of crisaborole ointment, 2% BID will be investigated in Asian pediatric and adult participants (ages 2 years and older) with mild to moderate AD.

In addition, a global phase 3 study (C3291031) is also planned to assess the efficacy, safety, and local tolerability of crisaborole ointment, 2%, applied twice a day in participants who are 1 month to less than 24 months of age with mild to moderate AD.

The purpose of this long-term extension study (C3291027) is to assess the one-year long-term safety of crisaborole ointment, 2% BID in Japanese AD pediatric and adult participants who completed study intervention period in Study C3291032 or Study C3291031.

2.2. Background

AD, also referred to as atopic eczema, is a chronic and relapsing disease affecting an increasing number of persons. Although AD affects patients of all ages, it is one of the most common, chronic, relapsing childhood dermatoses. The lifetime prevalence of AD is estimated to be 15% to 30% in children while the incidence of AD has increased by 2- to 3-fold during the past 3 decades in industrialized countries.[3] Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US and Japan.[4-6]

AD is a distinctive inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.[5,7] The majority of patients (up to 90%) with AD present with mild to moderate disease.[8] Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, lichenification, and bacterial colonization.[9] Continuous scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections. AD is often associated with other conditions including asthma, allergic rhinitis, and food allergy.[10,11]

AD is a condition associated with significant morbidity. The burden of the clinical symptoms of AD coupled with the stigma associated with highly visible skin lesions correlates with significant morbidity and extensive impairments on HRQOL for patients, especially in children, and caregivers.[7,12-14] Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.[15] The negative impact on HRQOL caused by childhood AD exceeds that in asthma, epilepsy, and diabetes, is comparable to that in renal disease or cystic fibrosis, and is equal (child) or exceeds (parents) that in psoriasis.[13,16,17] The hallmark symptom of itching causes scratching which is associated with sleep disturbance in greater than 60% of patients. Sleep deprivation leads to physical and mental exhaustion in patients and other family members resulting in loss of concentration and impaired performance at school or work.[18,19] AD is often associated with significant childhood behavioral problems and psychological disorders including depression, attention deficit hyperactivity disorder, anxiety, stress, and autism.[15] Preschool children with AD show a significant increase in behavioral symptoms compared with age-matched controls.[20] Absolon et al[21] reported that the rate of psychological disturbance in school age children with AD doubled compared with age-matched matched controls. For older children with AD, in addition to problems associated with itching and sleep disturbance, their social and school life may be substantially affected. Social embarrassment, due to visible signs of the disease (crusted, excoriated, oozing, bleeding lesions), teasing, and bullying, often results in social isolation leading to depression.[16]

AD has a significant impact on day to day functioning, as evidenced by its impact on the overall wellbeing of the patient and their family on multiple levels; medical management and treatment; HRQOL; and psychosocial implications. In summary, AD is a disease with multiple comorbidities and significant impact on the health, day to day functioning, and HRQOL of AD patients, their caregivers, and family members.

AD may also be a source of significant economic burden[22] as this relapsing disease is often misdiagnosed, misunderstood, and ineffectively treated.[5]

Currently, there is no cure for AD. AD is a chronic disease with treatment focused on the management of flares and maintenance of remissions. Due to the chronic, relapsing nature of the disease, treatment may be needed for many years.

Crisaborole is a novel, non-steroid, topical anti-inflammatory PDE-4 inhibitor that will serve an unmet need in the treatment of AD. Supporting evidence of the safety and efficacy of this product in patients 2 years and older represent a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the limitations on patient age, location, duration of use and line of therapy of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in favor of crisaborole ointment, 2% BID versus vehicle ointment BID in the two Phase 3 pivotal studies, AN2728-AD-301 and AN2728-AD-302.[23] Across the development program, crisaborole demonstrated an acceptable safety profile; the majority of AEs was mild and deemed unlikely or not related to study intervention, with no crisaborole treatment-related SAEs (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related). Efficacy, safety and tolerability of crisaborole ointment, 2% BID in patients younger than 2 years of age was investigated in Study C3291002 (NCT03356977) conducted in participants aged 3 months to less than 24 months. This product was well-tolerated, and overall the safety profile and efficacy observed in this study was consistent with that observed in previous studies of crisaborole in participants 2 years of age and older.

2.2.1. Drug Development

Crisaborole has been formulated as a topical ointment. Crisaborole has demonstrated clinical benefit in 10 AD clinical studies in Phases 1, 2, and 3. Details of the nonclinical and clinical data are provided in the investigator's brochure.

2.2.2. Nonclinical Studies

Crisaborole demonstrated inhibitory capacity against human leukocyte cytokine release with IC_{50} and EC_{50} values ranging from high nanomolar to low micromolar concentrations. Crisaborole also inhibits the release of chemokines that are important inflammatory mediators. The primary mechanism of the anti-inflammatory effect of crisaborole is through inhibition of PDE-4, which causes elevation of cAMP in leukocytes and subsequent protein kinase A mediated phosphorylation of transcription factors that are important for cytokine-, chemokine-, or prostaglandin-forming enzyme synthesis and release from cells. Crisaborole proved efficacious against an inflammatory challenge in vivo in a mouse PMA-induced ear edema model. AN7602 and AN8323, the predominant oxidative metabolites of crisaborole, lack anti-inflammatory activities against PDE-4 and a panel of cytokines.

Based on the nonclinical safety studies conducted to date, crisaborole ointment, 2% has an acceptable safety profile.

2.2.3. Pharmacokinetics

The efficacy of crisaborole for the topical treatment of AD is not by systemic exposure. The development program evaluated systemic exposure to crisaborole and its main metabolites relative to establishing the safety of topically applied crisaborole. Systemic exposures to crisaborole following topical application were assessed in healthy volunteers and patients (AD and psoriasis). Crisaborole was shown to have penetrated through the stratum corneum, epidermis, and dermis of human skin and had measurable systemic exposures.

A review of the PK data across the studies reveals an apparent relationship between exposure and %BSA treated with crisaborole topical ointment, 2%. In studies conducted in AD patients (AN2728-AD-203 and AN2728-AD-102), absorption of crisaborole across the skin was rapid, as evidenced by median T_{max} values of 3.0 hours or less following single and multiple doses of crisaborole topical ointment, 2%. Crisaborole was rapidly metabolized to AN7602 and then to AN8323; both metabolites are inactive as PDE-4 inhibitors. Exposure to crisaborole and AN7602 was limited, while AN8323 was the predominant metabolite in plasma, as shown by comparison of C_{max} and AUC values both following single and multiple doses of crisaborole topical ointment, 2%. Overall, the extent of systemic exposure (C_{max} and AUC) of crisaborole, AN7602, and AN8323 increased with higher %BSA treated. Minimal accumulation of crisaborole or AN7602 occurred over 8 days of dosing. AN8323 displayed moderate accumulation, consistent with its long $t_{½}$ (33.5 hours on Day 8 in Study AN2728-AD-203). Steady state was apparently achieved within 4 to 6 days for all 3 analytes in both studies. The systemic exposure of crisaborole following topical administration was higher in participants with AD relative to healthy volunteers. Based on observed systemic exposures observed in healthy adults, children, adolescent participants (2 to 17 years of age) with AD, and adult participants with psoriasis, at similar percent treated BSA, crisaborole systemic exposures across age groups are expected to be in a similar range. Crisaborole systemic exposure in children (≥2 years) at maximum possible dose are unlikely to exceed the exposures at the maximum possible dose in adults.

