A PHASE 4, MULTICENTER, OPEN-LABEL SAFETY STUDY OF CRISABOROLE OINTMENT 2% IN CHILDREN AGED 3 MONTHS TO LESS THAN 24 MONTHS WITH MILD TO MODERATE ATOPIC DERMATITIS

Investigational Product Number:	PF-06930164
Investigational Product Name:	Crisaborole
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number	C3291002
Phase:	4

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	01 May 2018	To address the recommendations made by the Food and Drug Administration (FDA) following review of the protocol (ordered as they first appear in the protocol): CCI [redacted] • Sections 6.4; 6.5; 6.6; 6.7; 6.8; 6.10.1; 6.10.2; 6.11.1; 6.11.2 and 6.11.3: Added text instructing investigators to monitor for potential hypersensitivity reactions at all visits; • Section 6.10.2: Added that any subject with a new or ongoing adverse event at the time of the Day 57 (end of study) follow-up contact, should be seen in the clinic for evaluation of that adverse event; • Section 6.12: Provided more specific withdrawal criteria relative to known and potential toxicities associated with systemic PDE4 inhibition CCI [redacted] • Section 7.1.2: Added guidance to standardize the method for measuring both height (length) and weight, including that three reproducible measurements should be recorded and the average of the 3 recordings be entered onto the eCRF. In addition, protocol inconsistencies and clarifications have been corrected as follows (ordered as they first appear in the protocol): • SoA: Added subject height/length and weight at screening. Added ECG at screening. Added that treatable Atopic Dermatitis (AD) areas and the body map should be updated at clinic visits Day 8 and Day 15. Corrected one spelling mistake. Clarified the CCI [redacted] days; [redacted]

		[redacted] • Section 4.2: Exclusion criteria 3 corrected so subjects with creatinine clearance based on the age-appropriate calculation below the lower limit of normal (LLN), or serum creatinine that is greater than the upper limit of normal (ULN) are excluded; • Section 4.4: Updated lifestyle guidelines pertaining to nursing women or women of childbearing potential; • Section 5.2: Corrected the number of doses that must be applied for subjects to be considered compliant with the dosing regimen; • Section 5.5: Clarified that large areas that need to be treated can have the ointment applied slowly and segmentally to minimize pain associated with application; • Section 6.3: Added that subject weight and height/length will be measured at Screening; • Section 6.3; 6.4 and 7.1.3: Updated to reflect that an ECG may be taken at screening and that a 6-lead ECG may be taken in the event a 12-lead ECG is not possible to obtain; • Section 6.4: Added that subjects will be randomized; • Sections 6.5 and 6.6: Added that updated documentation for treatable AD areas may be provided to parent(s)/legal guardian, if required; • Section 6.10.1: Removed reference to prohibited concomitant treatments; • Section 6.12: Clarified that follow-up contacts must be completed for all withdrawn subjects;

		[redacted] • Section 7.2.3: Table 5 corrected; • Sections 7.3.1 and 7.3.2: Clarified that the '168 hours' CCI [redacted] may be described as 'Day 8 (0 hours)'; • Section 9.1: Corrected spelling error.
Original Protocol	06 July 2017	Not applicable (N/A)

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PROTOCOL SUMMARY

Background and Rationale:

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that penetrates into the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. While the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, it is thought that crisaborole reduces the production of several inflammatory cytokines implicated in the pathophysiology of atopic dermatitis (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 pivotal studies. Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related serious adverse events (SAEs) (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related), and the majority of adverse events (AEs) were mild and deemed unlikely or not related to investigational product. Safety and efficacy have not yet been established in patients younger than 2 years of age.

This 4-week study will evaluate the safety, CCI [redacted], and efficacy of crisaborole ointment 2%, applied twice daily (BID) in subjects who are 3 months to less than 24 months of age with mild-to-moderate AD. The dose selected for this study has been shown to be safe, well tolerated and efficacious in patients and healthy volunteers 2 years of age and older who participated in previously conducted studies. Based on these results and the observed CC[redacted] profile of crisaborole, it is anticipated that crisaborole ointment 2% will demonstrate similar efficacy and satisfactory safety and local tolerability in the pediatric population to be enrolled in this study.

Objectives and Endpoints:

Primary Objective	Primary Endpoint(s)
To study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild to moderate AD	Incidence of treatment emergent AEs (including application site reactions), SAEs, and clinically significant changes in height, weight, vital signs, ECG and clinical laboratory parameters
[redacted]	

Abbreviations: AD=atopic dermatitis; AE=adverse event; BID=twice a day; [redacted]; ECG=electrocardiogram; EOT=end of treatment; [redacted]; SAE=serious adverse event; [redacted] t; CCI [redacted] C_{max} =maximum observed plasma concentration; $AUC_{(0-12)}$=area under the plasma concentration-time curve from 0 to 12 hours post dosing; T_{max}= time to reach maximum observed plasma concentration

Study Design:

This is a Phase 4, multicenter, open-label safety study to evaluate the safety of crisaborole ointment 2% in approximately 125 subjects who are 3 months to less than 24 months of age, with mild-to-moderate AD involving at least 5% treatable [redacted] In addition, a cohort of at least 16 of the 125 subjects enrolled will be included in a subgroup for CC assessment. These subjects must have moderate AD with a minimum of [redacted], excluding the scalp, and must complete all CC assessments to be included in the CC analysis. Of these subjects, at least 3 subjects who are less than 9 months of age will be enrolled.

