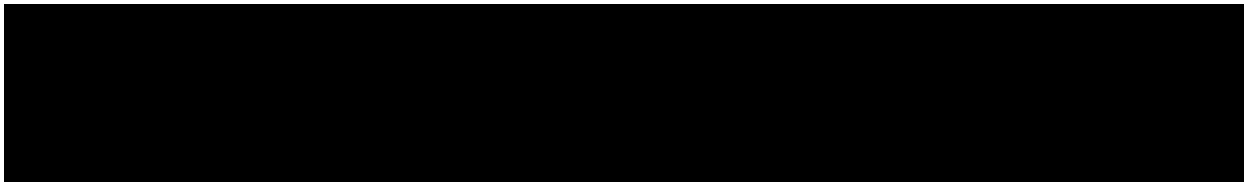




A PHASE 2B, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, INTRA-PARTICIPANT STUDY, TO EVALUATE EFFICACY AND SAFETY OF TWO REGIMENS OF CRISABOROLE OINTMENT 2% IN JAPANESE PEDIATRIC AND ADULT PARTICIPANTS (2 YEARS AND OLDER) WITH MILD TO MODERATE ATOPIC DERMATITIS

Investigational Product Number:	PF-06930164
Investigational Product Name:	Crisaborole
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3291028
Phase:	Phase 2b

Short Title: A Phase 2b, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Intra-Participant Study, to Evaluate Efficacy and Safety of Two Regimens of Crisaborole Ointment 2% in Japanese Pediatric and Adult Participants (2 Years and Older) with Mild to Moderate Atopic Dermatitis



Protocol Amendment Summary of Changes Table

Document History		
Document	Version Date	Summary of Changes and Rationale
Original protocol	22 Feb 2019	Not applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES	6
LIST OF FIGURES	7
1. PROTOCOL SUMMARY	8
1.1. Synopsis	8
1.2. Schema	8
1.3. Schedule of Activities (SoA).....	9
2. INTRODUCTION	12
2.1. Study Rationale	12
2.2. Background	12
2.2.1. Nonclinical Safety Studies.....	13
2.2.2. Pharmacokinetics.....	14
2.2.3. Cutaneous Sensitization, Irritancy Potential and Tolerability	15
2.2.3.1. Skin Irritation Study.....	15
2.2.3.2. Local Tolerability in Sensitive Skin Areas	15
2.2.3.3. Sensitizing and Cumulative Irritation Potential	15
2.2.4. Clinical Overview	16
2.3. Benefit/Risk Assessment.....	18
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS	18
4. STUDY DESIGN.....	20
4.1. Overall Design.....	20
4.2. Scientific Rationale for Study Design	21
4.3. Justification for Dose	21
4.4. End of Study Definition	21
5. STUDY POPULATION.....	22
5.1. Inclusion Criteria.....	22
5.2. Exclusion Criteria.....	24
5.3. Lifestyle Considerations.....	25
5.3.1. Contraception.....	25
5.3.2. Other Lifestyle Requirements.....	26
5.4. Screen Failures	26

6. STUDY INTERVENTION.....	26
6.1. Study Intervention(s) Administered.....	27
6.1.1. Administration.....	27
6.2. Preparation/Handling/Storage/Accountability.....	29
6.2.1. Preparation and Dispensing.....	30
6.3. Measures to Minimize Bias: Randomization and Blinding.....	30
6.3.1. Allocation to Investigational Product.....	30
6.3.2. Breaking the Blind.....	31
6.4. Study Intervention Compliance.....	32
6.5. Concomitant Therapy.....	32
6.5.1. Medications Prohibited Prior to Baseline/Day 1.....	32
6.5.2. Medications Prohibited During the Study (Days 1-15).....	33
6.5.3. Medications Allowed During the Study.....	34
6.6. Dose Modification.....	35
6.7. Intervention After the End of the Study.....	35
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL.....	35
7.1. Discontinuation of Study Intervention.....	35
7.2. Participant Discontinuation/Withdrawal From the Study.....	36
7.3. Lost to Follow-up.....	37
8. STUDY ASSESSMENTS AND PROCEDURES.....	37
8.1. Efficacy Assessments.....	38
8.1.1. Lesion Investigator Static Global Assessment (Lesion ISGA).....	38
8.1.2. Lesion Total Sign Score (Lesion TSS).....	39
8.1.3. Pruritus assessments.....	39
8.1.4. %BSA with Atopic Dermatitis.....	41
8.1.5. Investigator Static Global Assessment (ISGA).....	42
8.1.6. Rater Qualifications.....	42
8.2. Safety Assessments.....	42
8.2.1. Physical Examinations.....	42
8.2.2. Vital Signs.....	42
8.2.3. Clinical Safety Laboratory Assessments.....	43

8.2.4. Pregnancy Testing	43
8.2.5. Photography.....	43
8.3. Adverse Events and Serious Adverse Events.....	43
8.3.1. Time Period and Frequency for Collecting AE and SAE Information.....	44
8.3.1.1. Reporting SAEs to Pfizer Safety	44
8.3.1.2. Recording Nonserious AEs and SAEs on the CRF	44
8.3.2. Method of Detecting AEs and SAEs	45
8.3.3. Follow-up of AEs and SAEs.....	45
8.3.4. Regulatory Reporting Requirements for SAEs.....	45
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure	46
8.3.5.1. Exposure During Pregnancy.....	46
8.3.5.2. Exposure During Breastfeeding	46
8.3.5.3. Occupational Exposure	46
8.3.6. Medication Errors	46
8.4. Treatment of Overdose.....	47
8.5. Pharmacokinetics	47
8.6. Pharmacodynamics.....	47
8.7. Genetics	47
8.8. Biomarkers	47
8.9. Health Economics	48
9. STATISTICAL CONSIDERATIONS	48
9.1. Estimands and Statistical Hypotheses	48
9.1.1. Estimands.....	48
9.2. Sample Size Determination.....	48
9.3. Populations for Analysis	49
9.4. Statistical Analyses	49
9.4.1. Efficacy Analyses	49
9.4.2. Safety Analyses	51
9.5. Interim Analyses	51
9.5.1. Data Monitoring Committee.....	51

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	52
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	52
10.1.1. Regulatory and Ethical Considerations	52
10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP	52
10.1.2. Informed Consent Process	53
10.1.3. Data Protection	54
10.1.4. Dissemination of Clinical Study Data	54
10.1.5. Data Quality Assurance	55
10.1.6. Source Documents	57
10.1.7. Study and Site Closure	57
10.1.8. Publication Policy	57
10.1.9. Sponsor’s Qualified Medical Personnel	58
10.2. Appendix 2: Clinical Laboratory Tests	59
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	60
10.3.1. Definition of AE	60
10.3.2. Definition of SAE	61
10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs	62
10.3.4. Reporting of SAEs	65
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	67
10.4.1. Female Participant Reproductive Inclusion Criteria	67
10.4.2. Woman of Childbearing Potential (WOCBP)	67
10.4.3. Contraception Methods	68
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	71
10.6. Appendix 6: Abbreviations	73
11. REFERENCES	76

LIST OF TABLES

Table 1.	Treatment Allocation for Intra-Participant Design	31
Table 2.	Investigator’s Static Global Assessment (ISGA)	38

Table 3. Lesion Total Sign Score (Lesion TSS)39
Table 4. Handprint Determination of Body Region Surface Area for Participants aged ≥ 8 years old41
Table 5. Handprint Determination of Body Region Surface Area for Participants aged < 8 years old42
Table 6. Protocol-Required Safety Laboratory Assessments59

