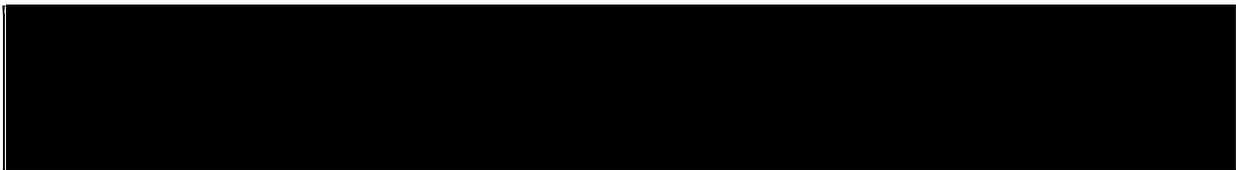




**A PHASE 1, SINGLE-CENTER, RANDOMIZED, VEHICLE-CONTROLLED,
PARALLEL-COHORT STUDY OF CRISABOROLE OINTMENT 2%
TO EVALUATE THE SKIN IRRITATION POTENTIAL
IN ADULT JAPANESE HEALTHY SUBJECTS,
AND TO EVALUATE THE SAFETY, TOLERABILITY AND
PHARMACOKINETICS IN ADULT JAPANESE SUBJECTS
WITH MILD TO MODERATE ATOPIC DERMATITIS**

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Amendment 1	14 July 2017	<ol style="list-style-type: none">1. Section 4.2. Exclusion Criteria, Cohort 2-2: Clarify the strong potency topical corticosteroids.2. Section 4.2. Exclusion Criteria, Cohort 2-8: Remove “cryosurgery or”.3. Section 7.1.1. Laboratory Tests, Table 3: Remove “Total CO₂ (bicarbonate)”.4. Appendix 2. Diagnostic Criteria for Atopic Dermatitis (Cohort 2): Incorporate administrative edits.
Original Protocol	23 June 2017	N/A

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SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the **STUDY PROCEDURES** and **ASSESSMENTS** sections 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 schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Cohort 1

Day ^a	-28 to -2 Screening	-1	1	2	3	4/ET	29 (+7 days) FU Contact ^b (EOS)
Informed Consent	X						
CRU confinement		X ^c	→	→	→	X ^d	
Inclusion/Exclusion Criteria	X	X	X				
Medical History	X	X					
Physical Examination	X	X				X	
Safety laboratory	X	X ^e					
Demographics	X						
Height and Weight	X						
Vital Signs ^f	X						
ECG ^g	X						
HIV, HepBsAg, HepBcAb, HCVAb and syphilis testing	X						
Urine drug testing	X	X ^h					
Visual Assessment of application field	X		X				
Treatments/patch application			X ⁱ	→ ⁱ	→ ⁱ		
Patch removal					X		
Skin irritation assessment					X ^j	X ^j	
Review and record prior and concomitant medications	X ^k	X	X	X	X	X	
Assess for AEs and SAEs ^l	X	X	X	X	X	X	X

Abbreviations: →= ongoing/continuous event; CRU=clinical research unit; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; FU= Follow-up; HIV=human immunodeficiency virus; HepBsAg=hepatitis B surface antigen; HepBcAb=hepatitis B core antibody; HCVAb=hepatitis C antibody; AE=adverse event; SAE=serious adverse event;

- a. Day relative to start of study treatment (Day 1).
- b. Follow-up contact will be completed on Day 29 (28+7 calendar days after the application of the investigational product patches on Day 1) to capture any potential adverse events.
- c. Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1.
- d. Subjects will discharge from CRU on Day 4 after completion of all assessment on Day 4.
- e. Day -1 clinical labs do not have to be repeated if clinical labs are completed within 7 days prior to Day -1.
- f. Vital signs (pulse rate and blood pressure) taken supine position after subject has been calmly lying for 5 minutes.
- g. Single ECG will be collected.
- h. Day -1 urine drug testing does not have to be repeated if urine drug testing is completed within 7 days prior to Day -1.
- i. Day 1 patches remains in place through Day 3.
- j. Skin irritation assessment of the patch sites will be conducted on Day 3 (approximately 30 minutes after removal of the patches) and Day 4 (approximately 24 hours after removal of the patches).
- k. All medications and non-medication therapies used within 28 days prior to the planned first dose.
- l. If AEs/SAEs occur at a patch site, the patch site location must be recorded.

Cohort 2

Day ^a	-28 to -2	-1	1	2	3	4	5	6	7	8/ET	9	36 (+7 days) FU Contact ^b (EOS)
	Screening											
Informed Consent	X											
CRU confinement		X ^c	→	→	→	→	→	→	→	→	X ^d	
Inclusion/Exclusion Criteria	X	X	X									
Medical History	X	X										
Confirmation of Diagnosis of AD	X											
Physical Examination	X	X								X ^e	X	
Physical Examination ^f (skin examination)	X		X								X	
Assess ISGA	X		X									
Record treatable AD areas			X									
Calculate and Record Treatable %BSA ^g	X		X									
Safety laboratory	X	X								X		
Demographics	X											
Height and Weight	X		X ^h									
Vital Signs ⁱ	X		X							X		
ECG	X ^j		X ^j							X ^j		
Urine Pregnancy test	X	X										
Contraception check	X	X									X	X
FSH ^k	X											
HIV, HepBsAg, HepBcAb, HCVAb and syphilis testing	X											
Urine drug testing	X	X ^l										
AM Dosing: Weigh dose and apply			X	X	X	X	X	X	X	X		
PM Dosing: Weigh dose and apply				X	X	X	X	X	X			
Obtain PK samples			X ^m	X ⁿ					X ⁿ	X ^m	X ⁿ	

Day ^a	-28 to -2	-1	1	2	3	4	5	6	7	8/ET	9	36 (+7 days)
	Screening											FU Contact ^b (EOS)
Review and record prior and concomitant medications	X ^o	X	X	X	X	X	X	X	X	X	X	
Assess for AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X
CCI		X										

Abbreviations: → ongoing/continuous event; AD=atopic dermatitis; CRU=clinical research unit; ISGA=investigator’s static global assessment; %BSA=percent of body surface area; ECG=electrocardiogram; EOS=End of Study; ET=Early Termination; FSH=follicle-stimulating hormone; FU= Follow-up; HIV=human immunodeficiency virus; HepBsAg=hepatitis B surface antigen; HepBcAb=hepatitis B core antibody; HCVAb=hepatitis C antibody; PK=pharmacokinetic; AE=adverse event; SAE=serious adverse event;

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

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that penetrates into the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. While the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, crisaborole reduces the production of several inflammatory cytokines implicated in the pathophysiology of atopic dermatitis (AD).

Crisaborole is currently being developed for the treatment of mild to moderate AD in patients 2 years of age and older. On 14 Dec, 2016, crisaborole ointment 2% received its first approval from United States (US) Food and Drug Administration (FDA) for the topical treatment of mild to moderate AD in patients 2 years of age and older.

1.2. Background

AD, also referred to as atopic eczema or in layperson terms as eczema, is a chronic and relapsing disease affecting an increasing number of patients. Although AD affects patients of all ages, it is one of the most common, chronic, relapsing childhood dermatoses, impacting 15%-30% of all children in the US with 85% of affected individuals showing signs of the disease before 5 years of age.^{1,2} Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US and Japan.^{3,4,5}

AD is an 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.^{1,4} The majority of patients (up to 90%) with AD present with mild to moderate disease.⁶ Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, and lichenification.⁷ 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. AD has been cited as a major risk factor for the development of asthma in a number of longitudinal studies, and children with AD are at increased odds in developing asthma compared to children without AD.^{8,9} 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 health related quality of life measures (HRQoL) for patients, especially in children, and caregivers.^{1,10,11,12} Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.¹³

AD has a significant impact on day to day functioning, as evidenced by its impact on the overall well-being of the patient and their family on multiple levels; medical management and treatment, HRQoL, and psycho-social implications. AD may also be a source of significant economic burden¹⁴ as this relapsing disease is often misdiagnosed, misunderstood, and ineffectively treated.⁴ AD is a condition associated with significant morbidity. 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.

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.

1.3. Drug Development

Crisaborole is a novel, non-steroidal, 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 treatment-limiting effects of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in favor of crisaborole ointment 2% BID versus vehicle BID in the two Phase 3 registration studies in the US. Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related serious adverse events (SAE) (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related) and with the majority of adverse events (AE) being mild and deemed unlikely or not related to investigational product. Safety has not yet been evaluated in patients younger than 2 years of age.

The Investigator's Brochure (IB) contains summaries of nonclinical and clinical studies performed with crisaborole. A brief summary as background to this study protocol is presented here.

1.3.1. Nonclinical Safety Studies

Crisaborole demonstrates inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration (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 (PKA)-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 phorbol 12-myristate 13-acetate (PMA)-induced ear edema model. AN7602 and AN8323, main metabolites of crisaborole, lack anti-inflammatory activities against PDE-4 and a panel of cytokines.