In the 8-days, safety, tolerability and PK study (Cohort 2 in Study C3291029), 10 adult Japanese participants with mild to moderate AD (20-55 years old) received crisaborole ointment, 2% (mean treatable %BSA 63.9%; range 35%-87%), absorption across the skin was rapid, with a median of time to reach T_{max} of 3.0 hours on both Day 1 and Day 8. Mean C_{max} values in plasma were 199 ng/mL on Day 1, and 185 ng/mL on Day 8, respectively. Overall, the extent of systemic exposure (plasma C_{max} and AUC) of crisaborole, AN7602, and AN8323 increased with higher %BSA treated. Minimal plasma accumulation of crisaborole and AN7602 was observed at steady state whereas AN8323 displayed an approximately 3-fold accumulation based on C_{max} and AUC_{12}. Steady state was achieved by Day 7 for crisaborole and its metabolites. The %BSA normalized systemic exposure of crisaborole, AN7602, and AN8323 (C_{max} and AUC_{12}) were similar between C3291029 study and AD-102 study.

The PK profiles of crisaborole and its metabolites were assessed in 3 months to 2-year-old infants as a PK sub-study in a Phase 4, multicenter, open label safety study (Study C3291002). The participants in the PK sub study ranged in age from 3 to 23 months with

7 participants <9 months of age and 14 participants of 9 to 24 months of age. The %treatable BSA ranged from 35% to 79% at baseline. Following multiple BID administration systemic exposures were characterized on Day 8. 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.

2.2.4. Cutaneous Sensitization, Irritancy Potential and Tolerability

2.2.4.1. Skin Irritation Study

The investigational products (crisaborole ointment, 2% and vehicle) were applied topically to 1-side of the infrascapular area of the back once on Day 1 and remained under occlusion for 48 hours (Cohort 1 in Study C3291029) to Japanese healthy participants. The skin irritancy was to be evaluated approximately 30 minutes after removal of the patches on Day 3 and 24 hours after removal of the patches on Day 4. The degree of erythema, edema and other signs of skin irritation at the application site was evaluated using the visual scale. All participants for the crisaborole ointment, 2% patch had a maximum irritation score of 0 (No reaction) or 0.5 (Mild erythema) except for the 3 participants with a maximum irritation score of 2 (Erythema + edema, papula).

2.2.4.2. Local Tolerability in Sensitive Skin Area

In a study of healthy participants (16 men and 16 women) who applied crisaborole ointment, 2% or vehicle for 21 days to sensitive area application sites (including extensor areas, intertriginous areas, genitals, and face/hairline), 99% of assessments of local tolerability were graded as 0 (none), with an overall maximum grade of 2 (moderate) and only 0.1% of assessments graded higher than 1 (mild) (Study AN2728-PSR-107). There were no marked differences in burning/stinging, erythema, or pruritus at any of the application sites over the course of the study between participants who received crisaborole ointment, 2% or vehicle. Overall, crisaborole ointment, 2% was well tolerated over 21 days of dosing in sensitive skin areas of healthy participants.

2.2.4.3. Sensitizing and Cumulative Irritation Potential

In a repeat-insult patch test and cumulative irritation study in healthy participants (Study AN2728-RIPT-101), the potential for inducing cutaneous sensitization was assessed in 238 participants randomized in Cohort 1. None of the participants demonstrated cutaneous evidence of sensitization potential (a reaction of at least Grade 4 [definite edema] or a pattern suggestive of contact sensitization in the opinion of the Investigator) to the investigational products, crisaborole ointment, 2% or vehicle. The potential for causing cutaneous irritation was evaluated among 40 participants randomized in Cohort 2. There were no statistically significant differences in irritation between the crisaborole ointment, 2% and vehicle. Crisaborole ointment, 2% and vehicle showed no evidence of sensitization and only very minimal irritation.

2.2.5. Clinical Overview

Eleven (11) clinical trials of topical formulations of crisaborole have been completed to date in participants with AD. Key study information is summarized below.

- In a multicenter, MUSE study in 34 pediatric participants with mild to moderate AD involving ≥35% BSA (ages 2 to 11 years) or ≥25% BSA (ages 12 to 17 years), who applied crisaborole ointment, 2% BID (AN2728-AD-102), participants had overall plasma levels of crisaborole that were low and similar to those previously observed in adults after adjusting for %BSA treated. Absorption across the skin was rapid, with a median T_{max} of 3.0 hours on both Day 1 and Day 8. Systemic levels of crisaborole and its main metabolites, AN7602 and AN8323, were similar among 3 age cohorts.

- In a 4-week, single arm, open-label safety, tolerability, and PK trial in adolescents with mild to moderate AD involving 10% to 35% BSA (AN2728-AD-203), disease severity improved over the 28-day treatment period.

- In a PK study conducted in adult Japanese participants with mild to moderate AD (C3291029 Cohort 2) having at least 25% treatable BSA, crisaborole showed minimal accumulation and steady state was achieved by Day 7. Absorption across the skin was rapid, with a median T_{max} of 3.0 hours on both Day 1 and Day 8. Systemic levels of crisaborole and its metabolites were in the same range as that observed for non-Japanese participants in the MUSE study (AN2728-AD-102).

- In a 6-week, randomized, vehicle-controlled intra-participant efficacy and biomarker study of adult participants with mild to moderate AD (C3291001), crisaborole ointment, 2% applied BID statistically significantly improved lesion TSS more than vehicle at Day 15 (primary efficacy endpoint). Crisaborole significantly reduced 7 key skin biomarkers of AD from Baseline to Day 15 (primary biomarker endpoint).

- In a 6-week bilateral comparison trial of participants with mild to moderate AD (AN2898-AD-202), 68% of AD lesions treated with crisaborole ointment, 2% BID showed greater improvement in ADSI than vehicle treated lesions (20%) at 4 weeks (primary endpoint). These response rates were similar at Day 14 and Day 42 (EOT).