LIST OF FIGURES

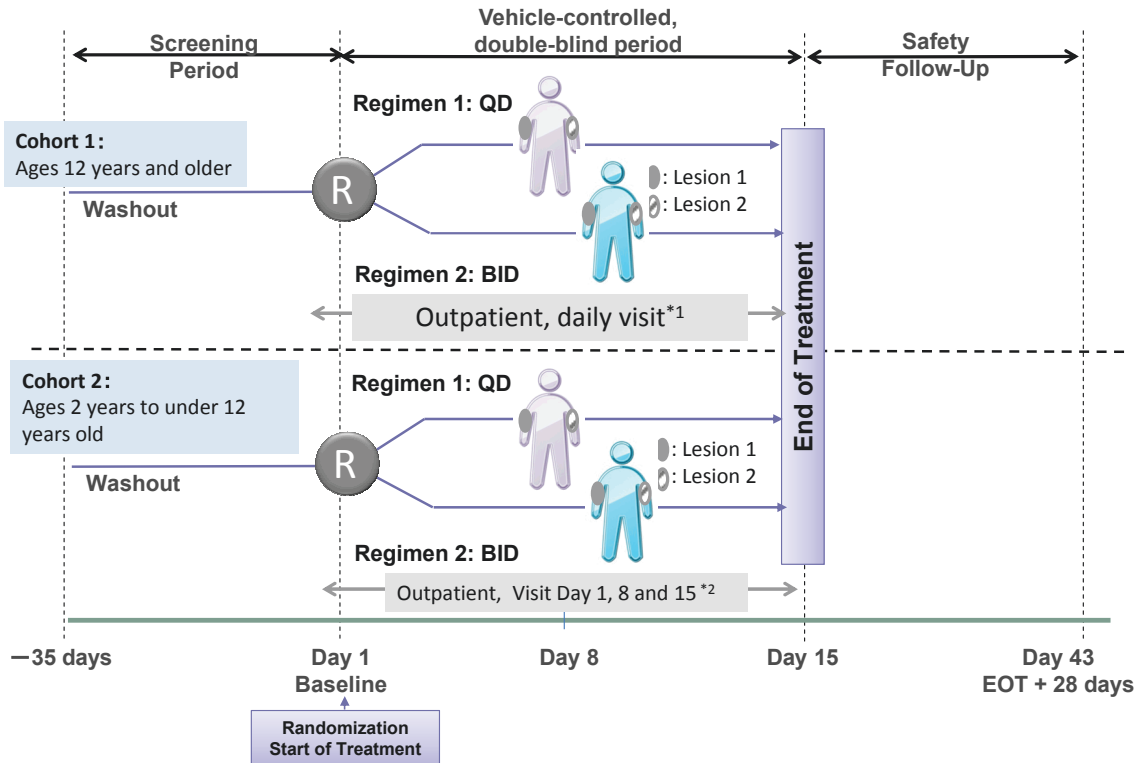
CCI [REDACTED] 40
CCI [REDACTED] 40
CCI [REDACTED] 41

1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable

1.2. Schema



BID: twice daily, QD: once daily

* 1 Visit study site and application by site staff

* 2 Investigational products will be applied by parent/caregiver with site staff check (directly or via live video chat, etc.) and/or by site staff (site staff will visit participant's home as needed).

1.3. Schedule of Activities (SoA)

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

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

Visit Identifier ^a	Day -35 to Day -1 Screening	Day 1 Baseline	Day 8	Day 15 End of Treatment/ Early Discontinuation ^b	Day 43 Follow-up ^c
Visit Window			±1 Day	±1 Day	+3 Days
Informed consent, including assent	X				
Medical history	X	X			
Vital signs ^d	X				
Physical examination	X			X	
Laboratory					
Hematology	X				
Blood chemistry	X ^e				
Urinalysis	X				
Pregnancy test ^f	X	X		X	
Contraception check ^g	X	X	X	X	X
Identify two target lesions		X			
Randomization		X			
Study treatment					
Cohort 1: Site staff applies the investigational products to the participant at the site. ^h		X	→	X ⁱ	
Cohort 2: Parent/caregiver and/or the site staff applies the investigational products to the participant. ^h		X	→	X ⁱ	
Dispense Investigational Products (Cohort 2)		X	X		
Collect Returned Investigational Products (Cohort 2)			X	X	
Weigh Investigational Products		X	X	X	
Compliance confirmation		X	→	X ^j	

Visit Identifier ^a	Day -35 to Day -1 Screening	Day 1 Baseline	Day 8	Day 15 End of Treatment/ Early Discontinuation ^b	Day 43 Follow-up ^c
Visit Window			±1 Day	±1 Day	+3 Days
Assessments					
%BSA for eligibility	X	X			
ISGA for eligibility	X	X			
Lesion ISGA for each target lesion		X	X	X	
Lesion TSS for each target lesion		X	X	X	
Pruritus assessments for each target lesion ^k Cohort 1: Peak Pruritus NRS (age ≥12) Cohort 2: Itch Severity Scale (age 6-11) Cohort 2: Observer Reported Itch Severity NRS (age 2-11)		X	→	X	
Photographs ^l		X	X	X	
Review Prior/Concomitant treatment(s)	X ^m	→	→	→	X
Serious and nonserious adverse event monitoring	X	→	→	→	→

Abbreviations: → = ongoing/continuous event; AD = atopic dermatitis; BID = twice daily; %BSA = percent of body surface area; FSH = follicle stimulating hormone; ISGA = Investigator’s Static Global Assessment; NRS = numerical rating scale; QD = once daily; TSS = Total Sign Score.

- a. Day relative to start of study treatment (Day 1).
- b. If a participant is discontinued, the efficacy evaluation at the timing of the early termination will be conducted as early as possible (the same day is preferable).
- c. Follow-up contact will be completed during 28 to 35 days from administration of the final dose of investigational products to capture any potential adverse events and to confirm appropriate contraception usage and concomitant treatments. Visit is planned to occur as a telephone contact.
- d. Temperature (tympanic or axillary), pulse rate, and blood pressure taken in the seated or supine position, after the participants have been sitting or lying calmly for a minimum of 5 minutes. Assessment of vital signs should precede blood draw for clinical laboratory tests.
- e. Serum FSH concentration will be determined for all females who are amenorrheic only for confirmation postmenopausal status.
- f. For females of childbearing potential only. Local urine testing will be standard for the protocol.
- g. For females of childbearing potential only. Confirm that contraception is used consistently and correctly.
- h. Cohort 1: From Day 1 to Day 15, participants will visit the site once or twice daily to apply investigational products by site staff. If it becomes difficult for the participant to visit the study site, the site staff will visit participant’s home and investigational products will be applied by site staff as a backup option upon sponsor’s agreement.
 Cohort 2: From Day 1 to Day 15, investigational products will be applied once or twice daily by parent/caregiver and/or site staff. When investigational products are applied by parent/caregiver, site staff will check the compliance directly or via live video chat. When investigational products will be applied by site staff, site staff will visit the participant’s home as needed.
- i. Regimen 1 (QD): Participant will be applied investigational products from Day 1 to Day 14.
 Regimen 2 (BID): When participant will be applied investigational products from AM in Day 1, the last administration will be PM in Day 14. When participant will be applied investigational products from PM in Day 1, the last administration will be AM in Day 15.
- j. Compliance will be confirmed by parent/caregiver and/or the site staff confirmation.
- k. Pruritus assessment will be completed by participants who are ≥6 years old and by observers [parents/caregivers] for the participants (age 2-11) when applicable, once daily from Day 1 to Day 15 before investigational products application preferably at the same time of each day if applicable.
- l. Photographs of target lesions will be obtained. Photographs will be taken by local standard procedures.

Visit Identifier^a	Day -35 to Day -1 Screening	Day 1 Baseline	Day 8	Day 15 End of Treatment/ Early Discontinuation^b	Day 43 Follow-up^c
Visit Window			±1 Day	±1 Day	+3 Days

m. Record all treatments (including medications and non-medication therapies) used for AD 90 days prior to screening and all other medications (including bland [non-medicated] emollients, over the counter drugs, vitamins, and antacids) used within 30 days prior to Screening.



2. INTRODUCTION

Crisaborole, also referred to as PF-06930164 or AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that penetrates into the skin to the sites of inflammation and is currently being investigated for topical treatment in patients with mild to moderate atopic dermatitis (AD). 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 AD.