Approximately 30 investigational sites will participate in this study. Only selected study sites will participate in the CC assessment.

Scheduled study visits/telephone contacts for all subjects will occur at Screening (up to 28 days prior to Baseline/Day 1), Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (end of treatment/early termination), Day 36, and Day 57 (end of study). Days 22 and 36 will be conducted through a telephone contact with the subject's parent(s)/legal guardian. A follow-up telephone call (end of study) will be made by site staff to the subject's parent(s)/legal guardian on Day 57 (approximately 28 days after the last dose application) to assess AEs (nonserious and serious). Subjects in the [redacted] cohort will also have twice daily clinic visits on Days 2 through 7 for application of investigational product and a minimum of 1 clinic visit on Day 8 for [redacted] sample collection and additional study procedures. Following the Baseline/Day 1 AM investigational product application, some or all of the remaining applications through Day 8 AM as well as 2 of the 3 scheduled Day 8 [redacted] sample collections may be performed by a qualified health care professional in the subjects' home at the discretion of the Investigator and subject's parent(s)/legal guardian. One on-site visit is required on Day 8 to perform the remaining visit assessments.

For the 16 subjects in the [redacted] Cohort 3 additional blood samples of approximately 1 mL each (approximately 3 mL total), will be collected for plasma [redacted] analysis, according to the following schedule:

- Before the Day 8 AM dose (ie, 168 ±1 hour after recorded time of completion of the Day 1 dose application);
- 3 hours ±20 min after recorded time of completion of the Day 8 AM dose application;
- 12 hours ±1 hour after recorded time of completion of the Day 8 AM dose application.

Refer to the Schedule of Activities for a complete list of assessments to be performed during the study.

Statistical Methods:

Safety

Treatment emergent adverse events (TEAEs) will be summarized by the number of subjects reporting any TEAE, system organ class (SOC), preferred term (PT), severity, relationship to investigational product, and seriousness.

Serious adverse events (SAEs) will be summarized by SOC and PT, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinue from the study due to an AE will be provided.

[redacted]

[redacted]

[redacted]

[redacted]

Efficacy

All efficacy data will be summarized using descriptive statistics. No imputation will be made for missing efficacy data.

SCHEDULE OF ACTIVITIES

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

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

All Subjects (Including non-PK and [redacted] Cohorts)

Day		**1**	**8**	**15**	**22**	**29**	**36**	**57**
Window	**-28 to -2 day(s)**		**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**+3 days**
Visit	**Screening**	**Baseline**			**Telephone Contact**	**End of Treatment/Early Termination**	**Telephone Contact**	**Follow-up Contact[a] (End of Study)**
Informed Consent	X							
Demographics	X							
Review Inclusion/Exclusion Criteria	X	X						
Medical History	X	X						
Confirmation of Diagnosis of AD	X	X						
Height/Length and Weight	X	X				X		
Vital Signs[b]	X	X	X	X		X		
Full Physical Examination	X[c]					X		
12-Lead Electrocardiogram (ECG)	X or	X	X			X		
Limited Physical Examination		X[d]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]		[redacted]		[redacted]		[redacted]		
Body Site checklist of AD lesions		X	X	X				
[redacted]		[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]						

Day		**1**	**8**	**15**	**22**	**29**	**36**	**57**
Window	**-28 to -2 day(s)**		**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**+3 days**
Visit	**Screening**	**Baseline**			**Telephone Contact**	**End of Treatment/Early Termination**	**Telephone Contact**	**Follow-up Contact[a] (End of Study)**
Blood collection for serum chemistry and hematology	X[g]					X		
[redacted]	[redacted]					C Cl		
Record treatable AD areas (excluding scalp) in source and provide parent(s)/legal guardian with documentation of the designated treatment areas		X						
Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use		X	X	X				
Dispense and weigh the investigational product tube(s) and apply first dose. First dose applied in office by study staff		X						
Dispense and weigh new investigational product tube(s) and provide for at-home dosing		X[i]	X	X				
At-home dosing, applied by parent(s)/legal guardian[i,j]		**2nd dose (PM) on Day 1, then BID up to PM dose prior to Day 29 visit**						
Review dosing diary; assess compliance; re-train parent(s)/legal guardian if doses missed			X	X	X	X		
Collect and weigh empty, partially used and unused investigational product tubes			X[i]	X		X		
Review and record prior and concomitant medications	X[k]	X	X	X	X	X	X	X