Crisaborole was generally well tolerated in all species studied in toxicology studies, including a single-dose intravenous (IV) study in dogs, a 3-month study in mice using dermal application of ointment, up to 6-month oral studies in rats, and up to 9-month dermal studies in minipigs. Toxicokinetic data were collected as part of various toxicology studies. Crisaborole was not identified as a reproductive toxicant or a teratogenic agent. Based on exposure in a maximal use systemic exposure (MUSE) study (Study AN2728-AD-102) conducted in pediatric subjects (2–17 years old) with mild to moderate AD, calculated safety

margins for crisaborole are 2× to 13× for embryo-fetal development and reproductive toxicity, 215× for acute (eg, cardiovascular) effects, and 11× for chronic effects. Refer to the IB for further information on the nonclinical experience with crisaborole ointment 2%.

1.3.2. Pharmacokinetics (PK)

The efficacy of crisaborole for the treatment of AD is not dependent on systemic exposure. The development program evaluated systemic exposure to crisaborole and its main metabolites relative to establishing the safety of topically applied crisaborole. Clinical studies in healthy adult volunteers, in pediatric and adolescent subjects with AD, and in adults with psoriasis demonstrated similar PK profiles and systemic exposure, irrespective of underlying disease or age, and establish that following topical application, crisaborole penetrated through the stratum corneum, epidermis, and dermis of human skin, as evidenced by the presence of crisaborole and its main metabolites in plasma. Upon reaching the systemic circulation, biotransformation of crisaborole is rapid and extensive and primarily consists of oxidative deboronation/hydrolysis to produce AN7602 by CYP3A4 and CYP1A1/2, followed by subsequent downstream oxidation of this metabolite to form AN8323, without notable species-related qualitative differences. These two main metabolites of crisaborole observed in plasma following topical application to several species, including humans, were found to be inactive against PDE-4. Further, as a result of rapid biotransformation, systemic exposure of crisaborole is limited following topical application of crisaborole.

In the clinical PK study conducted under maximal use conditions (maximal use systemic exposure [MUSE] study) in children and adolescents aged 2-17 years with extensive AD (mean treatable percent body surface area [Treatable %BSA] 48.7%; range 27%-92%), absorption across the skin was rapid, with a median of time to reach maximum observed concentration (T_{max}) of 3.0 hours on both Day 1 and Day 8 (Study AN2728-AD-102). Steady state was achieved within the first 8 days of dosing, with a mean crisaborole of maximum observed concentration (C_{max}) of 127 ng/mL. Minimal plasma accumulation of crisaborole and AN7602 was observed at steady state whereas AN8323 displayed an approximately 3-4-fold accumulation based on C_{max} and area under the concentration-time curve from time zero to the 12 hours (AUC₁₂).

Table 1. Key Pharmacokinetic Parameters in AD Subjects (2–17 years) (AN2728-AD-102)

Analyte	Study Day	Mean Parameter (SD) (N = 23)		
		C _{max} (ng/mL)	T _{max} (median [range]) (h)	AUC ₁₂ (ng·h/mL)
Crisaborole	Day 1	111 (113)	3.00 (3.00–12.0)	759 ^a (730)
	Day 8	127 ^b (196)	3.00 ^b (3.00–24.0)	949 ^a (1,240)
AN7602	Day 1	37.8 (35.0)	3.00 (3.00–12.0)	247 ^a (224)
	Day 8	40.8 ^b (48.6)	3.00 ^b (0.00–12.0)	290 ^a (313)
AN8323	Day 1	2,270 (2,640)	12.00 (3.00–24.0)	16,800 ^a (16,900)
	Day 8	6150 ^b (4790)	3.00 ^b (0.00–24.0)	63,400 ^a (49,000)

Abbreviations: AD=atopic dermatitis; AUC₁₂ = area under the plasma concentration-time curve from 0–12 hours after dosing; C_{max} = maximum observed plasma concentration; SD = standard deviation; T_{max} = time to reach maximum observed plasma concentration.

a: N = 32; b: N = 33.

1.3.3. Cutaneous Sensitization, Irritancy Potential and Tolerability

1.3.3.1. Local Tolerability in Sensitive Skin Areas

In a study of healthy subjects (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), and only 0.1% of assessments graded higher than 1 (mild), with an overall maximum grade of 2 (moderate) (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 subjects 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 subjects.

1.3.3.2. Sensitizing and Cumulative Irritation Potential

In a repeat-insult patch test (RIPT) and cumulative irritation study in healthy subjects (Study AN2728-RIPT-101), the potential for inducing cutaneous sensitization was assessed in 238 subjects randomized in Cohort 1. None of the subjects 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 subjects randomized in Cohort 2 with daily patch applications for 21 consecutive days. 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 (minimal erythema, barely perceptible).

1.3.4. Clinical Experience

Seven (7) clinical trials of topical formulations of crisaborole have been completed to date in subjects with AD. Key study information is summarized below.

- In a 4-week, multicenter, MUSE study in 34 children and adolescents aged 2-17 years with mild-to-moderate AD (Study AN2728-AD-102) who applied crisaborole ointment 2% twice daily (BID), subjects had overall blood levels of crisaborole that were low and similar to those previously observed in adults psoriasis patients (Study AN2728-PSR-106) after adjusting for %BSA treated.
- A total of 63 AEs were reported in 23/34 subjects (67.6%): 40 were mild, 20 were moderate, and 3 were severe. No treatment-emergent adverse event (TEAE) was considered serious, and no deaths occurred. The most common TEAEs were application site reactions that were generally mild or moderate in severity and resolved spontaneously without sequelae. The TEAEs reported for more than 1 subject were application site pain (12/34, 35.3%), worsening of atopic dermatitis (7/34, 20.6%), upper respiratory tract infection (3/34, 8.8%), and application site paresthesia (2/34, 5.9%). About half (36/63, 57.1%) of the TEAEs were considered related to study drug, two of which (application site pain) were severe and occurred in a 2-year-old female subject who experienced intermittent application site burning on Study Days 6, 7, 10, 11, and 12 (nonserious, mild to severe, possibly to definitely related). On Study Day 13, this subject was withdrawn from the study at her father's request. The events resolved following the final application of study drug on Study Day 12. Overall, no clinically important safety signals were observed in a review of TEAEs, topical TEAEs (application site reactions), and laboratory test, vital sign, and physical examination results.
- In a 4-week, open-label, safety, tolerability and PK trial in adolescents with mild-to-moderate AD involving 10%-35% BSA, crisaborole ointment 2% BID improved disease severity over the 28-day treatment period (Study AN2728-AD-203). A total of 19 TEAEs were reported in 43.5% (10/23) subjects. All TEAEs were either mild (57.9% [11/19]) or moderate (42.1% [8/19]). The majority of TEAEs (68.4% [13/19]) were unrelated or unlikely to be related to study drug. All drug-related AEs were application site reactions. The most commonly reported TEAEs, application site pain and nasopharyngitis, were each reported by 3 subjects. No other TEAE was reported by more than 1 subject. No SAEs or deaths were reported. No clear correlation was observed between plasma exposure levels and the incidence of AEs. Overall, no safety signals were observed in a review of local tolerability, AEs, TEAEs, clinical laboratory results, and vital sign results.

- In a 6-week bilateral comparison trial of subjects with mild-to-moderate AD (Study AN2898-AD-202), 68% of AD lesions treated with crisaborole ointment 2% BID showed greater improvement in AD severity index (ADSI) than vehicle-treated lesions (20%) at 4 weeks (primary endpoint). These response rates were similar at Day 14 and Day 42 (end of treatment). In a 4-week bilateral comparison trial of 86 adolescent subjects with mild-to-moderate AD (Study 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 once daily (QD).
- In two Phase 3, multicenter, randomized, double-blind, vehicle controlled studies in subjects ≥ 2 years of age and older with AD, crisaborole ointment 2% outperformed the vehicle in the primary efficacy analysis (success in investigator's static global assessment [ISGA] defined as an ISGA score of clear or almost clear with at least a 2-grade improvement from Baseline) and the difference between the treatment groups was statistically significant (Study AN2728-AD-301 and Study AN2728-AD-302).
- An additional Phase 3, multicenter, open-label, long-term extension study of crisaborole ointment 2% for the treatment of mild to moderate AD in adults and children as young as 2 years of age evaluated the long-term safety of topical crisaborole (Study AN2728-AD-303). Crisaborole showed an acceptable safety profile for long-term topical treatment of mild to moderate AD in adults and children as young as 2 years of age.

Crisaborole has been well tolerated across completed clinical studies. No clinically important safety signals have been identified, including during a Phase 3 multicenter, open-label, long-term extension study of crisaborole ointment 2% for mild to moderate AD in adults and children as young as 2 years of age. Most AEs have been mild, and most considered unrelated or unlikely to be related to investigational product. The most common drug-related AEs have been application site reactions.