2.1. Study Rationale

Confirmatory evidence of efficacy and safety was provided by two well-controlled Phase 3 studies conducted in the US in AD patients 2 years of age and older. Long-term safety was evaluated in an open label study that enrolled participants from the Phase 3 studies. Based on the outcome of these studies, crisaborole ointment 2% was approved and is on US and Canada market under the tradename of EUCRISA (crisaborole) ointment, 2% twice daily (BID) indicated for topical treatment of mild to moderate AD in patients 2 years of age and older.

In Japan, phase 1 study (C3291029) was conducted and safety and tolerability crisaborole ointment 2% BID has been shown in Japanese participants. Based on this study results, it is considered that similar pharmacokinetics (PK) profile and systemic exposure were shown between Japanese and Non-Japanese participants.

In this study, two regimens of crisaborole ointment 2%, BID and once daily (QD), will be compared relative to corresponding vehicle. In addition, a descriptive comparison between crisaborole BID and crisaborole QD will be conducted to select the dose regimen for next clinical phase in each age group; adults/adolescents (12 years or older) and pediatrics (2 years to under 12 years) in Japanese AD patients.

2.2. 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 distinctive inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.^{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, lichenification and bacterial colonization.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.^{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.

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 ointment BID in the two Phase 3 registration studies (Study AN2728-AD-301 and Study AN2728-AD-302) 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 (AEs) being mild and deemed unlikely or not related to investigational product.

2.2.1. Nonclinical Safety Studies

Crisaborole demonstrates inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration (EC₅₀) 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.

Based on the nonclinical safety studies conducted to date, crisaborole ointment 2% has an acceptable safety profile. Refer to the investigator's brochure (IB) for further information on the nonclinical experience with crisaborole ointment 2%.

2.2.2. Pharmacokinetics

A total of 11 clinical pharmacology studies were conducted in healthy volunteers or in participants with AD or psoriasis. The clinical pharmacology studies demonstrated 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.

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 participants 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 [%BSA] 48.7%; range 27%-92%), absorption across the skin was rapid, with a median of time to reach maximum observed plasma 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 maximum observed plasma 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 (AUC_{12}).

In the 8-days, safety, tolerability and PK study (Cohort 2 in Study C3291029), 10 adult Japanese participants with mild to moderate AD (20-55 years old) received crisaborole ointment 2% (mean treatable %BSA 63.9%; range 35%-87%), absorption across the skin was rapid, with a median of time to reach T_{max} of 3.0 hours on both Day 1 and Day 8. Mean C_{max} values in plasma were 199 ng/mL on Day 1, and 185 ng/mL on Day 8, respectively. Overall, the extent of systemic exposure (plasma C_{max} and AUC) of crisaborole, AN7602, and

AN8323 increased with higher %BSA treated. Minimal plasma accumulation of crisaborole and AN7602 was observed at steady state whereas AN8323 displayed an approximately 3-fold accumulation based on C_{max} and AUC_{12} . Steady state was achieved by Day 7 for crisaborole and its metabolites.

The %BSA normalized systemic exposure of crisaborole, AN7602, and AN8323 (C_{max} and AUC_{12}) were similar between C3291029 study and AD-102 study.

2.2.3. Cutaneous Sensitization, Irritancy Potential and Tolerability

2.2.3.1. Skin Irritation Study

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

2.2.3.2. Local Tolerability in Sensitive Skin Areas

In a study of healthy participants (16 men and 16 women) who applied crisaborole ointment 2% or vehicle for 21 days to sensitive area application sites (including extensor areas, intertriginous areas, genitals, and face/hairline), 99% of assessments of local tolerability were graded as 0 (none), 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 participants who received crisaborole ointment 2% or vehicle. Overall, crisaborole ointment 2% was well tolerated over 21 days of dosing in sensitive skin areas of healthy participants.

2.2.3.3. Sensitizing and Cumulative Irritation Potential

In a repeat-insult patch test (RIPT) and cumulative irritation study in healthy participants (Study AN2728-RIPT-101), the potential for inducing cutaneous sensitization was assessed in 238 participants randomized in Cohort 1. None of the participants demonstrated cutaneous evidence of sensitization potential (a reaction of at least Grade 4 [definite edema] or a pattern suggestive of contact sensitization in the opinion of the Investigator) to the investigational products, crisaborole ointment 2% or vehicle. The potential for causing cutaneous irritation was evaluated among 40 participants randomized in Cohort 2 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).

2.2.4. Clinical Overview

Eight (8) clinical trials of topical formulations of crisaborole have been completed to date in participants with AD. Key study information is summarized below.

- In a 4-week, multi-center, 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% BID, participants had overall blood levels of crisaborole that were low and similar to those previously observed in adults psoriasis participants (Study AN2728-PSR-106) after adjusting for %BSA treated.

A total of 63 AEs were reported in 23/34 participants (67.6%): 40 were mild, 20 were moderate, and 3 were severe. No treatment emergent adverse event (TEAE) was considered serious, and no death 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 participant 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 participant 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 participant 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, single arm, 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) participants. 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 participants. No other TEAE was reported by more than 1 participant. 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 participants 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 difference in response rates compared to vehicle were similar at Day 14 and Day 42 (end of treatment).

- In a 4-week bilateral comparison trial of 86 adolescent participants 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 BID was more efficacious than either concentration applied QD. BID shows greater improvement from baseline than QD group at each visit (Day 8, Day 15, Day 22 and Day 29).
- In two Phase 3, multi-center, randomized, double-blind, vehicle controlled studies in participants ≥ 2 years 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, multi-center, 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.
- Phase 1, single center, randomized, vehicle-controlled, parallel cohort study of crisaborole ointment 2% conducted in 2 cohorts evaluating the skin irritation potential in adult Japanese healthy participants in Cohort 1, and safety, tolerability and PK in adult Japanese participants with mild to moderate AD in Cohort 2 (Study C3291029). In Cohort 1, there were no TEAEs. In Cohort 2, a total of 9 participants in the crisaborole ointment 2% group and 2 participants in the vehicle group experienced a TEAE. All AEs were mild in severity in the crisaborole ointment, 2% group and mild or moderate in severity in the vehicle group. Two participants discontinued due to a TEAE (crisaborole ointment, 2% group: one application site pain, vehicle treatment group: one dermatitis atopic aggravated). No serious TEAEs or severe TEAEs were reported in either treatment group. Overall, there were no clinically significant changes for laboratory values, vital signs or Electrocardiogram (ECG).
Based on these results, crisaborole ointment 2% BID was found to be well tolerated in Japanese participants with mild to moderate AD.

Crisaborole has been well tolerated across completed clinical studies. No clinically important safety signals have been identified, including during a Phase 3 multi-center, 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 where were mild to moderate.

In a thorough QT (TQT) study (Study AN2728TQT108) in which healthy participants were treated with crisaborole ointment 2% at a therapeutic dose (15 g, representing 30%BSA treatment) or a suprathereapeutic 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 suprathereapeutic dose groups, respectively, at Day 9. At both therapeutic and suprathereapeutic doses had no effect on cardiac repolarization based on results from the primary assessment and the pharmacokinetic (PK)-pharmacodynamic (PD) analysis.

2.3. Benefit/Risk Assessment

The benefit/risk balance of crisaborole ointment 2% application in this study is considered favorable and supported by the following:

- The expected efficacy of crisaborole ointment 2% for the treatment of AD based on the results of clinical studies conducted to date.
- The expected limited crisaborole systemic exposure when applied topically based on the results of clinical studies conducted with crisaborole ointment 2% to date.
- The satisfactory safety and local tolerability demonstrated in non-clinical and clinical studies conducted with crisaborole ointment 2% to date.