Day		**1**	**8**	**15**	**22**	**29**	**36**	**57**
Window	**-28 to -2 day(s)**		**±1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**+3 days**
Visit	**Screening**	**Baseline**			**Telephone Contact**	**End of Treatment/Early Termination**	**Telephone Contact**	**Follow-up Contact[a] (End of Study)**
Assess for AEs (including application site reactions) and SAEs	X	X[l]	X	X	X	X	X	X
Review lifestyle requirements	X	X	X	X	X	X		
Schedule/reconfirm next study visit/contact	X	X	X	X	X	X	X	
Remind parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to the next visit		X	X	X	X			

Abbreviations: AD=atopic dermatitis; BP=blood pressure; [redacted] PR=pulse rate; RR=respiratory rate; AE=adverse event; SAE=serious adverse event; CCI [redacted]; BID=twice a day

a. Follow-up contact will be completed 28 +3 calendar days after the last administration of the investigational product to capture any adverse events.
b. Vital signs (temperature, respiratory rate, pulse rate, and BP) taken in seated or supine position after subject has been seated or lying face up for 5 minutes.
c. A full physical examination will be performed at the Screening visit. If the full examination cannot be completed during screening, an unscheduled visit may be performed prior to Baseline/Day 1 to complete the full assessment.
d. A limited physical examination will be performed at Baseline/Day 1.
[redacted]
g. Blood draw for clinical labs may be completed any time during the screening period, (Day -28 to Day -2) however the results must be available and reviewed by the PI prior to the Baseline/Day 1 visit and investigational product application. If the laboratory sample cannot be obtained due to an upset child, parent or other collections issues, the subject will not be enrolled into the study. Serum chemistry laboratory assessments include lactate and parameters needed to perform calculation of osmolal gap and anion gap.
[redacted] CCI [redacted].
i. Not applicable to subjects in C [redacted] cohort through Day 8.
j. In the event the scheduled Day 29 visit does not fall exactly on Day 29, instruct parent(s)/legal guardian to keep dosing BID until the evening dose prior to the Day 29 visit.
k. All medications and non-medication therapies used within 30 days prior to Screening.
l. Assess for AEs (including application site reactions) /SAEs before and after in clinic dose at Baseline/Day 1.

[redacted] Cohort Subjects Only

Day	**1**[a]	**2-7**	**8**[b] **Prior to AM dose** (168 hours ±1 hour post time of AM application on Day 1)	**8** 3 hours ±20 minutes after completion of AM dose	**8** 12 hours ±1 hour after completion of AM dose	**Non-PK Study Schedule (see above)**[c]
Visit	[redacted]					
[redacted]			[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]			
Blood collection for serum chemistry[d,f]			X			
[redacted]	[redacted]	[redacted]	[redacted]			
Review lifestyle requirements	X	X	X			
Assess and record any pre- and/or post-dose AEs (including application site reactions) and SAEs	X	X	X			
Assess and record any changes in concomitant medications	X	X	X			
Weigh amount of investigational product to be applied before each dose application	X	X	X[h]			
Dispense dosing diary and train parent(s)/legal guardian on use			X			
Dispense and weigh investigational product tube(s) and provide for at-home dosing			X			
Review the schedule of upcoming study visits with the parent(s)/legal guardian	X	X	X			
Remind parent(s)/legal guardian to bring all investigational product tubes and the dosing diary to the next visit			X			

Abbreviations: [redacted]

a. Perform Day 1 assessments prior to dosing procedures, as applicable (See All Subjects (Including non-[redacted] and [redacted] Cohorts)).

b. Aside from AM dose application, first [redacted] sample collection, serum chemistry [redacted] sample collection which must all be performed at the first [redacted] collection time point, all other Day 8 procedures may be performed at any of the 3 PK collection time points.

c. Subject to resume regular study schedule following completion of Day 8/PK 8 final PK sample collection.

- CCI [redacted]
- CCI [redacted]

f. Serum chemistry laboratory assessments include lactate and parameters needed to perform calculation of osmolal gap and anion gap.

- CCI [redacted]

h. Weighing of investigational product on Day 8 applies to the AM dose only.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

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

On 14th December 2016, EUCRISA™ (Crisaborole) Ointment 2% was approved by the US Food and Drug Administration (FDA) for the treatment of mild to moderate AD in patients 2 years of age and older.

1.2. Background

AD, also referred to 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 United States (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.[3,4]

AD is a distinctive inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.[1, 4] The majority of patients (up to 90%) with AD present with mild to moderate disease.[5] Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, lichenification, and bacterial colonization.[6] Continuous scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections. AD is often associated with other conditions including asthma, allergic rhinitis, and food allergy. AD has been cited as a major risk factor for the development of asthma in a number of longitudinal studies, and children with AD are at increased odds of developing asthma compared to children without AD.[7,8] 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 (HRQL) for patients, especially in children, and caregivers.[1,9,10,11] Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.[12]