- In a 4-week bilateral comparison trial of 86 adolescent participants with mild to moderate AD (AN2728-AD-204), crisaborole ointment, 2% BID showed greater improvement than the lower concentration of crisaborole ointment, 0.5% applied BID for 29 days, and was more efficacious than either concentration applied QD.

- In two Phase 3 multicenter, randomized, double-blind, vehicle-controlled studies in participants ≥2 years of age and older with mild to moderate AD, crisaborole ointment, 2% BID outperformed the vehicle in the primary efficacy analysis of success in ISGA and the difference between the treatment groups was statistically significant (AN2728-AD-301, AN2728-AD-302).

- An additional Phase 3 multicenter, open-label, long-term extension study of crisaborole ointment, 2% BID for the treatment of mild to moderate AD in adults and children as young as 2 years of age affirmed the long-term safety of topical crisaborole (AN2728-AD-303). No clinically important systemic safety signals were identified by this study.

- In a Phase 4, multicenter, open-label safety study to evaluate the safety of crisaborole ointment, 2% in children 3 to <24 months of age, with mild to-moderate AD involving ≥5% treatable BSA, exploratory efficacy was assessed and results showed that the treatment response of crisaborole in this population of participants 3 to <24 months of age is consistent with that from the Phase 3 studies. In this study, crisaborole was well-tolerated, no evidence of propylene glycol-related AEs, such as cardiac or neurologic disorders, was apparent in the 3 to <24 month age group (C3291002). Overall the safety profile observed in this study was consistent with that observed in previous studies of crisaborole in participants 2 years of age and older.

- In a Phase 2b, multicenter, randomized, double-blind, vehicle-controlled, intra-participant study to evaluate efficacy and safety of two regimens of crisaborole ointment, 2% in Japanese pediatric and adult participants with mild to moderate AD involving at least 1.0% and no more than 30% treatable %BSA (C3291028), superiority of crisaborole ointment, 2% relative to the corresponding vehicle was shown in both regimens (QD and BID) for both age groups of 12 years and older and 2 to under 12 years old, and its primary endpoint was met. In addition, in the descriptive comparison of BID and QD regimens under unblinded, crisaborole ointment, 2% BID was more effective than crisaborole ointment, 2% QD for both age groups, and both regimens were well-tolerated.

In summary, crisaborole has been well tolerated across completed clinical studies. No clinically important systemic safety signals have been identified in adults and children as young as 3 months of age. Most AEs have been mild and most considered unrelated or unlikely to be related to study intervention. The most common drug-related AEs were application site reactions, such as application site pain (stinging or burning) and application site pruritus. Full details of crisaborole clinical trial data are provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of crisaborole may be found in the investigator's brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): crisaborole ointment, 2%		
There are no important identified risks nor important potential risks for crisaborole.	The most common drug-related AEs from the Phase 3 clinical trials were application site reactions (5.6% and 3.6% for crisaborole and vehicle groups, respectively) and most were classified as mild. Of these drug-related application site reactions, application site pain was the only treatment related AE that showed a clinically relevant difference in rates between the treatment groups (4.4% and 1.2% for crisaborole and vehicle groups, respectively). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.	N/A

2.3.2. Benefit Assessment

The expected efficacy of crisaborole ointment, 2% BID for the treatment of AD is based on the results of clinical studies conducted to date.

Clinical efficacy of a BID regimen of crisaborole ointment, 2% was demonstrated in two Phase 3, randomized, double-blind, vehicle-controlled studies (AN2728-AD-301 and AN2728-AD-302), and a Phase 3 open-label long-term safety study up to 48 weeks (AN2728-AD-303) in participants with mild to moderate AD aged 2 years and older. In addition, a Phase 2b study (C3291028) also demonstrated efficacy of a BID regimen of crisaborole ointment, 2% in Japanese patients with mild to moderate AD aged 2 years and older. Furthermore, exploratory efficacy assessments of Phase 4 open-label study in participants with mild to moderate AD aged 3 to <24 months (C3291002) showed results that were consistent with the results observed in the Phase 3 studies.

2.3.3. Overall Benefit/Risk Conclusion

The benefit/risk is favorable in adults and children ≥3 months of age. In Study C3291027, the benefit/risk is further being assessed in Japanese adult and pediatric AD patients. Study participants will be monitored closely during the study for safety and local tolerability AEs by the investigators, sponsor, and an E-DMC.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To study the safety of crisaborole ointment, 2% applied BID in Japanese	• There is no defined estimand for this objective and these	• The incidence of treatment emergent adverse events and serious adverse events

Objectives	Estimands	Endpoints
pediatric and adult participants with mild to moderate AD	endpoints will be analyzed descriptively.	
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To characterize the efficacy of long-term administration of crisaborole ointment, 2% • To characterize the patient/observer reported outcomes for pruritus of long-term administration of crisaborole ointment, 2%	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	**Efficacy*** • % change from baseline in EASI over time • Achievement of EASI50 (≥50% improvement from baseline) over time • Achievement of EASI75 (≥75% improvement from baseline) over time • Change from baseline in Treatable %BSA over time • Achievement of success in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time • Achievement of improvement in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1)] over time • Achievement of success in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time • Achievement of improvement in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1)] over time • Incidence of the use of rescue medication (topical corticosteroids or topical calcineurin inhibitors) **Patient/Observer Reported Outcomes** • Change from baseline in Peak Pruritus NRS over time - for participants ≥12 years • Changes from baseline in Patient Reported Itch Severity Scale over time - for participants ≥6 years and <12 years • Change from baseline in Observer Reported Itch Severity Scale over time - for participants <6 years
• To assess the PK profile of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment, 2% BID from C3291032 on Day 1	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	• Plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) on Day 1

* Baseline refers to the baseline data of Study C3291032 or Study C3291031.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 3, multicenter, open-label, long-term safety extension study of Studies C3291032 and C3291031 in Japanese pediatric and adult participants with mild to moderate AD to support the registration of crisaborole in Japan. After completion of the study intervention period in Study C3291032 or Study C3291031 and confirmed Study C3291027 eligibility, participants will be offered participation in the study from investigator sites in Japan. The sample size of this study is approximately 150 participants but will be determined by the number of participants who complete Study C3291032 treatment period or Study C3291031 treatment period and meet eligibility criteria of this study. Scheduled study visits will occur every 4 weeks (1 cycle) with On-Treatment or Off-Treatment cycles to be decided by the investigator based on the ISGA score. PK blood sampling will be conducted at the selected study sites for the participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032.

When the investigator assessment of ISGA is Almost Clear (1) or greater, an On-Treatment Cycle will be initiated. When the investigator assessment of ISGA is Clear (0), crisaborole ointment, 2% treatment will not be initiated and the participant will enter an Off-Treatment Cycle. Based on the ISGA score throughout the study, a participant may be administered a variable number of cycles of crisaborole ointment, 2% treatment (On-Treatment Cycle) during their up to 52 weeks of study participation.