In a thorough QT (TQT) study (Study AN2728TQT108) in which healthy subjects were treated with crisaborole ointment 2% at a therapeutic dose (15 g, representing 30% BSA treatment) or a suprathreshold dose (45 g, representing 60% BSA treatment), mean C_{max} values of 36.9 ng/mL and 87.4 ng/mL were observed in therapeutic and suprathreshold dose groups, respectively, at Day 9. At both therapeutic and suprathreshold doses had no effect on cardiac repolarization based on results from the primary assessment and the pharmacokinetic-pharmacodynamic analysis.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is current version of the crisaborole IB.

1.4. Rationale

1.4.1. Study Rationale

This Phase 1 study is planned to evaluate the skin irritation potential of crisaborole ointment 2% and vehicle in healthy adult male Japanese subjects in Cohort 1, and safety and PK of crisaborole ointment 2% in adult Japanese subjects with AD in Cohort 2.

There have been reports about racial difference in skin pathophysiology,^{15,16} and conflicting literatures about the racial difference in irritant response with topical therapy.^{17,18,19} Even though there was no evidence of cutaneous sensitization in the RIPT study, and the cutaneous irritation was very minimal in Western subjects (Section 1.3.3), it is considered useful to evaluate the irritant response in Japanese subjects. All subjects in Cohort 1 will be treated topically under occlusive patch conditions with 2 study products (crisaborole ointment 2% and vehicle) on the infrascapular area of the back for 48-hour duration before irritant response assessment. The assessment will be based on the Japan standard evaluation methods.^{20,21,23} The cohort will be conducted as an observer-blinded design to minimize evaluation bias for skin irritation.

Cohort 2 will be conducted in adult Japanese subjects with mild to moderate AD with Treatable %BSA >25%. This cohort will investigate the safety and PK of crisaborole ointment 2% in Japanese subjects with AD under MUSE condition. The Cohort 2 can provide useful information to evaluate the safety and possible maximum systemic exposure of crisaborole ointment 2% in Japanese subjects under the maximal use condition to enable further development in Japan. The cohort will be conducted as a double-blind design to minimize evaluation bias for safety. Considering the well acceptable safety results in previous MUSE study, the two Phase 3 and one long-term safety studies, and the securement of safety by confinement, the Cohort 2 can be conducted in parallel with Cohort 1 study.

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1.4.2. Dose Rationale

Crisaborole ointment 2% BID was selected as the recommended clinical dose based on the superior efficacy to vehicle, lower concentration of 0.5% applied BID, 0.5% and 2% concentration applied QD (Study AN2898-AD-202 and Study AN2728-AD-204). The efficacy and safety of this dose has also been confirmed in two Phase 3 studies and one long-term safety study in AD patients 2 years of age and older (Studies AN2728-AD-301, 302 and 303). Crisaborole ointment 2% BID was approved by the FDA as the clinical dose in US.²⁴ Considering the current available highest dose strength is crisaborole ointment 2%, the efficacy and well tolerated safety profile of this dose strength obtained in Western subjects, crisaborole ointment 2% will be used in the Cohort 1 of this study to assess its skin irritant potential in Japanese healthy subjects. Crisaborole ointment 2% BID will be used in Cohort 2 to investigate the safety and PK of crisaborole in Japanese AD subjects.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective for Cohort 1	Primary Endpoint for Cohort 1
<ul style="list-style-type: none"> To investigate the skin irritation potential of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects 	<ul style="list-style-type: none"> Skin irritation index^a
Secondary Objective for Cohort 1	Secondary Endpoint for Cohort 1
<ul style="list-style-type: none"> To investigate the safety and tolerability of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects 	<ul style="list-style-type: none"> Assessment of adverse events (AEs)
Primary Objective for Cohort 2	Primary Endpoint for Cohort 2
<ul style="list-style-type: none"> To investigate the safety and tolerability of multiple topical doses of crisaborole ointment 2% BID in adult Japanese subjects with mild to moderate AD 	<ul style="list-style-type: none"> Assessment of AEs, clinical laboratory tests, vital signs, and 12 lead electrocardiogram (ECG)
Secondary Objective for Cohort 2	Secondary Endpoint for Cohort 2
<ul style="list-style-type: none"> To characterize plasma PK of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment 2% BID in adult Japanese subjects with mild to moderate AD 	<ul style="list-style-type: none"> PK parameters: C_{max}, T_{max}, AUC_{last}, AUC_{24}, AUC_{τ} on Day 1 and Day 8, and R_{ac} (C_{max}) and R_{ac} (AUC_{τ}) on Day 8
<ul style="list-style-type: none"> CCI 	<ul style="list-style-type: none"> CCI
<ul style="list-style-type: none"> CCI 	<ul style="list-style-type: none"> CCI

Abbreviations: AD=atopic dermatitis; AE=adverse event; C_{max} =maximum observed plasma concentration; AUC_{τ} = area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval, where τ = 12 hours for BID dosing; BID=twice daily; AUC_{last} = area under the plasma concentration-time curve from zero time until the last measurable concentration (C_{last}); AUC_{24} = area under the plasma concentration-time curve from time zero to the 24 hours postdose; T_{max} =time to reach maximum observed plasma concentration; ECG=electrocardiogram; PK=pharmacokinetics.

a: Skin irritation index is calculated as the sum of the individual maximum irritation scores divided by the number of subjects and multiplied by 100, which ranges from 0 to 400.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1, single-center, randomized, vehicle-controlled, parallel-cohort study of crisaborole ointment 2% to evaluate the skin irritation potential in adult Japanese healthy subjects in Cohort 1, and to evaluate the safety, tolerability and PK in adult Japanese subjects with mild to moderate AD in Cohort 2. Both cohorts will be run in parallel and completion of Cohort 1 is not required to make a decision to proceed with Cohort 2.

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

Cohort 1

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

The investigational products will be applied to one side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites will be assessed clinically using a visual scale that rates the degree of erythema, edema, and other signs of skin irritation (see [Section 7.1.6](#)).

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

All applications of the investigational product will be conducted by the study site staff.

The observer and subjects will be blinded to minimize evaluation bias for skin irritation.

Cohort 2

This is a randomized, double-blind cohort of crisaborole ointment 2% BID to evaluate the safety, tolerability and PK in adult Japanese subjects with mild to moderate AD. The cohort will enroll male and female subjects with AD aged 20 years to 55 years, inclusive, at the time of screening. Approximately 12 subjects having at least 25% Treatable %BSA, defined as the percent of a subject's total body surface area (BSA) that is AD-involved and is not on the scalp or in designated venous access areas, will be enrolled into the study. The Treatable %BSA will be calculated at Screening and Day 1. The investigational product will be applied BID to the Treatable %BSA areas identified on Day 1 for 8 days, except on Days 1 and 8, when investigational product will be administered QD in the AM. All investigational product doses will be dispensed and applied by study site staff.

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

Refer to the [SCHEDULE OF ACTIVITIES](#) for a complete list of assessments to be performed during the study.

Eligibility criteria for the study population are described in [Section 4](#). Detailed information about the investigational product treatment regimen is provided in [Section 5](#). Detailed information about study procedures and assessments is provided in [Section 6](#) and [Section 7](#).

3.2. Number of Sites

Both cohorts will be conducted in one study site.

3.3. Duration of Study

Cohort 1

Subjects will be screened for the study no more than 28 days before the initial day of dosing (Day 1). Investigational products will be applied topically once on Day 1 and remain under a patch occlusion for 48 hours. The study will comprise the following study periods:

- Screening Period: maximum duration of 28 days;
- Investigational product patch Application Period: 48 hours;
- Patch Sites Observation Period: Day 3 and 4;
- Post-Treatment Follow-up Period: a telephone call on Day 29 (28 +7 days after the application of investigational product patch on Day 1).

Cohort 2

Subjects will be screened for the study no more than 28 days before the initial day of dosing (Day 1), and will receive investigational products topically BID for 8 days, except on Days 1 and 8, when investigational product will be administered QD in the AM. The study will comprise of the following study periods:

- Screening Period: maximum duration of 28 days;
- Investigational product Application Period: 8 days;
- Post-Treatment Follow-up Period: a telephone call on Day 36 (28 +7 days after the last application of investigational product).

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

Cohort 1

1. Healthy male Japanese subjects who, at the time of screening, are between the ages of 20 and 55 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including blood pressure (BP) and pulse rate (PR) measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests.
2. Body mass index (BMI) of 17.5 to 30.5 kg/m²; and a total body weight >50 kg (110 lb).
3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
4. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.
5. Healthy skin on which reddening can be easily recognized in the area of the test fields.