The negative impact on HRQoL caused by childhood AD exceeds that in asthma, epilepsy, and diabetes, is comparable to that in renal disease or cystic fibrosis, and is equal (child) or exceeds (parents) that in psoriasis.[2,10,13] The hallmark symptom of itching causes scratching which is associated with sleep disturbance in greater than 60% of patients. Sleep deprivation leads to physical and mental exhaustion in patients and other family members resulting in loss of concentration and impaired performance at school or work.[14,15] AD is often associated with significant childhood behavioral problems and psychological disorders

including depression, attention deficit hyperactivity disorder, anxiety, stress, and autism.[16] Pre-school children with AD show a significant increase in behavioral symptoms compared with matched controls.[17] Absolon et al[18] reported that the rate of psychological disturbance in school-age children with AD doubled compared with matched controls. For older children with AD, in addition to problems associated with itching and sleep disturbance, their social and school life may be substantially affected. Social embarrassment, due to visible signs of the disease (crusted, excoriated, oozing, bleeding lesions), teasing, and bullying, often results in social isolation leading to depression.[2]

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. In summary, AD is a disease with multiple comorbidities and significant impact on the health, day to day functioning, and HRQoL of AD patients, their caregivers, and family members.

AD may also be a source of significant economic burden[19] 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.

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 pivotal studies. Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related SAEs (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related), and the majority of AEs were mild and deemed unlikely or not related to investigational product. Safety and efficacy have not yet been established in patients younger than 2 years of age.

CCI [redacted]

1.2.1. Anticipated Benefits and Risks

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 atopic dermatitis 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 main benefit for subjects participating in this study is based on access to regular clinical assessments and active atopic disease management as well as expected efficacy of treatment with crisaborole during the study. Based on the favorable clinical safety profile as well as the limited systemic exposure of crisaborole, the risk to subjects treated with crisaborole is deemed to be minimal and appropriately monitored.

1.3. Drug Development

Crisaborole ointment 2% is an oxaborole compound developed as a topical anti-inflammatory agent. It demonstrates in vitro inhibition of a wide range of pro-inflammatory cytokines implicated in the pathogenesis of AD and other inflammatory skin diseases. Crisaborole has been formulated as a topical ointment. The formulation ingredients for crisaborole ointment 2% are listed in Section 5.

Crisaborole inhibits a range of cytokines implicated in the pathogenesis of inflammatory skin diseases, including TNF-α, IFN-y, IL-2, IL-5, IL-6, IL-10, IL-12, and IL-23.[22] The level of inhibitory activity, ie, the concentrations needed to produce 50% inhibition, ranges from the high nanomolar to the low micromolar concentrations. Crisaborole also inhibits the release of chemokines that are important inflammatory mediators. One mechanism of the anti-inflammatory effect of crisaborole is through inhibition PDE-4. Crisaborole proved efficacious against an inflammatory challenge in vivo, in a mouse model of ear edema induced by phorbol 12-myristate 13-acetate (PMA). Crisaborole formulated as ointment and cream formulations for topical use has demonstrated clinical benefit in nine psoriasis clinical studies and seven AD clinical studies. Safety has been evaluated in a total of 23 completed clinical studies.

The Investigator's Brochure (IB) contains summaries of nonclinical and clinical studies performed with crisaborole.[22] A brief summary as background to this study protocol is presented here.

1.3.1. Nonclinical Studies

Crisaborole demonstrated inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration (EC_{50}) values ranging from high nanomolar to low micromolar concentrations.[23-29] 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 PDE4,[30] 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.[31] Crisaborole proved efficacious against an inflammatory challenge in vivo in a mouse PMA-induced ear edema model.[32,33] AN8323, a metabolite of crisaborole, lacks anti-inflammatory activities against PDE4[34] and a panel of cytokines.[35]

In support of the current clinical study to evaluate crisaborole ointment 2% in children (aged 3 to less than 24 months), a juvenile toxicity study in rats was conducted. Juvenile rats were administered crisaborole by oral gavage once daily for 4 weeks (from postnatal Days 7 to 35) at 0, 15, 50, and 100 mg/kg/day followed by a 2-week recovery period. Exposures at the No-Observed-Adverse-Effect Level (NOAEL, 100 mg/kg/day) in this study were approximately 9× higher than those observed in the AD Maximal Use Systemic Exposure (MUSE) clinical study.

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

CCI [redacted]

[redacted]

[redacted]

- In a TQT study (Study AN2728-TQT-108) in which healthy subjects were treated with crisaborole ointment 2% at a therapeutic dose (15 g, [redacted] a supratherapeutic dose (45 g, representing [redacted], mean C_{max} values of 36.9 ng/mL and 87.4 ng/mL were observed in therapeutic and supratherapeutic dose groups, respectively, at Day 9. At both therapeutic and supratherapeutic doses had no effect on cardiac repolarization based on results from the primary assessment and the CCI [redacted]-pharmacodynamic analysis.

1.3.3. Cutaneous Sensitization, Irritancy Potential and Tolerability

1.3.3.1. Local Tolerability in Sensitive Skin Areas

In a study of healthy subjects (16 men and 16 women) who applied crisaborole ointment 2% or vehicle for 21 days to sensitive area application sites (including extensor areas, intertriginous areas, genitals, and face/hairline), 99% of assessments of local tolerability were graded as 0 (none), with an overall maximum grade of 2 (moderate) and only 0.1% of

assessments graded higher than 1 (mild) (Study AN2728-PSR-107). There were no marked differences in burning/stinging, erythema, or pruritus at any of the application sites over the course of the study between subjects who received crisaborole ointment 2% or Vehicle. Overall, crisaborole ointment 2% was well tolerated over 21 days of dosing in sensitive skin areas of healthy subjects.