The benefit will be limited due to this study design which is an intra-participant design to evaluate each target lesion treated with crisaborole or vehicle. Based on the favorable clinical safety profile as well as the limited systemic exposure of crisaborole, the risk to participants treated with crisaborole is deemed to be minimal.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of crisaborole may be found in the IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary:	Primary:	Primary:
<ul style="list-style-type: none"> • To compare the efficacy of crisaborole ointment 2%, administered QD or BID relative to the corresponding vehicle (QD or BID), on Total Sign Score (TSS) assessment in target lesions, in the treatment of mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2). 	<ul style="list-style-type: none"> • Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (regimen 1: QD, regimen 2: BID) for each cohort. 	<p>This estimand is the hypothetical estimand, which estimates the effect as if all participants maintain their randomized treatment.</p> <ul style="list-style-type: none"> • Population: Participants with mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2) as defined by the inclusion and exclusion criteria and are randomized and received at least one of the investigational products;

Objectives	Endpoints	Estimands
		<ul style="list-style-type: none"> • Intercurrent event: All efficacy data after discontinuation of treatment will not be considered; • Population-level summary: Least-square means of intra-participant difference between crisaborole ointment 2% vs corresponding vehicle in each regimen for each cohort and pooled cohort.
Secondary:	Secondary:	Secondary:
<ul style="list-style-type: none"> • To evaluate the efficacy of crisaborole ointment 2% BID relative to crisaborole ointment 2% QD, on TSS assessment in target lesions, in the treatment of mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2). 	<ul style="list-style-type: none"> • Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort. 	<p>This estimand is the hypothetical estimand, which estimates the effect as if all participants maintain their randomized treatment.</p> <ul style="list-style-type: none"> • Population: Participants with mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2) as defined by the inclusion and exclusion criteria and are randomized and received at least one of the investigational products; • Intercurrent event: All efficacy data after discontinuation of treatment will not be considered; • Population-level summary: Difference in least square means between crisaborole ointment 2% BID and crisaborole ointment 2% QD for each cohort and pooled cohort.
<ul style="list-style-type: none"> • To evaluate the efficacy of crisaborole ointment 2%, administered QD or BID, on TSS, ISGA and Pruritus assessments in target lesions, in the treatment of mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2). 	<ul style="list-style-type: none"> • Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 8 in each regimen for each cohort. • Change from baseline in ISGA in target lesions treated with crisaborole ointment or vehicle at each visit up to Day 15 in each regimen for each cohort. • Change from baseline in pruritus assessments in target lesions treated with crisaborole ointment or 	<ul style="list-style-type: none"> • The other secondary efficacy endpoints will be analyzed using the estimands described above.

Objectives	Endpoints	Estimands
	vehicle at each day up to Day 15 in each regimen using following scales; Cohort 1: Peak Pruritus numerical rating scale (NRS) (age ≥12) Cohort 2: Itch Severity Scale (age 6-11) Cohort 2: Observer Reported Itch Severity NRS (age 2-11).	
<ul style="list-style-type: none"> To assess the safety and local tolerability of crisaborole ointment 2%, administered QD or BID, in the treatment of mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2) 	<ul style="list-style-type: none"> Incidence of TEAEs and SAEs in each regimen for each cohort. 	<ul style="list-style-type: none"> There is no defined estimand for these endpoints and they will be analyzed descriptively.
CCI [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, multi-center, randomized, double-blind, vehicle-controlled, intra-participant study to evaluate efficacy and safety of two regimens of crisaborole ointment 2% in Japanese pediatric and adult participants (cohort 1: 12 years and older, cohort 2: 2 to under 12 years old) with mild to moderate AD. After completing screening activities, including meeting eligibility criteria, two target lesions with same severity will be determined by the investigator, participants will be randomized to one of the regimens, QD or BID (randomization ratio; 1:1), and crisaborole ointment 2% or vehicle will be randomly assigned to each target lesion at Baseline/Day 1. Both target lesions are to be treated at the same assigned dosing regimen and dosing regimen is unblinded information to sponsor, investigators/study sites and participants. Participants will be treated with investigational products administered for 2 weeks and followed-up 28 days after the end of treatment.

Cohort	Regimen	Investigational Products	N	Study Treatment
Cohort 1 ^a	Regimen 1	Crisaborole ointment 2% QD vs Vehicle QD	20	Participants will visit the site <u>once</u> daily to be administered investigational products by site staff.
	Regimen 2	Crisaborole ointment 2% BID vs Vehicle BID	20	Participants will visit the site <u>twice</u> daily to be administered investigational products by site staff.
Cohort 2 ^b	Regimen 1	Crisaborole ointment 2% QD vs Vehicle QD	20	Investigational products will be applied <u>once</u> daily by parent/caregiver (site staff will confirm the compliance directly or via live video chat), or by site staff (site staff will visit the participant's home as needed).
	Regimen 2	Crisaborole ointment 2% BID vs Vehicle BID	20	Investigational products will be applied <u>twice</u> daily by parent/caregiver (site staff will confirm the compliance directly or via live video chat), or by site staff (site staff will visit the participant's home as needed).

BID: twice daily, N: number of participants, QD: once daily

a. ages 12 years and older

b. ages 2 years to under 12 years old

4.2. Scientific Rationale for Study Design

Not Applicable for this study.

4.3. Justification for Dose

In this study, in each of the two cohorts, the investigational products are applied by one of the following two usage methods;

Regimen 1: Apply Crisaborole ointment 2% or vehicle once daily for each target lesion

Regimen 2: Apply Crisaborole ointment 2% or vehicle twice a day to each target lesion

Crisaborole ointment 2% BID is selected as the highest well-tolerated dose to maximize the potential for efficacy with minimal safety risk based on the results of foreign clinical studies, and 2% was technically the maximum dose for commercial ointment formulation, therefore 2% is selected for dosage of this study. In Study C3291029, the safety and tolerability in Japanese patients with AD were confirmed and similar PK profile and systemic exposure shown between Japanese and non-Japanese participants. In this study, two regimens of crisaborole ointment 2%, BID and QD, will be compared relative to corresponding vehicle. In addition, a descriptive comparison between crisaborole BID and crisaborole QD will be conducted to select the dose regimen for next clinical phase in each age group; adults/adolescents (12 year or older) and pediatrics (2 years to under 12 years) in Japanese AD participants.

4.4. End of Study Definition

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

The end of the study is defined as the date of the last scheduled procedures shown in the schedule of activities for the last participant in the trial globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ages;
Cohort 1: 12 years and older at the time of consent.
Cohort 2: 2 years to under 12 years old at the time of consent.
 - Refer to Appendix 4 (Section 10.4.1) for reproductive criteria for female participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Participants who have confirmed clinical diagnosis of active AD at screening and Baseline/Day 1 according to Hanifin and Rajka criteria and who have at least 6 month history prior to Screening visit and that has been clinically stable for more than 1 month.
4. Participants who have a global ISGA of 2 (mild) or 3 (moderate) at Baseline/Day 1 visit.
5. Participants who have AD lesions on upper limbs, lower limbs or ventral of the body trunk and a body surface area (BSA) covered with AD of at least 1.0% and no more than 30% at Baseline/Day 1, excluding scalp, genitals and groin area. The presence of AD on these areas (scalp, genitals and groin area) is not exclusionary, but will not be included in the calculation for coverage of BSA with AD.
6. Participants who have two lesions of AD at least 3 cm x 3 cm with identical Lesion ISGA = 3 (moderate) for each lesion. These AD lesions must be at least 10 cm apart.

The target lesions must not be on the face, neck, scalp, axilla, genitals, groin area, palms, dorsal of the hands, dorsal of the body trunk and soles. In addition, two AD areas on the same limb must not be selected as the Target Lesions. [Note: When possible, AD areas on the bilateral (left/right) area should have been selected as target lesions].

- Cohort 2: If 0.5%BSA is smaller than 3 cm x 3 cm, 0.5%BSA is acceptable for each of the two AD lesions with identical Lesion ISGA = 3 (moderate) for each lesion.
7. Participants who received any of the following AD treatment regimens are eligible if the following minimum washout criteria are observed:

At least 12 Weeks or 5 half-lives (whichever is longer) prior to Baseline/Day 1:

- Biological drugs.