On Week 56 (End of Study), a follow-up telephone call will be made by site staff to assess for AEs that may have occurred since the last visit.

4.2. Scientific Rationale for Study Design

Crisaborole ointment, 2% BID is approved for use in atopic dermatitis in Australia, Canada, EU, Israel and US without any contraceptive precautions. There is no suspicion of human teratogenicity based on the results of nonclinical studies and the route of administration. See Appendix 4 for contraceptive requirements.

4.3. Justification for Dose

In this study, the participants will apply crisaborole ointment, 2% BID during On-Treatment Cycle.

Crisaborole ointment, 2% BID is selected as the highest well-tolerated dose to maximize the potential for efficacy with minimal safety risk based on the results of foreign clinical studies, and 2% was technically the maximum dose for ointment formulation. In addition, the descriptive comparison of BID and QD regimens in Japanese AD patients was conducted in Study C3291028, crisaborole ointment, 2% BID was more effective than crisaborole ointment, 2% QD for Japanese adults and pediatrics participants. Regarding safety, crisaborole ointment, 2% BID was safe and tolerable for both Japanese adults and pediatric participants. Parent studies C3291032 and C3291031 are conducted using crisaborole ointment, 2% BID.

This study also has Off-Treatment Cycle to evaluate long term safety and efficacy of crisaborole in a condition close to real world clinical practice.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants;
   who were patients with mild to moderate AD aged 2 years old or older and met eligibility criteria for Study C3291032 at the time when entering Study C3291032, and completed treatment period in Study C3291032 without safety issues.

   OR

   who were patients with mild to moderate AD aged 1 months to <24 months and met eligibility criteria for Study C3291031 at the time when entering Study C3291031, and completed treatment period in Study C3291031 without safety issues (see Exclusion Criteria 5).

   - Refer to Appendix 4 for reproductive criteria for female (Section 10.4.1) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, lifestyle considerations, and other study procedures.

Informed Consent:

3. The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original copy of each participant's signed consent/assent document.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

2. Has an anticipated concomitant use of topical or systemic therapies that might alter the course of AD.

Prior/Concurrent Clinical Study Experience:

3. Participates in other studies involving investigational drug(s) during study participation other than the parent studies C3291032 and C3291031.

Diagnostic Assessments:

Not applicable for this study.

Other Exclusions:

4. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5. Experienced a treatment related AE or SAE during participation in Study C3291032 or C3291031, which precludes treatment with investigational product in the judgment of the investigator (see Inclusion Criteria 1).

6. Early discontinuation from Study C3291032 treatment or C3291031 treatment, for any reason.

7. Has a significant active systemic or localized infection, including known actively infected AD.

8. Had a history of significant noncompliance during the Study C3291032 or C3291031 with investigational product dosing, concomitant medication restrictions, or study procedures, in the judgment of the investigator.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4 Section 10.4.3) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. General Care

- The participant or his/her parent/legal guardian will be instructed to avoid occluding the treated areas (with dry wraps, for example). Wet wraps are not permitted.

- Participants must avoid exposing the target treatment areas to water (e.g., swimming, bathing or washing) for at least 4 hours after investigational product application. Applying emollients/moisturizers, sunscreen, or make-up to facial lesions should also be avoided within 60 minutes before and after the applying study intervention.

- The participant or his/her parent/legal guardian should avoid wiping the investigational product off the skin. In the case of any investigational product inadvertently being wiped off, it should not be reapplied to wiped areas until the next scheduled dose.

- When applying investigational product, the participant or his/her parent/legal guardian will not be required to wear gloves when applying investigational product at home. However, they must be instructed to wash their hands with mild soap and water before and after each application. Caregivers who are pregnant, or women of childbearing potential who are trying to become pregnant, should avoid accidental exposure by either avoiding applying the study intervention or wearing gloves during its application, and by taking care when handling the child after study intervention has been applied.

- Loose fitting socks or mitts may be used on treated hands or feet to prevent inadvertent ingestion or contact with the eyes.

- If there are treated lesions on the hands or feet, participants should be encouraged, as much as possible, not to put these areas in the mouth to avoid ingestion of the study intervention.

- If there are AD lesions in the diaper area, they should be treated with the study intervention; however, following diaper change, any study intervention inadvertently wiped off soiled skin should not be reapplied until the next scheduled dose. Using diaper rash creams, lotions, ointments, powders, etc. where AD lesions are present should be avoided within 60 minutes before and after applying study intervention. In the case of rash in the diaper area without AD involvement, standard treatments may be applied.

- Routine preventative immunizations/vaccinations are permitted during the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to crisaborole ointment, 2%.

6.1. Study Intervention(s) Administered

Intervention Name	Crisaborole ointment, 2%
Type	Drug
Dose Formulation	Ointment
Unit Dose Strength(s)	2% (20 mg/g)
Dosage Level(s)	BID
Route of Administration	Topical
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by Sponsor
Packaging and Labeling	Study intervention will be provided in 60-gram tubes in cartons. Each tube and carton will be labeled as required per country requirement.
Aliases	PF-06930164 or AN2728

6.1.1. Administration

For this study, the investigational product is crisaborole ointment, 2%. Crisaborole ointment, 2% is formulated to contain PF-06930164 (2%), white petrolatum, propylene glycol, mono- and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

Ointment should be applied as an even layer of approximately 3 mg/cm^2.

The tool to standardize the calculation of the amount of ointment required for each participant will be provided by the sponsor to the study sites, which is based on each participant's own AD %BSA adjusted by height and weight.