1.3.3.2. Sensitizing and Cumulative Irritation Potential

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

1.3.4. Clinical Experience

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

- In a multicenter, maximal use, systemic exposure (MUSE) study in 34 pediatric subjects ranging in age from 2 to 17 years with mild-to-moderate AD who applied crisaborole ointment 2% BID,[36] subjects had overall blood levels of crisaborole that were low and similar to those previously observed in adults after adjusting for [redacted] Absorption across the skin was rapid, with a median T_{max} of 3.0 hours on both Day 1 and Day 8.

- In a 4-week, single arm, open-label safety, tolerability and [redacted] trial in adolescents with mild-to-moderate AD involving [redacted],[37] disease severity improved over the 28-day treatment period.

- In a 6-week bilateral comparison trial of subjects with mild-to-moderate AD,[38] 68% of AD lesions treated with crisaborole ointment 2% BID showed greater improvement in atopic dermatitis severity index (ADSI) than vehicle-treated lesions (20%) at 4 weeks (primary endpoint). These response rates were similar at Day 14 and Day 42 (end of treatment).

- In a 4-week bilateral comparison trial of 86 adolescent subjects with mild-to-moderate AD,[39] crisaborole ointment 2% BID showed greater improvement than the lower concentration of crisaborole ointment, 0.5% applied BID for 29 days, and was more efficacious than either concentration applied once daily (QD).

- In two Phase 3 multicenter, randomized, double-blind, vehicle controlled studies in subjects ≥2 years of age and older with AD, crisaborole ointment 2% outperformed the vehicle in the primary efficacy analysis, proportion of subjects achieving success in [redacted] at Day 29. [redacted]

- An additional Phase 3 multicenter, open-label, long-term extension study (AN2728-AD-303) 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. No clinically important safety signals were identified by this study.[42]

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

Refer to the IB for further information on the clinical experience with crisaborole ointment 2%.[22]

1.4. Rationale

1.4.1. Study and Dose Rationale

This 4-week safety study will evaluate the safety profile of crisaborole ointment 2% BID in subjects who are 3 months to less than 24 months of age with mild-to-moderate AD. In addition, CC will be assessed in a subgroup of at least 16 subjects under maximal use conditions, defined as systemic exposure conditions related to a high percent of body surface area involvement which would maximize the potential for drug absorption with anticipated clinical use of crisaborole. While crisaborole has been studied extensively in patients and healthy volunteers 24 months of age and older, it has not been tested in patients less than 2 years of age. As such, the current study is being conducted as a post-approval commitment to FDA as part of the pediatric study plan.

The dose strength and regimen selected for this study has been shown to be safe, well tolerated and efficacious in patients and healthy volunteers 2 years of age and older who participated in previously conducted studies of crisaborole. Crisaborole ointment 2% applied BID was studied in two Phase 3, randomized, double-blind, vehicle-controlled studies, and a Phase 3 open-label long-term safety study. Data from the two controlled studies showed a statistically significant therapeutic effect compared to vehicle with no safety concerns in patients 2 years and older. In the open-label study, crisaborole ointment 2% applied BID,

demonstrated that the long-term use was well tolerated and not associated with any systemic safety signals. The Phase 1 maximal use absorption study in children and adolescents aged 2 to 17 years old,[36] showed that subjects who were administered crisaborole ointment 2% BID (single dose on Days 1 and 8) to [redacted] had overall blood levels of crisaborole that were similar to those previously observed in adults after [redacted]. An analysis of variance (ANOVA) showed no statistically significant differences in CC[redacted] parameters between the age cohorts represented in the study (Cohort 1, ages 12–17 years; Cohort 2, ages 6–11 years; and Cohort 3, ages 2–5 years).

Based on the results of clinical studies conducted with crisaborole ointment 2% to date, it is anticipated that crisaborole ointment 2% will demonstrate similar efficacy and satisfactory safety and local tolerability in the pediatric population to be enrolled in this study.

1.4.2. Single Reference Safety Document

Additional information for crisaborole may be found in the Single Reference Safety Document (SRSD), which for this study is the current version of the crisaborole Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint(s)
To study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild to moderate AD	Incidence of treatment emergent AEs (including application site reactions), SAEs, and clinically significant changes in height, weight, vital signs, ECG and clinical laboratory parameters
[redacted]	[redacted]
[redacted]	[redacted] CCI [redacted]

	CCI [redacted]

Abbreviations: AD=atopic dermatitis; AE=adverse event; BID=twice a day; SAE=serious adverse event; [redacted]; ECG=electrocardiogram; EOT=end of treatment; CCI [redacted] Cmax =maximum observed plasma concentration; Tmax = time to maximum observed plasma concentration; AUC(0–12)=area under the plasma concentration-time curve from 0 to 12 hours post dosing.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 4, multicenter, open label, safety study to evaluate the safety of crisaborole ointment 2% in children aged 3 months to less than 24 months with AD. CCI [redacted]