At least 28 days prior to Baseline/Day 1:

- Systemic (oral/injectable) corticosteroids (Note: use of intranasal/inhaled or ophthalmic corticosteroids for stable medical conditions are allowed);
- Systemic immunosuppressive agents (eg, calcineurin inhibitors, cyclosporine);
- Sunbathing, tanning bed use, or phototherapy (eg, narrow band ultraviolet B [NbUVB], psoralen plus ultraviolet A [PUVA]).

At least 14 days prior to Baseline/Day 1:

- Systemic antimicrobials;
- Topical corticosteroids (all potencies) and topical calcineurin inhibitors.

At least 7 days prior to Baseline/Day 1:

- Topical antimicrobials;
- Use of antibacterial soaps (for bathing), bleach bath, bath oil, or topical sodium hypochlorite-based products;
- Topical antihistamines;
- Systemic sedating antihistamines (eg, hydroxyzine, diphenhydramine or other sedating antihistamines);

- Systemic and topical traditional Chinese medicine/herbal preparation that might alter the course of AD.

At least 8 hours prior to 1st dose of investigational products on Baseline/Day 1:

- Use of emollients and moisturizers.

Weight:

Not applicable for this study.

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. 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 participant inappropriate for entry into this study.
2. History of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of crisaborole ointment 2%.
3. Participants had previous treatment with any topical or systemic PDE-4 inhibitor.
4. Participants who have undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma or carcinoma in situ of the skin, curatively treated with surgical excision only).

Prior/Concomitant Therapy:

5. Participants who are receiving any of the following drugs and have to wash out to participate in this study:
 - Biological drugs;

- Systemic (oral/injectable) corticosteroids (Note: use of intranasal/inhaled or ophthalmic corticosteroids for stable medical conditions are allowed);
 - Systemic immunosuppressive agents (eg, calcineurin inhibitors, cyclosporine);
 - Phototherapy (eg, NbUVB, PUVA).
6. Participants who require treatment with prohibited concomitant medication(s)

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational product within 30 days or 5 half-lives preceding the first dose of investigational products used in this study (whichever is longer).
8. Participants who have participated in a clinical study of crisaborole.

Diagnostic Assessments:

Not applicable for this study.

Other Exclusions:

9. Participants are not willing to minimize or avoid natural and artificial sunlight exposure during the study.
10. 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 Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.3.2. Other Lifestyle Requirements

- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the participation.
- Participants should refrain from swimming, bathing, sauna or washing the treated areas for at least 4 hours after application.
- Use of sunscreen is permitted, but only on other areas than target lesions.
- The participants and/or parents/caregivers should avoid wiping the investigational products off the skin. In the case of any investigational product inadvertently being wiped off, it should not be reapplied to wiped areas until the next scheduled dose.
- When applying investigational products, the parent/caregiver will not be required to wear gloves when applying investigational products. However, they must be instructed to wash their hands with mild soap and water before and after each application of each investigational product.
- Participants will be instructed to be dressed in loose-fitting clothing and avoid occluding the treated areas (with dry wraps, for example). Wet wraps are not permitted.
- Parent/caregiver should be encouraged not to put hands in the mouth to avoid ingestion of investigational products. The parent/caregiver should be instructed for participants who are young children to avoid licking the application site of the investigational product.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number.

6. STUDY INTERVENTION

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




For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.


6.1. Study Intervention(s) Administered

Intervention Name	Crisaborole (PF-06930164)	Vehicle
Type	Drug	Drug
Dose Formulation	Ointment	Ointment
Unit Dose Strength(s)	20 mg of crisaborole per gram (2%)	—
Dosage Level(s)	Application of a thin layer of crisaborole once or twice daily to affected areas.	Application of a thin layer of vehicle once or twice daily to affected areas.
Route of Administration	Topical	Topical
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Crisaborole ointment 2% and vehicle will be provided in 60 g tubes by Pfizer. The tubes will be labeled according to local regulatory requirements. For details, please refer to investigational product manual (IP manual).	
Packaging and Labeling	Both crisaborole ointment 2% and vehicle for this study are packaged into a carton and are labeled in a way that is consistent with the study design and with the regulatory requirements for Japan in which the study is to be performed. For details, please refer to IP manual.	

6.1.1. Administration

At Baseline/Day 1, the participants who meet Inclusion/Exclusion Criteria will be randomized to one of the regimens, QD or BID, and for each of two target lesion (Lesion 1 and Lesion 2) meeting the inclusion criteria identified by the investigator, the investigational products (crisaborole ointment 2% or vehicle) will be assigned randomly. The sponsor, investigators/study sites and participants will be blinded with respect to which lesion is receiving the crisaborole ointment 2% or vehicle.

	Regimen 1 (QD)	Regimen 2 (BID)
Morning		
Evening	NA	



● Lesion 1
 ▨ Lesion 2

BID: twice daily, NA: not applicable, QD: once daily

In case of Regimen 1 (QD), once daily in the evening throughout the treatment period is acceptable as like as once daily in the morning throughout the treatment period.

For cohort 1, the participants will visit the site at every dosing timing [Regimen 1(QD): once daily in the morning or evening, Regimen 2 (BID): twice daily in the morning and evening] and the investigational products will be applied by the site staff. It may allow that the site staff applies the investigational products at the participant’s home as a backup option upon sponsor’s agreement when the participant is not able to visit the site. For Regimen 2 (BID), dosing interval should be 12±4 hours.

For cohort 2, the parent/caregiver and/or the site staff will apply the investigational products. When the parent/caregiver applies, it will be done with confirmation of the appropriate application by the site staff (directly or via live video chat). When site staff applies, site staff will visit the participant’s home as needed. For Regimen 2 (BID), dosing interval should be 12 ±4 hours.

For regimen 1 (QD), participant will be applied investigational products from Day 1 to Day 14. For regimen 2 (BID), when participant will be applied investigational products from AM in Day 1, the last administration will be PM in Day 14. When participant will be applied investigational products from PM in Day 1, the last administration will be AM in Day 15.

In order to better standardize the amount of investigational products applied to the target lesions, the Principal Investigator (PI) will measure the size of each target lesion at Baseline/Day 1 and determine the amount of medication to be applied by using finger-tip unit. The area of the lesion will be determined using the “handprint method”, wherein the area represented by the participant’s outstretched hand (including all five digits adducted together) equals approximately 1% of the participant’s BSA.¹⁵ Parent/caregiver for cohort 2

will receive verbal and written instructions on how much study medication to apply to treatment areas and how the investigational products should be applied. New investigational product tubes will be dispensed at Baseline/Day 1 and Day 8 for parents/caregivers of cohort 2. Parents/caregivers for cohort 2 will be instructed to return the investigational product tubes at Day 8 and Day 15.

Participants should be instructed to wait at least 15 minutes after bathing/showering allowing the skin to dry thoroughly prior to applying medication. Participants should not shower or wash off study medication within 4 hours after application. Crisaborole ointment 2% is for external use on the skin only. Contact with mucous membranes (ie, inside of nostrils, mouth, vagina, urethra, and rectum), and in the eyes should be avoided. Participants should avoid ingestion of investigational products.

The lesion size and prescribed amount of investigational products will be recorded in the source documentation and marked on the dosing instruction document for the parents/caregivers.

The investigational products will be applied only to Lesion 1 and Lesion 2, and not applied to other AD affected areas.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using investigational products accountability form/record.

New investigational product tubes will be dispensed at Baseline/Day 1 and Day 8 for parents/caregivers of cohort 2. Parents/caregivers for cohort 2 will be instructed to return the investigational product tubes at Day 8 and Day 15.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.
6. Study interventions should be stored in their original containers and in accordance with the labels.
7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
9. The sponsor or designee will provide guidance on the destruction of unused study intervention (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.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The investigational products will be dispensed using an interactive response technology (IRT) (interactive Web-based response [IWR]) drug management system at visit on Day 1 and Day 8. A qualified staff member will dispense the investigational products via unique container numbers in the tubes provided, in quantities appropriate for the study visit schedule. For cohort 2, the parent/caregiver should be instructed to maintain and return the tubes to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

At Baseline/Day 1, participants will be randomized to 1 of 4 treatment arms for each cohort as shown in [Table 1](#).