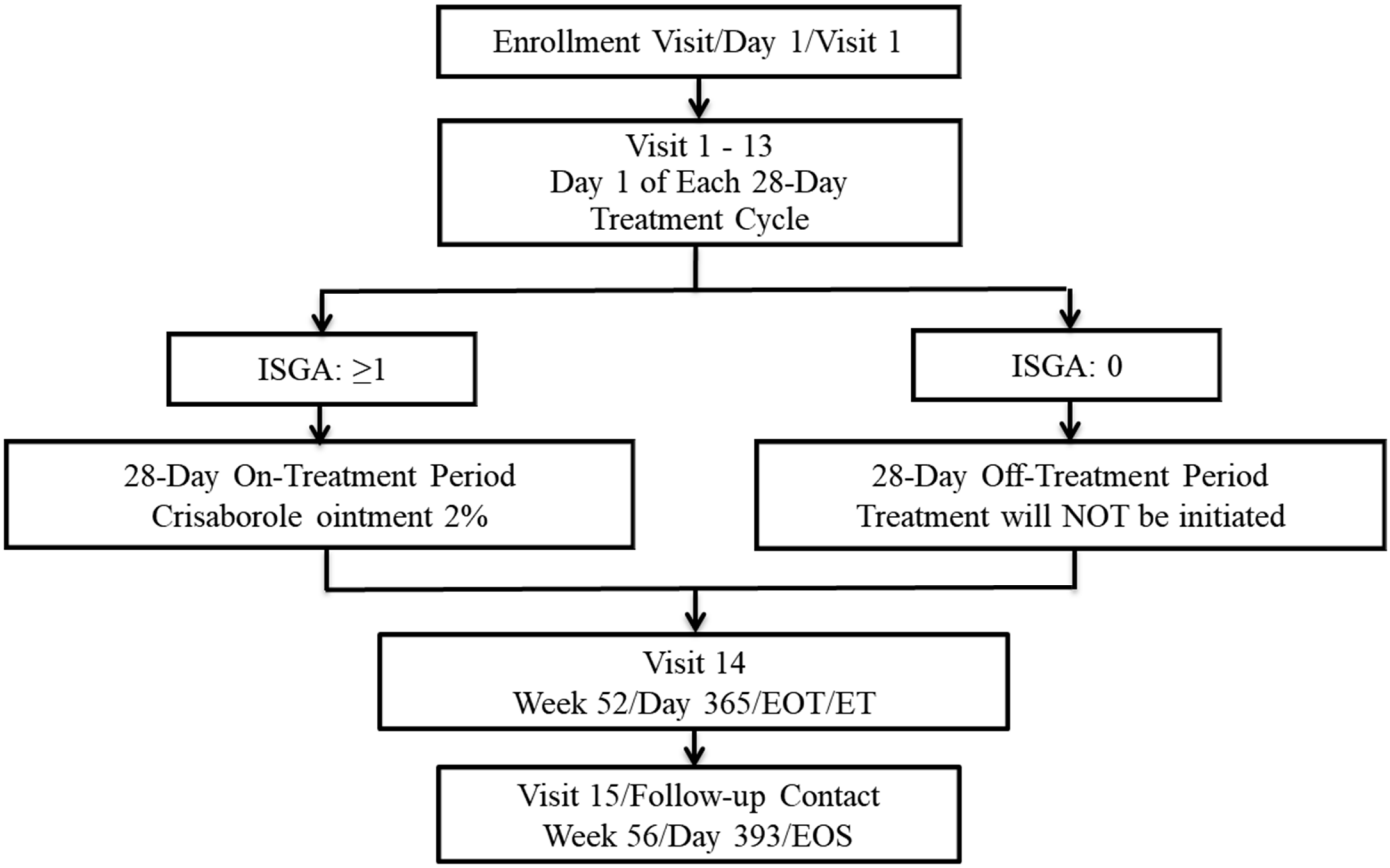
The investigator will determine whether the participant will receive crisaborole ointment, 2% (Figure 1), specified as follows:

- If the participant is assessed as Almost Clear (1) or greater on the ISGA, the participant will begin a 4 week On-Treatment Cycle, with a sufficient quantity of crisaborole ointment, 2% tubes dispensed to the participant or his/her parent/legal guardian to meet anticipated use based on the investigator identified AD-involved areas. The investigator will review the dosing instructions with the participant or his/her parent/legal guardian. Study intervention administration will be performed BID at home.

- If the participant is assessed as Clear (0) on the ISGA, treatment **will NOT** be initiated and the participant will begin a 4-week Off-Treatment Cycle, during which the participant is allowed to use emollient(s)/moisturizer(s) in all areas (AD-involved and uninvolved), as needed.

Any new lesion(s) that develop during an On-Treatment Cycle should also be treated.

Figure 1. Diagram of Study Intervention Allocation by Visit



If a participant has AD that becomes intolerable:

- If a participant has AD that becomes intolerable during an On-Treatment Cycle, the investigator may instruct the participant or his/her parent/legal guardian to discontinue crisaborole ointment, 2%. After study intervention discontinuation, weak- to strong-potency topical corticosteroids and/or topical calcineurin inhibitors could be prescribed up to 28 days based on clinical judgment is permitted (refer to Section 6.5.3).

- If a participant has AD that becomes intolerable during an Off-Treatment Cycle and cannot wait for the next scheduled visit to be treated by crisaborole ointment, 2%, the participant or his/her parent/legal guardian will be instructed to contact the study site to arrange an Unplanned Visit to initiate a regimen of crisaborole ointment, 2% BID for the remainder of a given 4 weeks interval. Depending upon the participant's AD condition, a weak- to strong-potency topical corticosteroids and/or topical calcineurin inhibitors could be prescribed directly based on clinical judgment by the investigator. Topical corticosteroids and topical calcineurin inhibitors must not be used on the same lesions concurrently, crisaborole ointment, 2% and topical corticosteroids or topical calcineurin inhibitors must not be used concurrently. In this case, the procedure for rescue treatment

during an Off-Treatment Cycle follows the instruction given for participants using rescue medication during an On-Treatment Cycle (refer to Section 6.5.3).

- At any treatment cycle, participant will be discontinued from the study when she/he requires prohibited medication usage or continuous rescue medication treatment >28 days.

Emollients/Moisturizer:

- During On-Treatment Cycle, continued use of emollient(s)/moisturizer(s) is permitted to manage dry skin, but use of them on treatable AD lesion should be avoided within 60 minutes before and after the applying study intervention.

- During Off-Treatment Cycle, use of emollient(s)/moisturizer(s) is permitted in all areas (AD-involved and uninvolved), as needed.

- During the use of rescue medication, use of emollient(s)/moisturizer(s) is permitted in all areas, as needed.

AD skin area in the scalp:

- Use of emollient(s)/moisturizer(s), weak- to strong-potency topical corticosteroids or topical calcineurin inhibitors is permitted on clinical judgment by investigator (see Section 6.5.2).

Crisaborole ointment, 2% is for external use on the skin only. Participant should avoid contact with mucous membranes (i.e., inside of nostrils, mouth, vagina, urethra, and rectum), and in the eyes. Participant should avoid ingestion of investigational product.

At the Start Day of each treatment cycle, the designated areas for treatment will be identified and documented in the source document. The participant or his/her parent/legal guardian will be provided with documentation of designated treatment areas. The documentation of the investigator identified treatable areas will be updated for any new AD lesions that appear after the Start Day of treatment cycle.

Crisaborole ointment, 2% will be applied at home. Those participants applying crisaborole ointment, 2% at home and having difficulty reaching a treatment area (e.g., back) may be assisted by another person who will need to apply it to the participant according to the instruction. The instruction for at home dosing will be reviewed with the participant or his/her parent/legal guardian at applicable study visit during a given 4 weeks On-Treatment Cycle. In the event the scheduled Start Day of the next treatment cycle visit does not fall exactly on the scheduled date, the participant or his/her parent/legal guardian will be instructed to continue investigational product application BID through the evening before the actual visit date.