Approximately 125 subjects will be enrolled. Subjects will be between 3 months (at the time of the Screening visit) to less than 24 months of age at the time of Baseline/Day 1 with mild-to-moderate AD involving [redacted] assessed on Baseline/Day 1. [redacted]

In addition, a cohort of at least 16 of the 125 subjects will be included in a subgroup for CC assessment. These subjects must have moderate AD and a minimum of 35% treatable %BSA, excluding the scalp, and must complete all CC assessments to be included in the CC analysis. Of these subjects, at least 3 subjects who are less than 9 months of age will be enrolled. Subjects discontinuing for reasons other than TEAE may be replaced at the discretion of the sponsor to ensure 16 subjects complete the CC assessments. Only selected study sites will participate in the CC assessment.

Written informed consent will be obtained from the parent(s)/legal guardian prior to any study procedures.

Scheduled study visits/telephone contacts for all subjects will occur at Screening (up to 28 days prior to Baseline/Day 1), Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (end of treatment/early termination), Day 36, and Day 57 (end of study).

Days 22 and 36 will be conducted through a telephone contact with the subject's parent(s)/legal guardian to assess the subject's condition, and whether any AEs, including application site reactions, have occurred since the last visit. Investigational product compliance, lifestyle requirements (Day 22 only) and concomitant medications will also be reviewed. The parent(s)/legal guardian will be contacted by site staff on Day 57

(approximately 28 days after the last dose application) for a follow-up telephone conversation (end of study) during which site staff will assess the subject's condition and whether any AEs, including application site reactions, have occurred since the last visit.

In addition, subjects in the CC cohort will have twice daily visits on Days 2 through 7 for application of investigational product at the site, as well as 3 CC sample collections from prior to AM dose until 12 hours post dose on Day 8. If desired, the protocol allows for a visiting health care professional to assist with twice daily dosing in the subject's home for some or all of the dose applications during the CC portion of the study and any 2 of the 3 CC sample collections. Further information on home-based dose application and CC sample collection for the CC cohort is provided in Sections 5.8.2 and Section 7.3.1, respectively.

For the approximately 16 subjects in the CC cohort, 3 additional blood samples of approximately 1 mL each (approximately 3 mL total) will be collected for plasma crisaborole and metabolites PK analysis, according to the following schedule:

- Before the Day 8 AM dose (ie, 168 hours ±1 hour after recorded time of completion of the Day 1 dose application);
- 3 hours ±20 minutes after recorded time of completion of the Day 8 AM dose application;
- 12 hours ±1 hour after recorded time of completion of the Day 8 AM dose application.

Selection criteria for the study population are described in Section 4. Detailed information about the investigational product treatment regimen is provided in Section 5.8. Detailed information about study procedures and assessments is provided in Section 6 and Section 7.

3.2. Number of Sites

Approximately 30 investigational sites will participate in this study. Only selected study sites will participate in the CC assessment.

3.3. Duration of Study

Subjects will be screened for the study no more than 28 days before the initial day of dosing (Baseline/Day 1), and will receive investigational product for approximately 28 days. The study will comprise the following study periods:

- Screening Period: maximum duration of 28 days;
- Investigational Product Application Period: approximately 28 days (until Day 29 visit);

- Post-Treatment Follow-up Period: approximately 28 days. The follow-up period includes a telephone contact 7 days after the last application of investigational product and a telephone contact 28 (+3 days) days after the last application of investigational product.

The total duration of a subject's participation in the study will range from a minimum of 59 days to a maximum of 88 days, depending on the length of a given subject's screening period.

4. SUBJECT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria

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

1. Is male or female aged at least 3 months at the Screening visit to less than 24 months on Baseline/Day 1.

2. Has a clinical diagnosis of AD according to the criteria of Hanifin and Rajka (1980) (See Appendix 2).

[redacted]

b. [redacted]

[redacted]

5. Evidence of a personally signed and dated informed consent document indicating that the subject's parent(s)/legal guardian has been informed of all pertinent aspects of the study.

6. Parent(s)/legal guardian who is/are willing and able to comply with all scheduled visits, treatment plan, laboratory tests and other study procedures.

4.2. Exclusion Criteria

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

1. Has any clinically significant dermatological condition or disease (including active or potentially recurrent non-AD dermatological conditions and/or known genetic dermatological conditions that overlap with AD such as Netherton Syndrome).

2. Was premature at birth, defined as less than 37 gestational weeks.

3. Has estimated creatinine clearance based on the age appropriate calculation that is below the lower limit of normal (LLN), or serum creatinine greater than the upper limit of normal (ULN).

4. Has aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than the ULN.

5. Has received any of the following AD treatment regimens without the required minimum washout:

   28 days prior to Baseline/Day 1

   - Systemic corticosteroids (use of intranasal/inhaled, and ophthalmic corticosteroids allowed);

   - Systemic immunosuppressive agents (eg, methotrexate, ciclosporin, azathioprine, hydroxychloroquine, mycophenolate mofetil).