Table 1. Treatment Allocation for Intra-Participant Design

Treatment Arm	Cohort ^a	Dosing Regimen	Investigational Product: Lesion 1 ^b	Investigational Product: Lesion 2 ^b	Target Number of Participants to be Randomized
1	1	QD	Crisaborole ointment 2%	vehicle	10
2	1	QD	vehicle	Crisaborole ointment 2%	10
3	1	BID	Crisaborole ointment 2%	vehicle	10
4	1	BID	vehicle	Crisaborole ointment 2%	10
5	2	QD	Crisaborole ointment 2%	vehicle	10
6	2	QD	vehicle	Crisaborole ointment 2%	10
7	2	BID	Crisaborole ointment 2%	vehicle	10
8	2	BID	vehicle	Crisaborole ointment 2%	10

- a. Cohort 1: Ages 12 years and older, Cohort 2: Ages 2 years to under 12 years old.
 b. First, Lesion 1 and 2 will be determined by the investigator at Baseline/Day 1. Then, participants are randomly assigned to one of the treatment arms.

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user’s identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, dosing regimen, and dispensable unit (DU) or container number when investigational products are being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, dosing regimen, and DU or container number assigned. The confirmation report must be stored in the site’s files.

Investigational products will be dispensed at the study visits summarized in the SoA.

Returned investigational products must not be redispensed to the participants.

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

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant’s treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant’s treatment assignment unless this could delay further management of the participant. If a participant’s treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

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

6.4. Study Intervention Compliance

Participant compliance with investigational products will be assessed throughout the treatment period. Compliance will be confirmed by parent/caregiver and/or the site staff. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF. Missing one or more dose will be reported as deviation.

6.5. Concomitant Therapy

All prior medications, including all medications and non-medication therapies used for AD within 90 days prior to Screening and all other treatments, including bland (non-medicated) emollients, over the counter drugs, vitamins, and antacids, used within 30 days prior to Screening will be recorded at the screening visit. Any changes in concomitant medications or dosage will be recorded at Baseline/Day 1 and at each subsequent visit. 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 participant's medical history or to an AE, except for vitamins/nutritional supplements and routine immunizations.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

6.5.1. Medications Prohibited Prior to Baseline/Day 1

Classes of medications and non-medication therapies that may alter the course of AD and for which washout is required prior to Baseline/Day 1 are listed below. If a participant requires a washout, the investigator or his/her designee will provide instructions on discontinuing the prohibited medication(s) or non-medication therapy(ies) at the Screening Visit.

Medications prohibited 12 weeks or 5 half-lives (whichever is longer) prior to Baseline/Day 1

- Biological drugs.

Medications prohibited 28 days prior to Baseline/Day 1

- Use of systemic (oral, injectable) corticosteroids.

Note: Please see Section 6.5.3 for stable use (regular regimen) of intranasal/inhaled/ophthalmic corticosteroids.

- Use of systemic immunosuppressive agents (eg, calcineurin inhibitors, cyclosporine).
- Use of sunbathing, tanning bed use, or phototherapy (eg. NbUVB, PUVA).

Medications prohibited 14 days prior to Baseline/Day 1

- Use of systemic antimicrobials.

- Use of topical corticosteroids (all potencies) and topical calcineurin inhibitors, anywhere on the body.

Note: Please see Section 6.5.3 for use of topical corticosteroids (all potencies) and topical calcineurin inhibitors during study.

Medications prohibited 7 days prior to Baseline/Day 1

- Topical antimicrobials.
- Use of antibacterial soaps (for bathing), bleach bath, bath oil, or topical sodium hypochlorite-based products anywhere on the body.
- Use of topical antihistamines anywhere on the body.
- Systemic sedating antihistamines (eg, hydroxyzine or diphenhydramine or other sedating antihistamines).
- Systemic and topical traditional Chinese medicine/herbal preparation that might alter the course of AD.

Medications prohibited 8 hours prior to 1st dose of investigational products on Baseline/Day 1

- Use of emollients and moisturizers on AD lesions.

Note: Please see Section 6.5.3 for use of emollients during study

6.5.2. Medications Prohibited During the Study (Days 1-15)

Classes of medications and non-medication therapies that may alter the course of AD and that are prohibited during the study [from Baseline/Day 1 through the end of treatment/Day 15 (until the completion of study procedures/assessments)] are listed below.

- Use of systemic (oral, injectable) corticosteroids.

Note: Please see Section 6.5.3 for stable use (regular regimen) of intranasal/inhaled/ophthalmic corticosteroids.

- Use of topical corticosteroids, or topical calcineurin inhibitors on target AD lesions.
- Use of systemic immunosuppressive agents, including (eg, calcineurin inhibitors, cyclosporine).
- Escalating, decreasing, or pro re nata (PRN) use of topical retinoids or benzoyl peroxide (BPO) on target AD lesions.

Note: Please see Section 6.5.3 for stable use (regular regimen) of topical retinoid and/or BPO during study.

- Use of systemic sedating antihistamines (eg, hydroxyzine or diphenhydramine or other sedating antihistamines).
- Use of systemic non-sedating antihistamines in a nonstable (eg, escalating, decreasing, or PRN) regimen.

Note: Please see Section 6.5.3 for stable use (regular regimen) of systemic non-sedating antihistamines during study.

- Use of systemic or topical traditional Chinese medicine/herbal preparation that might alter the course of AD.
- Use of systemic antimicrobials.

Note: Please see Section 6.5.3 for stable use (regular regimen) of Short courses of systemic antimicrobials during study.

- Use of topical antimicrobials on target AD lesions.
- Use of antibacterial soaps (for bathing), bleach baths, bath oil or topical sodium hypochlorite-based products anywhere on the body.
- Use of sunbathing, tanning bed use, or phototherapy (eg. NbUVB, PUVA) on target AD lesions.
- Use of topical antihistamines on target AD lesions.
- Participation in another drug or device research study.

6.5.3. Medications Allowed During the Study

Classes of medications that are allowed during the study (from Baseline/Day 1 through the end of treatment visit on Day 15) are summarized below.

- After investigator selected two target AD lesions at Baseline/Day 1, topical corticosteroids and topical calcineurin inhibitors can be used per product label at least 10 cm away from the selected target AD lesions throughout the remainder of the study.
- After investigator selected two target AD lesions at Baseline/Day 1, emollients and moisturizer can be used at least 10 cm of away from the selected target AD lesions throughout the remainder of the study.

- After investigator selected two target AD lesions at Baseline/Day 1, topical antimicrobials can be used at least 10 cm of away from the selected target AD lesions throughout the remainder of the study.
- Participants on a stable regimen of inhaled, intranasal, or ocular corticosteroids, with ≥ 14 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study.
- Short courses of systemic antimicrobials may be given during the course of the study, if clinically necessary for the treatment of new onset infections.
- Participants on a stable non-sedating systemic antihistamine regimen, with ≥ 14 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study.
- Participants on a stable topical retinoid and/or BPO regimen, with ≥ 14 days of consistent use prior to Baseline/Day 1, are permitted to continue (not on target AD lesions) but must not alter or stop their regimen during the study.
- Nonsteroidal anti-inflammatory drugs are allowed throughout the study.
- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the participation in study.
- Oral or intrauterine hormonal methods of contraception are permitted during the study, for female participants of childbearing potential.
- Concomitant medications for other chronic medical conditions are permitted during the study unless the medication/therapy is specifically prohibited by the protocol.