Cohort 2

1. Male or female Japanese subjects aged 20 years to 55 years (inclusive) at the time of screening, and in generally good health except for AD. Good health is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including BP and PR measurement, 12 lead ECG, and clinical laboratory tests.

Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

- a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

2. Diagnosis of AD based on the criteria of Hanifin and Rajka (1980) (see [Appendix 2](#)).
3. Has at least 25% Treatable %BSA on Day 1 (excluding the scalp and designated venous access areas).
4. Has an Investigator's static global assessment (ISGA) score of Mild (2) or Moderate (3) on Day 1 (see [Appendix 3](#)).
5. BMI of 17.5 to 35.0 kg/m²; and a total body weight >50 kg (110 lb).
6. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
7. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
8. Has adequate venous access to permit repeated PK sampling on Days 1–9 through uninfected skin to which investigational product will not be applied (Each designated venous access area must have an untreated margin of at least 5 cm radius around the venipuncture site).

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

Cohort 1

1. Subjects who have any visible skin disease at the application site which, in the opinion of the investigative personnel, will interfere with the evaluation of the test site reaction.
2. Subjects who have psoriasis and/or active AD/eczema.
3. Subjects who have a history of AD.
4. Subjects who have damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurements of the test site.
5. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
6. A positive urine drug test.
7. History of regular alcohol consumption exceeding 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.
8. Treatment with an investigational drug within 30 days or 5 half-lives preceding the first dose of investigational product (whichever is longer).
9. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:
 - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level $\geq 1.5 \times$ upper limit of normal (ULN);
 - Total bilirubin level $\geq 1.5 \times$ ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is \leq ULN.
10. Blood donation (excluding plasma and platelet donations) of approximately ≥ 400 mL within 3 months or ≥ 200 mL within a month prior to dosing.
11. History of sensitivity to heparin or heparin-induced thrombocytopenia.

12. Known sensitivity to any of the components of the investigational products (see [Section 5](#)).
13. History of the rash to the adhesive plaster, contact dermatitis to metal, or cosmetic and household articles.
14. History of human immunodeficiency virus (HIV), hepatitis B, hepatitis C or syphilis; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), hepatitis C antibody (HCVAb) or syphilis.
15. Unwilling or unable to comply with the criteria in the [Lifestyle Requirements](#) section of this protocol.
16. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
17. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Cohort 2

1. Has any clinically significant medical disorder, condition, disease (including active or potentially recurrent dermatological conditions other than AD), significant physical examination or laboratory findings that may interfere with study objectives, in the Investigator's opinion (eg, conditions or findings that may expose a subject to unacceptable risk by study participation, confound the evaluation of treatment response or adverse events, or otherwise interfere with a subject's ability to complete the study).
2. Has unstable AD or a consistent requirement for strong to strongest potency topical corticosteroids to manage AD signs and symptoms (see Concomitant Treatment(s) for washout periods).
3. Has a significant active systemic or localized infection, including known actively-infected AD.

4. Has a history or evidence of clinically significant or severe allergies (eg, seasonal, pet dander, environmental, food) requiring acute or chronic treatment (Subjects with allergic rhinitis that does not require treatment, or for whom an ongoing allergy treatment meets the definition of a stable regimen under [Concomitant Treatment\(s\)](#) section, may be eligible to participate in the study).
5. Has recent or anticipated concomitant use of topical or systemic therapies that might alter the course of AD, as specified in protocol (see [Concomitant Treatment\(s\)](#)).
6. Has a history of recent (within 4 weeks of Day 1) sunbathing, tanning bed use, or ultraviolet (UV) light B therapy (UVB) or psoralen plus UVA [PUVA] (Sunbathing, tanning bed use, and UV light therapy are prohibited during the study).
7. Has any planned surgical or medical procedure that would overlap with study participation from Screening through the end of study.
8. Has any cancer or have a history of cancers within the last 5 years (except curatively treated with surgical excised squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin).
9. Has a known sensitivity to any of the components of crisaborole ointment 2%.
10. A positive urine drug test.
11. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.
12. Treatment with an investigational drug within 30 days or 5 half-lives preceding the first dose of investigational product (whichever is longer).
13. Screening supine BP ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.
14. Screening supine 12-lead ECG demonstrating a QTc interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the subject's eligibility.
15. Subjects with ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

- Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level $\geq 1.5 \times$ upper limit of normal (ULN);
 - Total bilirubin level $\geq 1.5 \times$ ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is \leq ULN.
16. Use of prescription or nonprescription drugs, vitaminic and dietary supplements within 14 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product (refer to [Section 5.10.1](#) for drugs or therapies with different requirement for washout period). As an exception, acetaminophen/paracetamol may be used at doses of ≤ 1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.
- Herbal supplements (including St. John's Wort) must have been discontinued at least 28 days prior to the first dose of investigational product.
17. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
18. Blood donation (excluding plasma donations and platelet donations) of approximately ≥ 400 mL within 3 months or ≥ 200 mL within a month prior to dosing.
19. History of sensitivity to heparin or heparin-induced thrombocytopenia.
20. History of HIV, hepatitis B, hepatitis C or syphilis; positive testing for HIV, HepBsAg, HepBcAb, HCVAb or syphilis.
21. Unwilling or unable to comply with the criteria in the [Lifestyle Requirements](#) section of this protocol.
22. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
23. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

4.4. Lifestyle Requirements

The following guidelines are provided:

4.4.1. Alcohol

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during confinement in the CRU. Subjects may undergo an alcohol breath, blood or urine alcohol test at the discretion of the investigator.

4.4.2. Activity

Cohort 1

- Bathing, sauna or sunbathing are not allowed during confinement in the CRU.
- Activities which would lead to excessive sweating or any type of sun exposure are prohibited during confinement in the CRU.
- The use of any products in the patch area is prohibited during confinement in the CRU.

Cohort 2

- Occluding the treated areas (with wraps, for example) should be avoided.
- Subjects should refrain from swimming, bathing, sauna or washing the treated areas for at least 4 hours after application.
- Subjects should be encouraged not to put hands in the mouth to avoid ingestion of investigational product.
- Subjects should avoid wiping the investigational product off the skin.

4.4.3. Contraception (Cohort 2)

All female subjects who are of childbearing potential, as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use.

At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5. 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.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study 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 subject'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. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or vehicle being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are crisaborole ointment 2% and matching vehicle.

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

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

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

The investigator will assign subject numbers to the subjects as they are screened for the study by each cohort. Each subject enrolled in either Cohort 1 or Cohort 2 will sign the informed consent for the appropriate cohort and successfully complete the screening procedures.

Pfizer will provide a randomization schedule to the personnel who will conduct the subject allocation and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

All subjects enrolled in Cohort 1 will receive both products (crisaborole ointment 2%, and vehicle). The randomization schedule of Cohort 1 indicates the randomized sequence of application placement of the investigational product. According to the randomization sequence (Table 2), each subject will receive 2 patches, one is crisaborole ointment 2% and the other is vehicle.

For Cohort 1, subjects will be randomly assigned in a 1:1 ratio to either Randomization sequence 1 [Application placement 1 (Upper): Crisaborole ointment 2%, Application placement 2 (Lower): Vehicle] or Randomization sequence 2 [Application placement 1 (Upper): Vehicle, Application placement 2 (Lower): Crisaborole ointment 2%].

Table 2. Randomization sequence for Cohort 1

Randomization sequence	Application placement 1 (Upper)	Application placement 2 (Lower)
1	Crisaborole ointment 2%	Vehicle
2	Vehicle	Crisaborole ointment 2%

For Cohort 2, subjects will be randomly assigned in a 5:1 ratio to either crisaborole ointment 2% or vehicle.

5.2. Blinding of Site Personnel

Cohort 1

In this observer-blinded cohort, the observer and subject will be blinded, but all other study site staff, including the principal investigator and the study site staff who are involved in the preparation/application and removal of the patches, will be unblinded. However, the access to the unblinded information of any site staff other than the study site staff who are involved in the preparation/application and removal of the patches should be kept to a minimum.

The principal investigator will assign the responsibility to a blinded observer of the evaluation of skin irritation potential. A blinded observer should fulfill this role. The blinded observer must not be allowed to know the randomization sequence.

Cohort 2

In this double blind cohort, the personal who will conduct the subject allocation to the investigational products will be unblinded, but all other site study personnel will be blinded. The principal investigator will assign the unblinded staff. The unblinded staff will assign randomization number to the investigational product according to the randomization schedule provided by the sponsor, and will not participate in the evaluation of any study subject. One or two unblinded staff who will conduct the subject allocation to the investigational products will be assigned. The member(s) of the study site staff should fulfill this role.

Contact between the unblinded staff and study subjects should be kept to a minimum. The investigator, study coordinator, the study staff who are involved in the preparation/application of the investigational product and any site staff other than the unblinded staff who assign randomization number to the investigational product must not be allowed to know the investigational product assigned to any study subject.