   7 days prior to Baseline/Day 1

   - Use of high-or-mid-potency topical corticosteroids or calcineurin inhibitors anywhere on the body;

   - Topical antibiotics on treatable AD lesions;

   - Light therapy (ultraviolet light therapy);

   - Use of antibacterial soaps (for bathing), bleach baths, or topical sodium hypochlorite-based products on treatable AD lesions.

   3 days prior to Baseline/Day 1

   - Systemic antihistamines;

   - Use of low potency topical corticosteriod (eg hydrocortisone 1%) on treatable AD lesions.

8 hours prior to Baseline/Day 1

- Use of emollients on treatable AD lesions;
- Use of topical antihistamines on treatable AD lesions;
- Use of topical hydrocortisone <1% on treatable AD lesions.

6. Has unstable AD or a consistent requirement for high-potency topical corticosteroids to manage AD signs and symptoms (see "Prohibited Therapies" for washout periods), or the mother requires treatment with high-potency topical corticosteroids due to potential for topical corticosteroids to transfer to the child.

7. Child is nursing and the child's mother requires high dose systemic steroids or systemic immunotherapy or other medications that might be transmitted in the breast milk and that might alter the course of the child's AD.

8. Has a history of hyperactive airway disease requiring systemic corticosteroid therapy.

9. Has a significant active systemic or localized infection, including known actively infected AD, within two weeks prior to Baseline/Day 1.

10. Has a history of use of biologic therapy including intravenous immunoglobulin (IVIG) at any time prior to study.

11. Has recent or anticipated concomitant use of topical or systemic therapies that might alter the course of AD, as specified in protocol (see Concomitant Treatment(s)).

12. Participation in other studies involving investigational drug(s) within 30 days of Baseline/Day 1 and/or during study participation.

13. Has any planned surgical or medical procedure that would overlap with study participation from Screening through the final study visit on Day 57.

14. Has undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only).

15. Has a history of angioedema or anaphylaxis to topical products or a known sensitivity to any of the components of crisaborole ointment 2% (listed in Section 5).

16. Had previous treatment with crisaborole ointment 2%.

CCI [redacted]

18. Subjects who have parent(s)/legal guardian who is/are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or parent(s)/legal guardian who is/are Pfizer employees, including their family members, directly involved in the conduct of the study.

19. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

This open-label study will enroll subjects sequentially; no randomization will be performed.

4.4. 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 subject's participation.

- The parent(s)/legal guardian will be instructed to dress the subject in loose-fitting clothing and avoid occluding the treated areas (with dry wraps, for example). Wet wraps are not permitted.

- Subjects should not swim, be bathed or have treatment areas washed for at least 4 hours after application.

- Use of sunscreen is permitted, but only on skin areas without AD involvement.

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

- The parent(s)/legal guardian should avoid wiping the investigational product off the skin and investigational product should not be reapplied to wiped areas until the next scheduled dose.

- If there are AD lesions in the diaper area, they should be treated with investigational product; however, following diaper change, any investigational product inadvertently wiped off soiled skin should not be reapplied until the next scheduled dose. Diaper rash creams, lotions, ointments, powders, etc are not permitted where AD lesions are present. In the case of rash in the diaper area without AD involvement, standard treatments may be applied.

- When applying investigational product at home, the parent(s)/legal guardian will not be required to wear gloves. However, they must be instructed to wash their hands with mild soap and water before and after each application.

- Caregivers who are pregnant, or women of childbearing potential who are trying to become pregnant, should avoid accidental exposure by either avoiding applying investigational product or wearing gloves during its application. Care should also be taken when handling the child after investigational product has been applied.

- CCI [redacted]

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

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

5. STUDY TREATMENTS

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

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

5.1. Allocation to Treatment

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

All subjects will receive crisaborole ointment 2% during their participation in this study. Subjects will be enrolled through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The IRT system will provide a confirmation report containing the subject number and dispensable unit (DU) or container number(s) assigned. The confirmation report must be stored in the site's files.

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

5.2. Subject Compliance

For subjects in the CC [redacted] cohort, a subject will be considered compliant with the dosing regimen if they receive at least 12 investigational product doses (no more than 2 missed doses between Day 1 and Day 6) administered in accordance with the protocol. Thereafter, CC [redacted] cohort subjects will be considered compliant with the dosing regimen if they receive at least 33 but no more than 49 investigational product doses (ie, 80–120%, inclusive, of the expected number of doses) administered in accordance with the protocol.

For Non-PK subjects, a total of 56 doses are expected to be applied. A subject will be considered compliant with the dosing regimen if they receive at least 45 but no more than 67 investigational product doses (ie, 80–120%, inclusive, of the expected number of doses) administered in accordance with the protocol.

Following the Baseline/Day 1 visit, a parent/legal guardian will apply crisaborole ointment 2% to the subject at home for subjects in the nonPK cohort The CC [redacted] cohort will have investigational product applied either at the site or at home by a visiting healthcare professional during the PK portion of the study, and the remaining doses applied at home. Compliance with all at-home dosing will be recorded by the parent(s)/legal guardian using a dosing diary provided by the site.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

Crisaborole ointment 2% investigational product will be supplied in 60 g tubes. The tubes will be labeled according to local regulatory requirements.