Participant or his/her parent/legal guardian will be provided appropriate training for investigational product application and will be instructed to apply an even layer of crisaborole to all areas of the body with AD (except scalp) identified at Day 1 of the On-Treatment Cycle and at any Unplanned Visit where crisaborole ointment, 2% treatment is initiated, regardless of whether they become clinically clear during any given 4 weeks On-Treatment Cycle and the remainder of a given 4 weeks interval. If needed, additional amount of crisaborole ointment, 2% will be applied as needed (PRN) to ensure coverage of any newly identified treatable AD lesions that appear after Day 1 of the On-Treatment Cycle or any Unplanned Visit where crisaborole ointment, 2% is dispensed.

The dosing regimen is BID. The dosing interval should be at least 8 hours apart within each 24-hour day.

If 1 or more doses are withheld or missed due to a safety concern, then the AE or other reason must be documented and noted as having led to a dosing interruption.

Participant or his/her parent/legal guardian will apply at home all doses of any emollients or investigator prescribed weak- to strong-potency topical corticosteroids and/or topical calcineurin inhibitors.

If participants require continuous weak- to strong-potency topical corticosteroids or topical calcineurin inhibitors treatment for >28 days at any time during the study, they then will be discontinued from study. The use of weak- to strong-potency topical corticosteroids and/or topical calcineurin inhibitors for AD on the scalp will not have any limitation in duration of use, which should be based on investigator's discretion.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the

study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All crisaborole ointment, 2% that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention in the tube using an IRT system via unique container numbers provided, in quantities appropriate at Day 1 of the On-Treatment Cycle and at Unplanned Visit where crisaborole ointment, 2% BID treatment is initiated. A second staff member will verify the dispensing. The participant/parent/legal guardian should be instructed to maintain the product in the tube provided throughout the course of dosing and return the tube to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label, single arm study, and IRT will be used for the study intervention dispensing. The site will contact the IRT at Day 1 of each Treatment Cycle and at Unplanned Visit where crisaborole ointment, 2% BID treatment is initiated with or without

the study intervention dispensing. The site will record the study intervention assignment on the applicable CRF, if required. Specific measures to reduce potential bias will not be taken.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Compliance with the dose regimen will not be assessed; although all dispensed study intervention supplies in its original package (both used and unused) will be weighed and dosing diary will be recorded. If a participant has missed applications between the previous and the current visit, the investigator/designee is to counsel the participant's parent(s)/legal guardian to improve adherence. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of tubes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), or any non-medication therapies such as light treatment that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Start and end dates
- Dosage and regimen

The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) per Section 6.5.1, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor if required.

6.5.1. Medications/Therapies Prohibited During the Study (Day 1-Week 52/EOT)

- Biological drugs (e.g., dupilumab)
- Use of systemic (oral, parenteral) corticosteroids.
- Topical corticosteroids or topical calcineurin inhibitors, unless prescribed by the investigator as rescue therapy and treatment for the scalp
- Systemic immunosuppressive agents (e.g., methotrexate, cyclosporine, azathioprine, hydroxychloroquine, and mycophenolate mofetil)
- Topical JAK inhibitor on AD lesions
- Topical PDE-4 inhibitor on AD lesions
- Topical retinoid or benzoyl peroxide on AD lesions
- Herbal preparation that might alter the course of AD
- Use of systemic antibiotics for more than 14 consecutive days.
- Topical antibiotics (unless required for AE treatment)
- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body.
- Use of sunbathing, tanning bed use, light therapy (UV, UV-B, PUVA) anywhere on the body.
- Participation in another drug or device research study.

6.5.2. Medications/Therapies Allowed During the Study

Classes of medications/therapies that are allowed during the study are recorded as concomitant medications/therapies on CRF. Participants on certain stable regimens should minimize alteration of the stable regimen during the study. Any changes in stable dosages and/or regimens should be recorded on CRF. The permitted medications/therapies are summarized below:

- Stable regimen of intranasal, ophthalmic and inhaled corticosteroids.
- Emollient(s)/moisturizer(s) is permitted during the study as detailed in Section 6.1.1. Written instruction will be provided to participant or his/her parent/legal guardian at the beginning of the treatment period regarding the appropriate application of emollients.

- The use of weak- to strong- potency topical corticosteroids and/or topical calcineurin inhibitors is permitted during the study to treatment of the AD skin area in the scalp.
- Short courses (up to 14 days) of systemic antibiotics may be given during the course of the study, if clinically necessary for the treatment of new onset infections.
- Stable use (regular regimen) of systemic antihistamine regimen. If seasonal allergy, a stable regimen during certain period will be permitted.
- Topical antihistamine
- Nonsteroidal anti-inflammatory drug
- Routine preventative immunizations
- Concomitant medications for other chronic medical conditions are permitted during the study unless the medication/therapy is specifically prohibited by the protocol.
- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

6.5.3. Rescue Medicine

For participants with ISGA score >1 (i.e., mild, moderate or severe), crisaborole ointment, 2% therapy may be discontinued per investigator judgment to allow initiation of weak- to strong-potency topical corticosteroids and/or topical calcineurin inhibitors as rescue therapy for up to 28 days, after which crisaborole ointment, 2% BID may be restarted. Participants who continuously use topical corticosteroids or topical calcineurin inhibitors treatment >28 days will be discontinue from the study. The rescue medication prescription and relevant assessment should be recorded in the participant's source documents and in the CRF. Crisaborole ointment, 2% and topical corticosteroids or topical calcineurin inhibitors must not be used concurrently. Topical corticosteroids and topical calcineurin inhibitors must not be used on the same lesions concurrently.

Participant or his/her parent/legal guardian will be instructed on the dosage and administration requirements for any topical corticosteroids and/or topical calcineurin inhibitors prescribed by the investigator during the study. Instruction should follow the approved labeling for the indication and the product package insert, if provided.