5.3. Blinding of the Sponsor

Cohort 1

All study team members may be unblinded in order to evaluate safety and skin irritation (see [Section 9.6](#)).

Cohort 2

All study team members will remain blinded to the investigational product assigned/received throughout the study.

5.4. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.5. Subject Compliance

For Cohort 1, all patches will be prepared, applied and removed by study site staff. For Cohort 2, the dispensing and application of investigational product will be performed by study site staff. Treatment compliance for each subject will be ensured and documented during treatment period.

5.6. Investigational Product Supplies

5.6.1. Dosage Form and Packaging

Crisaborole ointment 2% and vehicle will be provided in 60 g tubes by Pfizer. The tubes will be labeled according to local regulatory requirements.

5.6.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

The investigational products will be prepared by study site staff according to the Investigational Product (IP) manual.

5.7. Administration

5.7.1. Administration for Cohort 1

Subjects will receive the investigational products once on Day 1 to the designated areas of the back according to the randomization sequence and remain under occlusion for 48 hours in accordance with a skin irritation manual.

All applications of the investigational product will be conducted by the study site staff.

5.7.2. Administration for Cohort 2

Crisaborole ointment 2% is for external use on the skin only. Avoid contact with mucous membranes (ie, inside of nostrils, mouth, vagina, urethra, and rectum), and the eyes. Additionally, Crisaborole ointment 2% should not be administered to the perioral area in order to reduce the possibility of accidental ingestion that could adversely affect PK results. Care must be taken to avoid study drug contamination of designated venous access areas used for PK sampling, by leaving an untreated margin of at least 5 cm radius around each venipuncture site.

5.7.2.1. Study Treatment Regimen

From Day 1 AM through the Day 8 AM dose, all applications of the investigational product will be dispensed and applied by study site staff. The subject-specific per application dose will be applied BID to all treatable AD-involved areas identified on Day 1 except on Days 1 and 8, when investigational product will be administered QD in the AM. Every effort must be made for the AM dose applications on Days 2–8 to be completed at 24 ± 1 hour intervals from the recorded time of completion of the Day 1 dose application, for each subject. The PM dose applications on Days 2–7 will be applied at 12 ± 1 hour after the recorded time of completion of the each AM dose application, for each subject.

The per application dose will be calculated using the formula provided below in [Section 5.7.2.4](#), based on each subject's total BSA in square meters ([Section 5.7.2.2](#)) and Treatable %BSA ([Section 5.7.2.3](#)) on Day 1. The intended dose of the investigational product application to the treatable AD-involved areas is approximately 3 mg/cm^2 . The investigational product should be applied evenly to all treatable areas. The per application dose will be expressed as the weight of ointment in grams. The per application dose will remain fixed and the investigational product will be applied to all treatable AD-involved areas identified on Day 1, regardless of whether they become clinically clear. Any AD-involved venous access areas and/or new AD lesions that appear after Baseline may be treated only with bland emollients until discharge from CRU on Day 9.

5.7.2.2. Calculation of Subject's Total BSA

The subject's total BSA (in m^2) will be calculated using the Mosteller formula:

$$\text{BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

5.7.2.3. Calculation of Treatable %BSA

Treatable %BSA is defined as the percent of the subject's total BSA that is AD-involved and is not on the scalp or in venous access areas, by leaving an untreated margin of at least 5 cm radius around each venipuncture site. The Treatable %BSA will be calculated for each subject at Screening and Day 1, and all calculations should exclude the scalp and venous access areas. To estimate the Treatable %BSA, the investigator may use one of two methods of approximation.

- The "Rule of Nines" provides a general estimation of total BSA for several anatomic areas (each arm = 9%, each leg = 18%, back = 18%, chest and abdomen = 18%, head = 9%, groin = 1%). The investigator may then visually estimate the proportion of the involved skin within each anatomic area and calculate the total percentage of BSA affected with AD;
- Alternatively, the investigator may use the "handprint method", wherein the area represented by the subject's outstretched hand (including all five digits adducted together) equals approximately 1% of the subject's BSA.²⁵

The Treatable %BSA calculated on Day 1 will be used for calculation of the per application dose as defined in [Section 5.7.2.4](#).

5.7.2.4. Calculation of Per Application Dose

The per application dose (expressed in g) will be calculated by study site staff once on Day 1, for each subject, using the formula below:

$$\begin{aligned} & \text{Total BSA at Baseline (m}^2\text{)} \times \text{Treatable \%BSA} \times 0.003 \left(\frac{\text{g}}{\text{cm}^2} \right) \times 100 \left(\frac{\text{cm}^2}{\text{m}^2} \right) \\ & = \text{Weight of investigational product (in g) per application} \end{aligned}$$

5.7.2.5. Dispensing of Investigational Product

Prior to application, the per application dose will be carefully weighed out by study site staff on a calibrated scale capable of readouts to 0.1 g. Investigational product must be applied within 2 hours of dispensing from the tube. If excess study drug is accidentally dispensed, the excess amount is to be weighed and documented in the drug accountability log as wastage from the specified tube of study drug, and then discarded.

5.7.2.6. Application of Investigational Product

Before the Day 1 AM dose is applied for each subject, the designated areas for treatment will be identified on Day 1 and documented in the subject's study records. For each subsequent investigational product application, study site staff will refer to the documented locations of treatable AD lesions as determined on Day 1.

Wearing gloves, study site staff will apply the per application dose to all treatable AD lesions determined on Day 1. If possible, the same study site staff should administer study drug to the subject at each dosing. Study drug will be applied as a thin layer of subject's skin. Care must be taken to avoid study drug contamination of designated venous access areas used for PK sampling, by leaving an untreated margin of at least 5 cm radius around each venipuncture site. Following investigational product application, subjects will be instructed to wear loose-fitting clothing, to not wipe investigational product off the skin, to avoid occluding the treated areas, and to refrain from swimming, bathing, sauna or washing the treated areas within 4 hours after application.

5.8. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Please see the Investigational Product Manual for additional details on storage conditions and actions to be taken when conditions are outside of the specified range.

5.9. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

Throughout the study, detailed investigational product accountability records, including tube weights, will be maintained for each subject by study site staff. Study site staff will record the weight (in g) of all applied doses, along with the weight of any amount(s) dispensed in error and discarded as waste.

The original study drug accountability log, or equivalent document, must be accurately completed, signed by the investigator, and retained at the CRU (with a copy supplied to the sponsor) when the study is complete.

5.9.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). 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, and all destruction must be adequately documented.

5.10. Concomitant Treatment(s)

Medication entries should provide the correctly spelled drug or therapy name and the dose, units, frequency, route of administration, start and stop date, and reason for use. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements and routine immunizations.

Cohort 1

Subjects will abstain from all concomitant treatments, except for the treatment of AEs. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

Treatments taken within 28 days before the first application of investigational product will be documented as a prior treatment. Treatments taken after the first application of investigational product will be documented as concomitant treatments.

Cohort 2

All treatments (including medications and non-medication therapies) used for the treatment of AD and all other medications (including over-the-counter drugs, vitamins, and antacids) used within 28 days prior to Screening will be recorded at the Screening visit. Any changes in concomitant medications or dosage will be recorded on Day 1 and at each subsequent visit. Treatments taken after the first application of investigational product will be documented as concomitant treatments.

5.10.1. Washout Periods for Medications/Therapies Prior to Day 1 (Cohort 2)

Classes of medications and non-medication therapies that might alter the course of AD and that require washout prior to Day 1 are summarized below with necessary washout periods:

28 Days Prior to Day 1

- Systemic (oral/injectable) corticosteroids (excluding intranasal, inhaled or ophthalmic);
- Systemic immunosuppressive agents (eg, methotrexate, ciclosporin, azathioprine, hydroxychloroquine);
- Topical retinoids or benzoyl peroxide (BPO);
- Sunbathing, tanning bed use, or UV light therapy (UVB or PUVA).

14 Days Prior to Day 1

- Systemic anti-inflammatory or immunomodulatory drugs (including biologics, but excluding systemic antihistamines and nonsteroidal anti-inflammatory drugs [NSAIDs]);
- Escalating, decreasing, or as needed (PRN) use of systemic antihistamine(s) (Subjects on a stable systemic antihistamine regimen [eg, QD, BID, three times a week], with at least 2 weeks consistent use prior to Day 1, are permitted to continue but should not alter or stop their regimen during the study);
- Systemic antibiotics;
- Strong potency topical corticosteroids or calcineurin inhibitors, on any skin (treatable AD lesions **and** skin not to be treated with study drug).

7 Days Prior to Day 1

- Topical antihistamines on any skin (treatable AD lesions **and** skin not to be treated with study drug) or systemic sedating antihistamines (eg, hydroxyzine or diphenhydramine or other sedating antihistamines);

- Topical antimicrobial medications on treatable AD lesions only;
- Medium potency topical corticosteroids on any skin (treatable AD lesions **and** skin not to be treated with study drug).