6.6. Dose Modification

Not applicable for this study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue investigational products. If investigational products are permanently discontinued, the participant will not remain in the study except to complete the early discontinuation procedures.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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

The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

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

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will not remain in the study except to complete the early termination procedures and follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational products or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured,

publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

The total blood sampling volume for individual participants in this study is approximately 15 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments upon investigator decision provided the total volume taken during the study does not exceed 50 mL during this study.

8.1. Efficacy Assessments

8.1.1. Lesion Investigator Static Global Assessment (Lesion ISGA)

The clinical evaluator of AD will perform an assessment of each target lesion severity of AD and assign a lesion ISGA score and category. For lesion ISGA assessment, refer to ISGA score and category as described in Table 2. The assessment will be a static evaluation without regard to the score at a previous visit.

For eligibility, please note that lesion ISGA at Baseline/Day 1 should be 3 (moderate) whereas ISGA can be 2 (mild) or 3 (moderate).

Table 2. Investigator's Static Global Assessment (ISGA)

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

8.1.2. Lesion Total Sign Score (Lesion TSS)

The Lesion TSS is an assessment of the severity of each of the following: erythema, induration/papulation, excoriation, and lichenification. Each of these is rated using the 4-point severity scale described in Table 3. These ratings are then added to create a total score (13-point scale; ranging from 0 to 12 points).

Table 3. Lesion Total Sign Score (Lesion TSS)

Signs of Atopic Dermatitis

Erythema (Redness)		
Score	Grade	Description
0	None	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
Induration/Papulation		
Score	Grade	Description
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Excoriation (Evidence of Scratching)		
Score	Grade	Description
0	None	No evidence of excoriation
1	Mild	Mild excoriation present
2	Moderate	Definite excoriation present
3	Severe	Marked, deep, or extensive excoriation present
Lichenification (Epidermal Thickening)		
Score	Grade	Description
0	None	No epidermal thickening
1	Mild	Minor epidermal thickening
2	Moderate	Moderate epidermal thickening; accentuated skin lines
3	Severe	Severe epidermal thickening; deeply accentuated skin lines

8.1.3. Pruritus assessments

The severity of itch (pruritus) due to AD at the target lesion will be assessed using the peak pruritus Numerical Rating Scale (NRS), an 11-category numeric rating scale from 0 to 10,¹⁶ which is participant (12 years and older) reported. A five-category pruritus assessment has been developed for participants ≥ 6 and < 12 years of age referred to as the Itch Severity Scale.

The Observer Reported Itch Severity NRS will be completed by a parent/caregiver for participants <12 years old. It is preferred that all observer reported outcomes for a given participant are completed by same individual throughout the study.

The pruritus assessment (participant and observer) will be completed once daily every day from Day 1 to Day 15 before investigational products are applied preferably at the same time of each day, as noted in the [Schedule of Activities \(SoA\)](#).

CCI

A large black rectangular redaction box covers the majority of the page content below the text. The letters "CCI" are visible in red at the top left corner of this redacted area.

CCI

A large black rectangular redaction box covers the majority of the page content below the text. The letters "CCI" are visible in red at the top left corner of this redacted area.

CCI

8.1.4. %BSA with Atopic Dermatitis

The overall BSA affected by AD will be evaluated (from 0% to 100%) to verify each participant's eligibility at the screening and Baseline/Day 1 visits. The Investigator may use the "handprint method" by which the area represented by the palmar (ie, outstretched) surface of the participant's hand with all five digits adducted together is approximately 1% of the participant's BSA.

The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with AD (Table 4 and Table 5).

Table 4. Handprint Determination of Body Region Surface Area for Participants aged ≥ 8 years old

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

* The numbers of handprints are for the entire body region; no adjustment for body regions excluded for assessment.

Table 5. Handprint Determination of Body Region Surface Area for Participants aged < 8 years old

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint
Head and Neck	20	5%
Upper Limbs	20	5%
Trunk (including axillae)	30	3.33%
Lower Limbs (including buttocks)	30	3.33%

* The numbers of handprints are for the entire body region; no adjustment for body regions excluded for assessment .

8.1.5. Investigator Static Global Assessment (ISGA)

The Investigator will perform an assessment of the overall severity of AD and assign ISGA score and category as described in [Table 2](#) to verify each participant’s eligibility at the screening and Baseline/Day 1 visits.

8.1.6. Rater Qualifications

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

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

8.2.2. Vital Signs

Vital signs will be measured with the participant in a seated or supine position after 5 minutes of rest and will include temperature (tympanic, or axillary), systolic and diastolic blood pressure, and pulse rate, only performed at screening.

8.2.3. Clinical Safety Laboratory Assessments

See [Appendix 2](#) for the list of clinical safety laboratory tests to be performed at screening visit for eligibility purpose except pregnancy test.

All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the [SoA](#) for timing and frequency.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.4. Pregnancy Testing

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

8.2.5. Photography

Photographs of target lesions will be obtained at Baseline/Day 1, Day 8 and Day 15/Early discontinuation. Photographs will be taken by local standard procedures. Photographs will not be evaluated as an endpoint, but will be referred as needed, such as incident of significant AE. Only for participants who consent, photographs will be utilized for illustrative purposes.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in [Appendix 3](#).

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see [Section 7](#)).

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

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

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

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a participant 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 products must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until the end of the active collection period.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. 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.

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

8.3.6. Medication Errors

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

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

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

Medication errors include:

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

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

In the event of a medication dosing error, the sponsor should be notified 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 nonserious, 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**.

8.4. Treatment of Overdose

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

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Genetics

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand of this study is the hypothetical estimand, which estimates the effect as if all participants maintain their randomized treatment. It includes the following four attributes:

- Population: Participants with mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2) as defined by the inclusion and exclusion criteria and are randomized and received at least one of the investigational products;
- Variable: Change from baseline to Day 15 in lesion severity in a continuous outcome measured such as TSS, ISGA and Pruritus assessment in target lesions treated with crisaborole ointment 2% or vehicle in each regimen for each cohort;
- Intercurrent event: All efficacy data after discontinuation of treatment will not be considered;
- Population-level summary: Least-square means of intra-participant difference between crisaborole ointment 2% vs corresponding vehicle in each regimen for each cohort and pooled cohort. Difference in least-square means between crisaborole ointment 2% BID and crisaborole ointment 2% QD for each cohort and pooled cohort.

The primary and secondary efficacy endpoints will be analyzed using this estimand.

CCI

9.2. Sample Size Determination

For each cohort and for each regimen, a sample size of 16 will have at least 85% power to establish the superiority of crisaborole ointment 2% to vehicle as measured by the change from baseline in TSS between crisaborole treated lesion and the corresponding vehicle treated lesion at Day 15 using paired t -test at 0.025 (one-sided) significance level, assuming the mean of intra-participant difference is 1.8 and standard deviation is 2.2 calculated based

on the pooled results of C3291001 and AN2898-AD-202 studies. In addition, considering that the non-compliance/discontinuation rate during the treatment period is approximately 20%, approximately 20 participants will be enrolled for each regimen, and for each cohort.

In addition, for each cohort, in the inter-participant comparison between crisaborole ointment 2% BID treated lesion and crisaborole ointment 2% QD treated lesion, the sample size of 32 (16 per regimen) and 40 (20 per regimen) will result in a 2-sided 95% confidence interval width of the difference of mean for the change from baseline in TSS will be approximately 1.32 and 1.18, respectively, assuming a common standard deviation is 1.9 based on the pooled results of C3291001 and AN2898-AD-202 studies and the normal approximation.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All participants randomized and receiving ≥ 1 dose of investigational product.
Per-Protocol Analysis Set (PPAS)	All participant randomized and receiving ≥ 1 dose of investigational product, with both baseline and Day 15 primary efficacy data, and without protocol violations that were thought to impact the efficacy evaluation during the treatment period. All protocol deviations will be reviewed and assessed by the study team prior to database release.
Safety Analysis Set	All participants receiving ≥ 1 dose of investigational product.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe in further detail the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Analysis will be conducted for each cohort. The pooled analysis of cohort 1 and cohort 2 may be conducted, as appropriate. In the intra-participant comparison, a Mixed effect Models for Repeated Measures (MMRM) will be used to derive least-square means of intra-participant difference and associated 2-sided 95% confidence intervals between crisaborole ointment 2% and corresponding vehicle. In the inter-participant comparison, a MMRM will be used to derive difference in least-square means and associated 2-sided 95% confidence interval between crisaborole ointment 2% BID and crisaborole ointment 2% QD. Further details will be provided in the SAP.