6.6. Dose Modification

This study design includes 4 week cycles with On-Treatment or Off-Treatment to be decided by the investigator based on the ISGA score. See Section 6.1.1 for details.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- The occurrence of AEs that require the participant to stop participation in the study, due to availability for, or intolerance to, the study procedures;
- AEs that are considered to be clinically significant by the investigator and/or physician in charge, and/or might be harmful to the participant' health;
- Need the continuous rescue therapy for >28 days;
- Concurrent disease that requires use of a prohibited medication.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- The occurrence of AEs that require the participant to stop participation in the study, due to availability for, or intolerance to, the study procedures;
- AEs that are considered to be clinically significant by the investigator and/or physician in charge, and/or might be harmful to the participant' health;
- Need the continuous rescue therapy for >28 days;
- Concurrent disease that requires use of a prohibited medication.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

Blood sampling will be occurred only for PK assessment at the selected study sites in participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032, and the total blood sampling volume for individual participants in this study is approximately 2 mL. Unscheduled samples may be taken for safety reasons for all participants.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Clinical evaluations of AD will be performed by an experienced and certified physician, dermatologist, or medical professional. The evaluator must have received documented training to conduct the protocol AD specific clinical evaluations prior to performing these evaluations. To assure consistency and reduce variability, the same evaluator must assess all clinical evaluation of atopic dermatitis for any individual participant throughout the study; a backup experienced and qualified, protocol trained evaluator will only be allowed and documented in case of emergency or special situation when the designated evaluator is unable to perform the evaluation. Identity (eg, initials) of the evaluator will be captured on the source documentation (eg, scale worksheet).

8.1.2. Calculation of Treatable %Body Surface Area (BSA)

The treatable %BSA is defined as the percentage of the participant's total BSA that is AD involved, excluding the scalp, and will be calculated at times specified in the SoA. The treatable %BSA should be evaluated based on all AD lesions present on the day of the visit, excluding the scalp. Score 0 in the ISGA definition will not be evaluated as BSA while Score 1-4 will be.

To estimate the treatable %BSA, the investigator or designee will use "handprint method", by which the area represented by the palmar (i.e., outstretched) surface of the participant's hand with all five digits adducted together is approximately 1% of the participant's BSA, regardless of the participant's age.

8.1.3. Investigator's Static Global Assessment (ISGA)

The ISGA is a 5-point scale (0-4), reflecting a global assessment of AD severity based on erythema, induration/papulation, and oozing/crusting (Table 1). ISGA will be assessed at times specified in the SoA to characterize participants' overall disease severity across all treatable AD lesions (excluding the scalp). ISGA should be completed prior to assessment of Regional ISGA-Face and EASI, whenever possible. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 1. Investigator's Static Global Assessment

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

8.1.4. Regional ISGA-Face

Severity of AD on the face will be assessed by evaluating the severity of all lesions occurring within that body region. The Regional ISGA-Face score will be assessed only for participants who completed Study C3291032 and had AD in face at Day 1 Visit of Study C3291032. At every scheduled visit, the Regional ISGA score will be documented for the face regardless of the presence or absence of AD in face. The Regional ISGA-Face assessment should use the scale in Table 1.

The assessment will be a static evaluation without regard to the score at a previous visit.

8.1.5. Eczema Area and Severity Index (EASI)

The EASI[24] quantifies the severity of a participant's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of 4 body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

The EASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of AD. Since the scalp will be excluded from the EASI assessment in this study, the maximum possible score will be less than 72.0.

The EASI will be assessed at times specified in the SoA.

Lesion Severity by Clinical Signs: The basic characteristics of AD lesions (erythema, induration/papulation, excoriation, and lichenification) provide a means for assessing the severity of lesions. Assessment of these 4 main clinical signs is performed separately for 4 body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in Table 2.

Table 2. Clinical Sign Severity Scoring Criteria for EASI

Score		Description
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

Note: The EASI will exclude scalp from the assessment/scoring.

Percent BSA with Treatable AD: The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with AD (Table 3). The handprint as a unit is defined by the area represented by the palmar (ie, outstretched) surface of the participant's hand with all 5 digits adducted (not spread apart) together equaling approximately 1% of the participant's BSA, regardless of the participants age.

Table 3. Handprint Determination of Body Region Surface Area

Body Region	Total Number of Handprints in Body Region[a]	Surface Area of Body Region Equivalent of One Handprint	Total Number of Handprints in Body Region[a]	Surface Area of Body Region Equivalent of One Handprint
	≥8 years of age		<8 years of age	
Head and Neck	10	10%	20	5%
Upper Limbs	20	5%	20	5%
Trunk (including axillae)	30	3.33%	30	3.33%
Lower Limbs (including buttocks)	40	2.5%	30	3.33%

a. The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp from the BSA assessment.

The extent (%) to which each of the 4 body regions is involved with AD is categorized using a nonlinear scaling method to derive a numerical area score according to the BSA scoring criteria (Table 4).

Table 4. Eczema Area and Severity Index (EASI) Area Score Criteria

Treatable Percent Body Surface Area with Atopic Dermatitis in a Body Region	Area Score
0%	0
>0% to <10%	1
10% to <30%	2
30% to <50%	3
50% to <70%	4
70% to <90%	5
90% to 100%	6

Body Region Weighting: Each body region is weighted according to its approximate percentage of the whole body (Table 5).

Table 5. Eczema Area and Severity Index (EASI) Body Region Weighting

Body Region	Body Region Weighting	
	≥8 years of age	<8 years of age
Head and Neck	0.1	0.2
Upper Limbs	0.2	0.2
Trunk (including axillae and groin/genitals)	0.3	0.3
Lower Limbs (including buttocks)	0.4	0.3

In each body region, the sum of the Clinical Signs Severity Scores for erythema, induration/papulation, excoriation, and lichenification is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all 4 body regions resulting in an EASI score as described in Equation 1 and Equation 2:

Equation 1 (participants aged ≥8 years old): EASI =0.1Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+Exu+Lu) + 0.3At(Et+It+Ext+Lt) + 0.4Al(El+Il+Exl+Ll)

Equation 2 (participants aged <8 years old): EASI =0.2Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+Exu+Lu) + 0.3At(Et+It+Ext+Lt) + 0.3Al(El+Il+Exl+Ll)

A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs.

8.1.6. Body Site Checklist for Atopic Dermatitis

A checklist of body areas currently affected by AD will be completed at times specified in the SoA. Location of skin lesions will be selected from a pre-specified list of body locations.

Any new lesion should be recorded and updated in the checklist. Study site staff (or the investigator) will determine whether a new AD lesion is reported as an AE or as part of the underlying disease based on medical judgement. The AD lesion checklist will be recorded in the participant's source documents and data entered onto the CRF.

8.1.7. Patient/Observer Reported Outcomes

The Patient/Observer Reported Outcomes questionnaires in this study include Peak pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale. They will be performed at the time points defined in the SoA. The age cut-offs are based on the age at Screening visit/informed consent/assent in the prior study.

On study visit days, participants or observers (ie, the one who provides the information to complete the questionnaires other than participant, eg, his/her parent/legal guardian/other caregiver) should complete the patient/observer reported outcomes at the clinic prior to any procedures being performed. The one who completed the questionnaires should be captured and stored in the database and available for analysis. It's preferred that all observer reported outcomes for a given participant are completed by same individual throughout the study.