3 Days Prior to Day 1

- Weak potency topical corticosteroids on any skin (treatable AD lesions **and** skin not to be treated with study drug) (Subjects who require step down therapy during a medication washout period are permitted to use weak potency topical corticosteroids until 3 days prior to Baseline).

At least 8 hours Prior to Application of Day 1

- Emollients on treatable AD lesions only.

If a subject requires a medication washout, the investigator will provide instructions on discontinuing the prohibited medication(s) at the Screening Visit. All screening examinations and tests/labs should be performed by the end of the washout period, if applicable.

5.10.2. Medications/Therapies Prohibited During the Study (Cohort 2)

Classes of medications and non-medication therapies that might alter the course of AD and that are prohibited during the study (from Day 1 through Day 9) are summarized below:

During the Study (Day 1 through Day 9 Visit):

- Systemic therapies that might alter the course of AD, including but not limited to:
 - Systemic (oral/injectable) corticosteroids (excluding intranasal, inhaled or ophthalmic);
 - Systemic immunosuppressive agents (eg, methotrexate, ciclosporin, azathioprine, hydroxychloroquine);
 - Systemic anti-inflammatory or immunomodulatory drugs (including biologics but excluding systemic antihistamines and NSAIDs);
 - Escalating, decreasing, or PRN use of systemic antihistamine(s) and stable systemic sedating antihistamines (eg, hydroxyzine or diphenhydramine or other).
- Topical therapies that might alter the course of AD, used on any skin (treatable AD lesions **and** skin not to be treated with study drug), including but not limited to:
 - Topical corticosteroids or calcineurin inhibitors;
 - Topical antihistamines;

- Topical therapies that might alter the course of AD, used on treatable AD lesions, including but not limited to:
 - Topical antimicrobial medications;
 - Topical retinoids or BPO.
 - Emollients.
- Sunbathing, tanning bed use, or UV light therapy (UVB or PUVA);
- Participation in another drug or device research study;
- Treatment with medications known to be potent CYP3A4 and strong CYP1A2 inhibitors.

5.10.3. Medications/Therapies Allowed During the Study (Cohort 2)

Classes of medications that are allowed during the study (from Day 1 through Day 9) are summarized below:

During the Study (Day 1 through Day 9 Visit):

- Inhaled, intranasal or ophthalmic corticosteroids are allowed throughout the study;
- Short courses of systemic antibiotics may be given during the course of the study, if clinically necessary for the treatment of new-onset infections;
- Stable dose of systemic non-sedating antihistamines (eg, fexofenadine, loratadine, desloratadine, cetirizine and levocetirizine) [eg, QD, BID, three times a week];
- NSAIDs are allowed throughout the study;
- Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception are permitted during the study, for female subjects;
- Concomitant medications for other chronic medical conditions are permitted during the study unless the medication/therapy is prohibited by the protocol.

6. STUDY PROCEDURES

6.1. Screening (Days –28 to –2)

Subjects will be screened within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the [Subject Information and Consent](#) section. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require rescreening if the Day –1 laboratory results meet the eligibility criteria.

6.1.1. Cohort 1

The following procedures will be completed:

- Obtain written informed consent;
- Confirm and document that the subject meets the inclusion/exclusion criteria;
- Collect demography;
- Collect height and weight;
- Obtain medical history, including history of illegal drug, alcohol, and tobacco use;
- Obtain complete medication history of all prescription or nonprescription drugs, and herbal supplements taken within 28 days prior to the planned first dose;
- Obtain supine BP and PR;
- Conduct physical examination;
- Collect 12-lead ECG.
- Collect blood and urine specimens for the following:
 - Safety laboratory tests: The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be given investigational product on Day 1;
 - Urine drug test;
 - HIV, HepBsAg, HepBcAb, HCVAb and syphilis testing.
- Assess the application field.
- Assess for AEs and SAEs.

To prepare for study participation, subjects will be instructed on the information in the Lifestyle Requirements and Concomitant Treatment(s) sections of the protocol.

6.1.2. Cohort 2

The following procedures will be completed:

- Obtain written informed consent;
- Confirm and document that the subject meets the inclusion/exclusion criteria;

- Collect demography;
- Collect height and weight;
- Confirm clinical diagnosis of AD;
- Complete the ISGA (the ISGA score must be 2 or 3 on Day 1 for subject to be eligible);
- Calculate and record Treatable %BSA;
- Obtain medical history, including history of illegal drug, alcohol, and tobacco use;
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary, vitamic and herbal supplements taken within 28 days prior to Screening;
- Obtain supine BP and PR;
- Conduct physical examination;
- Collect 12-lead ECG.
- Collect blood and urine specimens for the following:
 - Safety laboratory tests: The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be given investigational product on Day 1;
 - Urine drug test;
 - Serum FSH concentration for any female subject who has been amenorrheic for at least 12 consecutive months;
 - HIV, HepBsAg, HepBcAb, HCVAAb and syphilis testing;
 - Urine beta-human chorionic gonadotropin (β -hCG) level for all female subjects of childbearing potential.
- Assess for AEs and SAEs.
- Instruct highly effective contraception for all female subjects of childbearing potential.

To prepare for study participation, subjects will be instructed on the information in the [Lifestyle Requirements](#) and [Concomitant Treatment\(s\)](#) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital sign measurements, but prior to blood specimen collection;
- BP/PR: obtain prior to blood specimen collection;
- PK blood specimens: obtain at the scheduled time;
- Other procedures: may be obtained before or after blood specimen collection.

When an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (PR, BP) should be collected prior to the insertion of the catheter.

6.2.1. Cohort 1

6.2.1.1. Day –1

Subjects will be admitted to the CRU at least the day prior to Day 1 dosing. The following procedures will be completed following admission to the CRU:

- Review inclusion and exclusion criteria;
- Obtain blood and urine samples for safety laboratory tests. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be given investigational product on Day 1. Do not have to be repeated if clinical labs are completed within 7 days prior to Day –1;
- Collect urine for drug testing. Do not have to be repeated if urine drug testing is completed within 7 days prior to Day –1;
- Assess baseline symptoms/AEs;
- Review changes in the subject's medical history, including medication history since screening;
- Conduct physical examination.

6.2.1.2. Day 1

Prior to dosing, the following procedures will be completed:

- Review inclusion and exclusion criteria;
- Assess baseline symptoms /AEs;

- Review and record prior medications;
- Assess the application field;
- After all predose procedures have been completed, apply the investigational product patches (see the [Administration](#) section).

After application of the investigational product patches, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?” If AEs/SAEs occur at a patch site, the patch site location must be recorded.

6.2.1.3. Day 2

The following procedures will be completed:

- Review and record concomitant medications;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?” If AEs/SAEs occur at a patch site, the patch site location must be recorded;
- Confirm patches remain in place appropriately.

6.2.1.4. Day 3

The following procedures will be completed:

- Review and record concomitant medications;
- Remove the investigational product patches (48 hours post application on Day 1);
- Assess the skin irritation response of the patch sites by a blinded observer approximately 30 minutes after removal of the patches;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?” If AEs/SAEs occur at a patch site, the patch site location must be recorded.

6.2.1.5. Day 4

The following procedures will be completed:

- Review and record concomitant medications;
- Assess the skin irritation response of the patch sites by a blinded observer approximately 24 hours after removal of the patches;

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?” If AEs/SAEs occur at a patch site, the patch site location must be recorded;
- Conduct physical examination;
- Discharge from CRU confinement.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.2.2. Cohort 2

6.2.2.1. Day –1

Subjects will be admitted to the CRU at least the day prior to Day 1 dosing. The following procedures will be completed following admission to the CRU:

- Review inclusion and exclusion criteria;
- Obtain blood and urine samples for safety laboratory tests. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be given investigational product on Day 1;
- Collect urine for drug testing. Do not have to be repeated if urine drug testing is completed within 7 days prior to Day –1;
- Collect urine pregnancy test for female subjects of childbearing potential;
- Confirm highly effective contraception is being used for female subjects of childbearing potential;
- **CCI** [REDACTED]
- Assess baseline symptoms/AEs;
- Review changes in the subject’s medical history, including medication history since screening;
- Conduct physical examination except skin examination.