Endpoint	Statistical Analysis Methods
Primary	<ul style="list-style-type: none"> The primary efficacy endpoint will be the change from baseline in TSS in target lesions treated with crisaborole ointment 2% or vehicle on Day 15. As for the intra-participant comparison between crisaborole treated lesion and the corresponding vehicle treated lesion for each regimen, and for each cohort, the intra-participant difference of change from baseline in TSS between crisaborole treated lesion and vehicle treated lesion, will be analyzed using a MMRM that includes the fixed effect of visit and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. A MMRM analysis will be conducted including only the observed data in the model under the assumption of the missing at random (MAR) for the missing mechanism.
Secondary	<ul style="list-style-type: none"> As for the inter-participant comparison between crisaborole BID treated lesion and crisaborole QD treated lesion for each cohort, the change from baseline in TSS will be analyzed using a MMRM that includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. A MMRM analysis will be conducted including only the observed data in the model under the assumption of the MAR for the missing mechanism. For other continuous endpoints such as change from baseline in ISGA at all visits and pruritus assessment at all days, a MMRM will be applied. As for the intra-participant comparison between crisaborole treated lesion and the corresponding vehicle treated lesion for each regimen, and for each cohort, the intra-participant difference of change from baseline between crisaborole treated lesion and vehicle treated lesion, will be analyzed using a MMRM that includes the fixed effect of time point (visit or day) and an unstructured variance and covariance matrix will be used to model the dependence among the same participant across different time points (visits or days) up to Day 15. As for the inter-participant comparison between crisaborole BID treated lesion and crisaborole QD treated lesion for each cohort, the change from baseline will be analyzed using a MMRM that includes the fixed effects of dosing regimen, time point (visit or day), dosing regimen-by-time point (visit or day) interaction, and baseline value and an unstructured variance and covariance matrix will be used to model the dependence among the same participant across different time points (visits or days) up to Day 15. A MMRM analysis will be conducted including only the observed data in the model under the assumption of the MAR for the missing mechanism.

CCI



9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Safety data will be descriptively summarized, and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data. The following safety data will be summarized:

- TEAEs, including SAEs;
- Withdrawals from treatment due to AEs.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study.

9.5.1. Data Monitoring Committee

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 participants against any immediate hazard, and

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

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

10.1.3. Data Protection

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

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

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

10.1.4. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally 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 participant 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 [clinical study report (CSR) synopses in which any data that could be used to identify individual participants have been removed] on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

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

Data Sharing

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

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

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

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

Definition of what constitutes source data can be found in Study Data Monitoring Plan.

10.1.7. Study and Site Closure

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

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

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

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

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

10.1.8. Publication Policy

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

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to

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

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

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

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

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA 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.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
<u>At screening only:</u> Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	<u>At screening only:</u> BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO ₂ (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	<u>At screening only:</u> pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy ^a	<ul style="list-style-type: none"> • Pregnancy test (β-hCG)^c <u>At screening only:</u> <ul style="list-style-type: none"> • FSH^b • Urine drug screening

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CO₂ = carbon dioxide; FSH = follicle-stimulating hormone; qual = qualitative; RBC = red blood cell; WBC = white blood cell.

- Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
- For confirmation of postmenopausal status only.
- Local urine testing will be standard for the protocol unless serum testing is required by institutional review board/ethics committee (IRB/EC). For female participants of childbearing potential, if a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none">• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none">• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.• “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none">• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).• Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from

baseline is not considered an AE.
<p>d. Results in persistent disability/incapacity</p> <ul style="list-style-type: none">• The term disability means a substantial disruption of a person’s ability to conduct normal life functions.• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Other situations:</p> <ul style="list-style-type: none">• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.• Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	None	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating

the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance

with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

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

10.4.2. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy;
 - Documented bilateral salpingectomy;
 - Documented bilateral oophorectomy.

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

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

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

3. Postmenopausal female:

- A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.3. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.*
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner:
 - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - oral;
 - intravaginal;*
 - transdermal;*
 - injectable.*

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

*) Not approved or not certificated in Japan

Collection of Pregnancy Information

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 participant or participant's partner becomes or is found to be pregnant during the participant'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 participant 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 preprocedure 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

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

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants 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 participant 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 laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times$ ULN AND a TBili value $>2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $<2 \times$ ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times$ ULN; or $>8 \times$ 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 participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

10.6. Appendix 6: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
ADSI	atopic dermatitis severity index
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
β -hCG	beta-human chorionic gonadotropin
BID	twice daily
BPO	benzoyl peroxide
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatin kinase
C_{max}	maximum observed concentration
CO ₂	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DMC	data monitoring committee
DU	dispensable unit
EC	ethics committee
EC ₅₀	half maximal effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Term
HRQoL	health related quality of life measures
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISGA	investigator's static global assessment
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IWR	interactive Web-based response
LFT	liver function test
MAR	missing at random
MMRM	mixed effect models for repeated measures
MUSE	maximal use systemic exposure
N/A	not applicable
NbUVB	narrow band ultraviolet B
NIMP	noninvestigational medicinal product
NRS	numerical rating scale
PCD	primary completion date
PD	pharmacodynamic(s)
PDE-4	phosphodiesterase-4
PI	principal investigator
PK	pharmacokinetic(s)
PKA	protein kinase A
PMA	phorbol 12-myristate 13-acetate
PPAS	Per-Protocol Analysis Set
PRN	pro re nata
PT	prothrombin time
PUVA	psoralen plus ultraviolet A
QD	once daily
qual	Qualitative
RBC	red blood cell
RIPT	repeat-insult patch test
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
T _{max}	time to reach maximum observed plasma concentration
TQT	thorough QT
TSS	Total Sign Score
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential
%BSA	percent of body surface area

11. REFERENCES

1. Bieber T. Atopic dermatitis. *N Engl J Med* 2008 Apr;358(14):1483-94.
2. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60(8):984-92.
3. Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. *Semin Cutan Med Surg* 2012;31(3 Suppl):S3-5.
4. Leicht S, Hanggi M. Atopic dermatitis. How to incorporate advances in management. *Postgrad Med* 2001;109(6):119-27.
5. Saeki H. Management of Atopic Dermatitis in Japan. *J Nippon Med Sch* 2017;84(1):2-11.
6. Arkwright PD, Motala C, Subramanian H, et al. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract*. 2013;1(2):142-51.
7. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. *Allergol Int* 2013;62(2):151-61.
8. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol* 2014;5(2).
9. Saunes M, Oien T, Dotterud CK, et al. Early eczema and the risk of childhood asthma: a prospective, population-based study. *BMC Pediatr* 2012;12:168.
10. Garg N, Silverberg JI. Epidemiology of childhood atopic dermatitis. *Clin Dermatol* 2015;33(3):281-8.
11. Beatti PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006;155(1):145-51.
12. Carroll CL, Balkrishnan R, Feldman SR, et al. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr Dermatol* 2005;22(3):192-9.
13. Halvorsen JA, Lien L, Dalgard F, et al. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. *J Invest Dermatol* 2014;134(7):1847-54.
14. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol* 2011;7(Suppl 1):S4.
15. Thomas CL, Finlay AY. The 'handprint' approximates to 1% of the total body surface area whereas the 'palm minus the fingers' does not. *Br J Dermatol* 2007;157(5):1080-1.

16. Yosipovitch G, Reaney M, Mastey V, et al. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol* 2017;76(6):AB278.