8.1.7.1. Pruritus Assessment

Participants will be asked to assess their worst itch or scratching due to AD over the past 24 hours.

- Peak Pruritus NRS[25] is an 11-point scale and must be completed by participants ≥12 years of age at the time of signing the ICD in the prior study.
- Patient reported Itch Severity Scale is a 5-point scale must be completed by participants ≥6 years and <12 years at the time of signing the ICD in the prior study.

- Observer reported Itch Severity Scale is an 11-point scale and must be completed by the observers (caregivers of participants) for participants <6 years of age at the time of signing the ICD in the prior study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. In addition, an assessment will be made of the condition of all AD-involved skin. Weight for participants aged 18 years old or older and height and weight for participants aged under 18 years old will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layer or clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the

event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in

the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who

reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.3.8. Adverse Events of Special Interest

Not applicable

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

While overdose following topical administration is unlikely, there is a possibility that an excess of crisaborole may be applied. If too much crisaborole has been applied, the excess can be wiped off. Investigator should monitor the participant for any AEs/SAEs.

8.5. Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) as specified in the SoA at 1 sampling time point prior to the first dose of study intervention on Day 1 in C3291027 (around 12 hours post the last dose of C3291032).

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

The skin around venous access area must be thoroughly cleansed prior to blood sample collection with mild soap and water followed by an isopropyl wipe.

The date/time of the blood collection and the date/time of the last dose of study intervention in C3291032 captured in the CRF.

Samples will be used to evaluate the PK of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323). Each plasma sample will be divided into 1 aliquot for PK. Samples collected for analyses of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary objective in this study is the safety evaluation. There is no pre-specified estimand for the safety evaluation and the safety endpoints will be analyzed descriptively. In addition, there is no secondary objective in this study.

9.2. Sample Size Determination

Sample size will be determined by the number of participants who enroll from the qualifying parent studies. It is estimated that at least 150 participants (ie, 20 participants for under 2 years old and 130 participants for 2 years and older) are expected to join from the currently planned qualifying parent studies. Analyses performed, including interim evaluations, if any, will primarily be for safety though some measures of efficacy may be analyzed.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full Analysis Set	All participants who take at least one dose of study intervention.

Safety	All participants who take at least one dose of study intervention.
PK Analysis Set	All participants who take at least one dose of study intervention in Study C3291032 and who have at least one concentration value.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

The efficacy objective is exploratory in this study. Efficacy analyses will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported.

For the purpose of analysis of efficacy measures, the baseline values are defined as the baseline values from the participant's qualifying parent study.

9.4.2. Primary Endpoint(s)

The primary endpoint of incidence of safety events will be analyzed using descriptive measures such as percentages and exposure-adjusted incidence rates along with confidence intervals. No statistical hypotheses will be tested.

9.4.3. Secondary Endpoint(s)

There are no secondary endpoints in this study.

9.4.4. Tertiary/Exploratory Endpoint(s)

9.4.4.1. Efficacy Endpoints

The measures of efficacy (EASI and ISGA scores and other patient/observer reported outcome measures) will be summarized using descriptive statistics, such as number and percent, mean, standard deviation and quartiles at each visit where measured. Displays using stratification by participation in qualifying studies will also be included.

Exploratory analyses may also be performed.

Further details will be specified in the SAP.

9.4.4.2. Pharmacokinetic Endpoints

Predose (Ctrough) plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) will be listed and descriptively summarized.

9.4.5. Other Safety Analyses

For the purpose of analysis of safety measures, the baseline values are defined as the baseline values from the participant's qualifying parent study.

All the safety data, including the following, will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations:

- Adverse events will be summarized according to Pfizer standards;
- Serious infections, defined as any infection (viral, bacterial and fungal) requiring hospitalization or parenteral antimicrobials or meets other criteria that require it to be classified as a serious adverse event, will be summarized.

All safety analyses will be performed on the safety population.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label, long-term extension study, the sponsor may conduct reviews of the data during the course of the study for the purpose of internal decision making, due to regulatory requests, or to support regulatory submissions. The data cutoff may occur after 6-month follow-up data across this study and the parent study has been accumulated for approximately 100 participants enrolled in this study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use a DMC. The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., AAP) or health department guidelines.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her parent/legal guardian and answer all questions regarding the study. The participant or his/her parent/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.

A copy of the ICD(s) must be provided to the participant or the participant's parent/legal guardian.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

No safety laboratory test is performed according to the SoA section of this protocol, excluding pregnancy test. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 6. Protocol-Required Safety Laboratory Assessments

Other
Pregnancy test (β-hCG)[a]
FSH[b]

a. Serum or urine β-hCG for female participants of childbearing potential. Local urine testing will be standard for the protocol unless serum testing is required by IRB/EC.
b. For confirmation of postmenopausal status during study only.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms.
 	
  • Requires additional diagnostic testing or medical/surgical intervention.
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as

serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the investigator's brochure and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.2).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.2. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history

interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.3. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;

   - Intravaginal*;

- Transdermal*;
- Injectable*.

7. Progestogen-only hormone contraception associated with inhibition of ovulation*:
   - Oral;
   - Injectable.
8. Sexual abstinence:
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action*.
10. Male or female condom with or without spermicide.
11. Cervical cap*, diaphragm, or sponge with spermicide*.
12. A combination of male condom with either cervical cap*, diaphragm, or sponge with spermicide* (double-barrier methods).

* Not approved or not certificated in Japan

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
%BSA	percent body surface area
AAP	American Academy of Pediatrics
AD	atopic dermatitis
ADSI	Atopic Dermatitis Severity Index
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BID	bis in diem (twice a day)
BSA	body surface area
EASI	Eczema Area and Severity Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
E-DMC	External Data Monitoring Committee
EC	ethics committee
EC_{50}	half maximal effective concentration
eCRF	electronic case report form
ECG	electrocardiogram
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Term
HRQOL	health-related quality of life
HRT	hormone replacement therapy
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IFN	Interferon
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISGA	Investigator's Static Global Assessment
JAK	Janus kinase
LFT	liver function test
MMP	matrix metalloproteinase
MUSE	maximal use, systemic exposure
N/A	not applicable
NIMP	noninvestigational medicinal product
NRS	Numeric Rating Scale
PDE	phosphodiesterase
PK	pharmacokinetic(s)
PRN	pro re nata
PT	prothrombin time
PUVA	psoralen plus ultraviolet A
QD	once a day
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SRSD	single reference safety document
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TBili	total bilirubin
T_{max}	time to reach maximum observed plasma concentration
TNF	tumor necrosis factor
TSS	Total Sign Scores
ULN	upper limit of normal
US	United States
UV	ultraviolet

Abbreviation	Term
UV-B	ultraviolet B
WOCBP	woman of childbearing potential

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