6.2.2.2. Day 1

Prior to dosing, the following procedures will be completed:

- Review inclusion and exclusion criteria;
- Conduct physical examination for skin examination;
- Complete the ISGA (the ISGA score must be 2 or 3 on Day 1 for subject to be eligible);
- Record treatable AD areas;
- Calculate and record Treatable %BSA;
- Assess baseline symptoms/AEs;
- Collect weight;
- Collect 12-lead ECG measurements prior to insertion of the IV catheter;
- Collect supine BP and PR prior to insertion of the IV catheter;
- Collect a blood sample for PK analysis at predose;
- Review and record prior medications;
- After all predose procedures have been completed, apply the investigational product (see the [Administration](#) section);
- **AM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- Collect blood samples for PK analysis at 3 and 12 hours following application on Day 1;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.2.3. Day 2

The following procedures will be completed:

- Collect blood samples for PK analysis at 24 hours following application on Day 1;
- Review and record concomitant medications;

- **AM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- **PM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.2.4. Day 3 to 6

The following procedures will be completed:

- Review and record concomitant medications;
- **AM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- **PM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.2.5. Day 7

The following procedures will be completed:

- Collect blood samples for PK analysis at 24 hours following application on Day 6 AM;
- Review and record concomitant medications;
- **AM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- **PM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1;
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.2.6. Day 8

- Review and record concomitant medications.
- Collect single 12-lead ECG measurements prior to insertion of the IV catheter.

- Collect supine BP and PR prior to insertion of the IV catheter.
- Obtain blood and urine samples for safety laboratory tests.
- Collect a blood sample for PK analysis at predose.
- **AM application**: wearing gloves, study site staff will apply the calculated amount of study drug (per application dose) to all treatable AD lesions identified on Day 1.
- Collect blood samples for PK analysis at 3 and 12 hours following application on Day 8.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.2.7. Day 9

- Review and record concomitant medications.
- Collect blood samples for PK analysis at 24 hours following application on Day 8.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”
- Conduct physical examination.
- Confirm highly effective contraception is being used for all female subjects of childbearing potential.
- Discharge from CRU confinement.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Follow-up

6.3.1. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the [Time Period for Collecting AE/SAE Information](#) section) and to confirm appropriate contraception usage (Cohort 2 only, see the [Contraception](#) section). Contact with the subject may be done via a phone call.

6.4. Subject Withdrawal/Early Termination

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment 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 subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product 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 subject 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.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist study site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The study site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the [Withdrawal From the Study Due to Adverse Events](#) section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or

procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early-withdrawal visit, every effort must be made to complete the following assessments:

Cohort 1

- Review and record concomitant medications.
- Assess the skin irritation response of the patch sites.
- Conduct physical examination
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?" If AEs/SAEs occur at a patch site, the patch site location must be recorded.

Cohort 2

- Review and record concomitant medications.
- Collect 12-lead ECG measurements prior to insertion of the IV catheter.
- Collect supine BP and PR prior to insertion of the IV catheter.
- Obtain blood and urine samples for safety laboratory tests.
- Collect a blood sample for PK analysis.
- Conduct physical examination
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"

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

If the subject withdraws from the study and also withdraws consent 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.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

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 subject. 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.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [STUDY PROCEDURES](#) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

The clinical laboratory test parameters that will be reviewed for safety evaluation are presented in [Table 3](#).

Table 3. Safety Laboratory Tests			
Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (%) Eosinophils (%) Monocytes (%) Basophils (%) Lymphocytes (%)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy ^a	FSH ^b Urine drug screening β-hCG ^c HIV HepBsAg HepBcAb HCVAb, Syphilis
	Additional Tests, as applicable (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; β-hCG=beta human chorionic gonadotropin; BUN= blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; HIV=human immunodeficiency virus; HepBsAg=hepatitis B surface antigen; HepBcAb=hepatitis B core antibody; HCVAb=hepatitis C antibody; INR= international normalized ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; WBC = white blood Cell.

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b Any female subject who has been amenorrheic for at least 12 consecutive months.

c Urine β-hCG for female subjects of childbearing potential.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.
- Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive investigational product.

7.1.2. Pregnancy Testing (Cohort 2)

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, and at admission on Day -1, if applicable.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from application of investigational product and from the study.

7.1.3. Physical Examinations

Physical examinations may be conducted by a physician, and especially skin examination may be conducted by a dermatologist. A physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, neurological systems, general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of 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.

7.1.4. Blood Pressure and Pulse Rate

BP and PR will be measured at times specified in the [STUDY PROCEDURES](#) section of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and PR is acceptable; however, when done manually, PR will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection.

7.1.5. Electrocardiogram

A single 12-lead ECGs should be collected at times specified in the [STUDY PROCEDURES](#) section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position.

For Cohort 2, to ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥ 45 msec from the baseline, or an absolute QTc value is ≥ 500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (ie, is ≥ 45 msec from the baseline, or is ≥ 500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥ 500 msec (or ≥ 45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to < 45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.1.6. Skin Irritation Assessment (Cohort 1)

Skin irritation assessment of the patch sites will be conducted on Day 3 (approximately 30 minutes after removal of the patches) and Day 4 (approximately 24 hours after removal of the patches) by a blinded observer who is a dermatologist. The following grade and score will be used to evaluate the response observed at the time of examination^{20,21,22}:

Table 4. Skin Irritation Assessment Grades and Scores

Definition	Grade	Score
No reaction	-	0
Mild erythema	\pm	0.5
Erythema	+	1
Erythema + edema, papula	++	2
Erythema + edema + papula + small water blister	+++	3
Large water blister	++++	4

Expected reactions in the patch area (ie, irritation reactions outlined in Table 4 above) will not be recorded as AEs during the study. Unexpected reactions (eg, rash, hives) will be recorded as AEs.

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of crisaborole and main metabolites (Cohort 2)

During all study periods, blood samples (2 mL) to provide a minimum of 0.4 mL plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K₂EDTA) at times specified in the [SCHEDULE OF ACTIVITIES](#) section of the protocol.

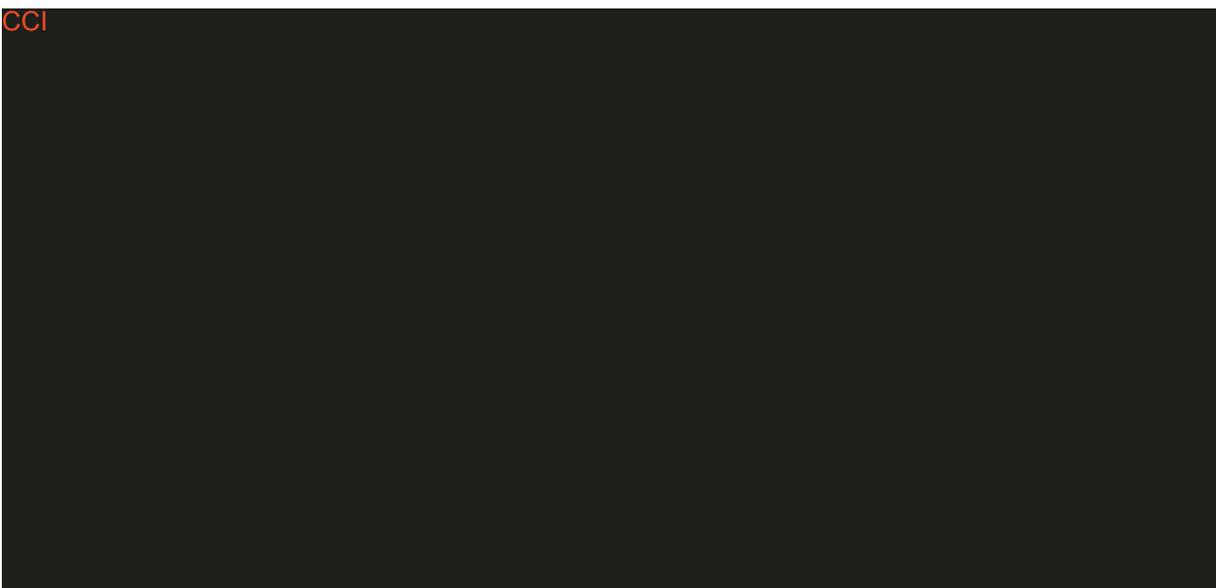
The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

CCI



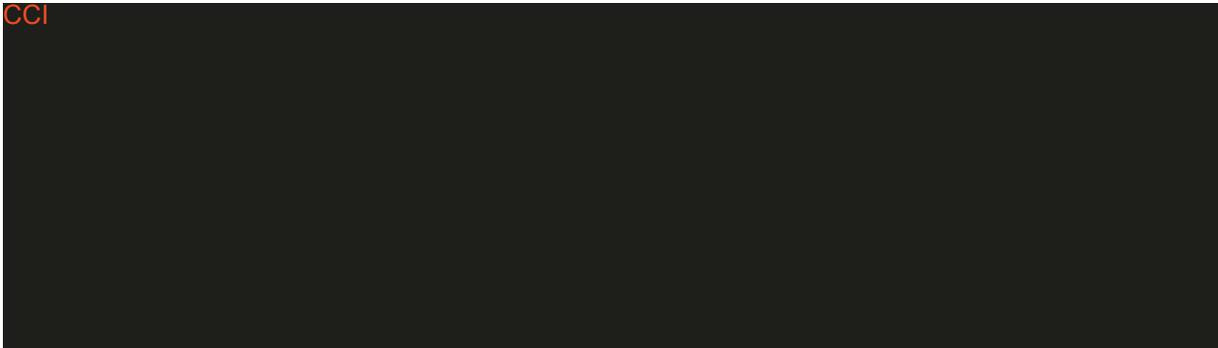
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7.4. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 20 mL for Cohort 1 or 53 mL for Cohort 2, respectively. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

Abbreviations: CRF=case report form; CT=clinical trial; SAE=serious adverse event; AE=adverse event.

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the [Serious Adverse Events](#) section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for [Serious Adverse Events](#), listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (\times ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations ($>2 \times$ ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times$ ULN (ie, AST/ALT and TBili values will be elevated within the same lab 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For subjects 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 $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (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 subject 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, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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 (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) 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.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 includes 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject 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.

8.4.4. Medication Errors

Other exposures to the investigational product 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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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 immediately.

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 non-serious, are recorded on an 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**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (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. Sample Size Determination

The total sample size will be approximately 32 in this study. This sample size has been determined by clinical judgment based on sponsor experience with other clinical studies with the investigational product and has not been based on statistical power.

For Cohort 1, a sample size of approximately 20 subjects has been selected empirically based upon the plan to confirm safety as for the skin irritation potential of crisaborole ointment 2% in healthy Japanese subjects^{20,21,23}.

For Cohort 2, a sample size of approximately 12 subjects (10 subjects for crisaborole ointment 2% and 2 subjects for vehicle) with at least 25% Treatable %BSA, excluding scalp and venous access area was selected empirically to minimize first exposure to Japanese subjects of a new drug.

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis (Cohort 2)

PK analysis sets are defined as follows:

- The PK concentration population is defined as all subjects randomized and treated who have at least 1 concentration.
- The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of primary interest.

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

Individual subject, mean and median profiles of the plasma concentration-time data will be plotted through Day 1 to Day 9, for crisaborole and its metabolites respectively. Mean and median profiles will be presented on both linear and semi-log linear scales.

All plasma concentration values and plasma PK parameters will be listed by subject.

For each subject, the following PK parameters will be calculated for crisaborole and its identified main oxidative metabolites (AN7602 and AN8323), whenever possible using noncompartmental analysis of concentration-time data. Concentration values that are below the lower limit of quantification (BLQ) will be set to zero for this analysis. Actual sample collection times will be used for this pharmacokinetic analysis:

Parameter	Day	Definition	Method of Determination
AUC_{τ}	1, 8	Area under the plasma concentration-time curve from time zero to time tau (τ), the dosing interval, where $\tau = 12$ hours for BID dosing	Linear/Log trapezoidal method
AUC_{last}	1, 8	Area under the plasma concentration-time curve from zero time until the last measurable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{24}	1, 8	Area under the plasma concentration-time curve from time zero to the 24 hours postdose	Linear/Log trapezoidal method
C_{max}	1, 8	Maximum observed plasma concentration over the dosing interval (12 hours) and over a 24 hour time period (total daily dose)	Observed directly from data
T_{max}	1, 8	Time to reach maximum observed plasma concentration	Observed directly from data as time of first occurrence
$R_{ac}(C_{max})$	8	Accumulation ratio for C_{max}	$C_{max, Day 8}/C_{max(first dose)}$
$R_{ac}(AUC_{\tau})$	8	Accumulation ratio for AUC_{τ}	$AUC_{\tau, Day 8}/AUC_{\tau(first dose)}$

CCI [REDACTED]

CCI [REDACTED]

9.5. Safety Analysis

The safety analysis will be conducted for Cohort 1 and Cohort 2, separately.

The safety analysis population is defined as all subjects who receive at least one dose of study medication.

AEs, ECGs, BP, PR and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Physical examination information collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.5.1. Electrocardiogram Analysis (Cohort 2)

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - <480	≥480
Absolute change	30 - <60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

9.5.2. Skin Irritation Analysis (Cohort 1)

For each subject, the maximum irritation score of the skin irritation assessment through all visits (ie, Day 3 and Day 4) will be calculated.

The primary endpoint for the skin irritation assessment will be the skin irritation index. For each investigational product, the skin irritation index will be calculated as the sum of the individual maximum irritation scores divided by the number of evaluable subjects who have the skin irritation assessment and multiplied by 100.²³ The calculated skin irritation index will range from 0 to 400. As show in Table 5, for example, when the skin irritation index is equal to or smaller than 5, the investigational product will be categorized as ‘Safe’.

Table 5. Safety Criteria of Skin irritation index

Skin irritation index ^a	Category
0 ≤ - ≤5	Safe
5 < - ≤15	Acceptable
15 < - ≤30	Improvable
30 < - ≤400	Risky

a: Skin irritation index = (Sum of higher scores in two assessments / number of evaluable subjects) × 100

For the maximum irritation score, the frequency (number and %) of individual maximum irritation scores will be presented for each investigational product. The descriptive statistics [number, mean, standard deviation (SD), median, minimum and maximum] of the maximum irritation score will also be calculated for each investigational product.

For the irritation score, the frequency (number and %) of individual irritation scores will be presented for each investigational product at each visit. The descriptive statistics (number, mean, SD, median, minimum and maximum) of the irritation score will also be calculated for each investigational product at each visit.

Individual irritation scores will be displayed in a data listing for all subjects.

9.6. Interim Analysis

No formal interim analysis will be conducted for this study. However, for Cohort 1, as this is a sponsor open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK/pharmacodynamics (PD) modeling, skin irritation assessment, and/or supporting clinical development.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial. End of Trial in Japan is defined as LSLV.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of crisaborole at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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 US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual patients have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
AD	atopic dermatitis
ADSI	atopic dermatitis severity index
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC ₁₂	area under the plasma concentration-time curve from time zero to the 12 hours
AUC ₂₄	area under the plasma concentration-time curve from time zero to the 24 hours
AUC _{last}	area under the plasma concentration-time curve from zero time until the last measurable concentration
AUC _τ	area under the plasma concentration-time curve from time zero to time tau (τ)
CCI	CCI
BID	twice daily
BLQ	below the lower limit of quantification
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BPO	benzoyl peroxide
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CK	creatin kinase
CT	clinical trial
C _{max}	maximum observed plasma concentration
CO ₂	carbon dioxide (bicarbonate)
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
EDP	exposure during pregnancy

Abbreviation	Term
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HRQoL	health related quality of life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
ISGA	investigator's static global assessment
IUD	intrauterine device
IV	intravenous
K ₂ EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LSLV	last subject last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MUSE	maximal use systemic exposure
N/A	not applicable
NSAIDs	nonsteroidal anti-inflammatory drugs
PCD	primary completion date
PD	pharmacodynamic(s)
PDE-4	phosphodiesterase-4
CCI	CCI
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PKA	protein kinase a
PMA	phorbol 12 myristate 13 acetate
PR	pulse rate
PRN	as needed
PT	prothrombin time

Abbreviation	Term
PUVA	psoralen plus UVA
QD	once daily
QTc	corrected QT
qual	qualitative
RBC	red blood cell
RIPT	repeat-insult patch test
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
SRSD	single reference safety document
TBili	total bilirubin
TEAE	treatment-emergent adverse event
T _{max}	time to reach maximum observed plasma concentration
THC	tetrahydrocannabinol
TQT	thorough QT
ULN	upper limit of normal
US	United States
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
WBC	white blood cell

Appendix 2. Diagnostic Criteria for Atopic Dermatitis (Cohort 2)

Per Inclusion Criterion 2 for Cohort 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.²⁶

Table 6. Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Major Criteria (must have at least three)

Pruritus

Typical morphology and distribution:

Adults: flexural lichenification or linearity

Children and infants: facial and extensor involvement

Chronic or chronically-relapsing dermatitis

Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria (must have at least three)

Xerosis

Ichthyosis/keratosis pilaris/palmar hyperlinearity

Immediate (type 1) skin test reactivity

Elevated serum immunoglobulin E (IgE)

Early age of onset

Tendency toward cutaneous infections (esp. staphylococcus aureus and herpes simplex),
impaired cell-mediated immunity

Tendency toward non-specific hand or foot dermatitis

Nipple eczema

Cheilitis

Recurrent conjunctivitis

Dennie-Morgan infraorbital fold

Keratoconus

Anterior subcapsular cataracts

Orbital darkening

Facial pallor, facial erythema

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool and lipid solvents

Perifollicular accentuation

Food intolerance

Course influenced by environmental and emotional factors

White demographism, delayed blanch

Appendix 3. Investigator's Static Global Assessment (Cohort 2)

The ISGA, a five-point global static assessment of AD severity (Table 7), will be assessed to characterize subjects' overall disease severity across all treatable AD lesions.

ISGA assessment must be done by the PI or designee.

Table 7. 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