5.4. Investigational Product Storage

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

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

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

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

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

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

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

Site staff will instruct the subject's parent(s)/legal guardian on the proper storage requirements for take home investigational products. For crisaborole ointment 2%, subject's parent(s)/legal guardian will be instructed to store investigational product at room temperature, away from sunlight or heat.

5.5. Administration

Crisaborole ointment 2% is for external use on the skin only. Large areas that need to be treated can have the ointment applied slowly and segmentally to minimize pain associated with application. Subjects should avoid contact with mucous membranes (ie, inside of nostrils, mouth, vagina, urethra, and rectum), and the eyes. Additionally, for subjects in the CC cohort, though AD lesions in the perioral area (within 2 cm of the mouth) or on the extremities (below wrists and below ankles) are exclusionary at baseline, if they occur following enrollment, crisaborole ointment 2% should not be applied to those areas during the CC phase (Day 1 AM dose through Day 8 final CC sample collection) in order to reduce the possibility of accidental ingestion that could adversely affect CC results.

5.6. Preparation and Dispensing of Investigational Product

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

The investigational product will be dispensed using an IRT drug management system from Baseline/Day 1 to the Day 15 visit. A qualified staff member will dispense the investigational product via unique container numbers in the cartons provided, in quantities appropriate for the study visit schedule.

For doses to be administered at home, the caregiver (parent(s)/legal guardian) or the visiting health care professional, where applicable, should be instructed to maintain the product in the package provided throughout the course of dosing and return all used and unused product and cartons to the site at the next study visit.

5.7. Investigational Product Application

5.7.1. Non-PK Cohort Subjects

Before the Day 1 initial investigational product application is performed, the designated areas for treatment will be identified at the Baseline/Day 1 visit and documented in the subject's study records. The subject's parent(s)/legal guardian will be provided with a body map documenting the designated treatment areas and a paper dosing diary for recording all investigational product applications applied at home.

Wearing gloves, study staff will apply a thin layer of crisaborole ointment 2% to all treatable AD lesions identified at Baseline/Day 1 for the purpose of instructing the parent(s)/legal guardian how to dispense and apply the ointment. All subsequent doses, including second dose on Day 1, will be applied at home. See Section 5.8 for details regarding study treatment regimen.

The parent(s)/legal guardian will not be expected to wear gloves when applying investigational product at home but will be instructed to wash their hands with mild soap and water before and after each application. The investigational product will be applied to all treatable AD lesions as instructed by study staff.

CCI

[redacted]

[redacted]

5.8. Study Treatment Regimen

5.8.1. Non-PK Cohort Subjects

The initial dose application on Baseline/Day 1 will be applied in the clinic, and all subsequent doses will be applied at home by the subject's parent(s)/legal guardian. The subject's parent(s)/legal guardian will be instructed to apply evening (PM) doses approximately 8–12 hours after the morning (AM) doses (eg, if an AM dose is completed at 8:00 AM, the PM dose can be applied anytime between 4:00 PM and 8:00 PM).

A thin layer of crisaborole ointment 2% will be applied BID to all treatable AD-involved areas identified at Baseline/Day 1. Investigational product will continue to be applied to all treatable AD-involved areas (excluding scalp) identified at Baseline/Day 1 regardless of whether they become clinically clear prior to Day 29. Investigational product may also be applied to any new treatable AD-involved areas that appear following Baseline/Day 1 after consultation with the Investigator at the next visit.

For each study visit, subjects will arrive at the clinic having had the morning dose applied at home, with the exception of Day 29/Early Termination visit. Dosing should continue up until the PM dose before that visit but no morning dose should be applied on Day 29. The parent(s)/legal guardian will be instructed regarding the preferred AM and PM time windows for dosing as well as the amount of crisaborole ointment 2% to be applied. The parent(s)/legal guardian will be provided with dosing instructions and a dosing diary to be completed and brought to all study visits after Day 8.

CCI [redacted]

[redacted]

[redacted]

However, if desired, the protocol allows for a visiting health care professional to assist with twice daily doses in the subject's home for some or all of the dose applications during the CC portion of the study. This service may be utilized after the Baseline/Day 1 AM dose, based on site and parent(s)/legal guardian agreement. Day 8 AM dosing application and with any 2 of the 3 scheduled CC sample collections may also be performed by the visiting health care professional if preferred, however the subject must visit the site for one of the scheduled CC sample collections in order to perform the remainder of the Day 8 assessments and procedures.

After the AM dose application on Day 8, the remainder of the doses following the last CC sample collection (Day 8 PM dose through the AM dose on the Day 29 visit) will be applied at home by the subject's parent(s)/legal guardian. If preferred, the Day 8 PM dose may be applied at the site. The weighed per application dose is no longer a requirement; rather the parent(s)/legal guardian will be instructed to apply a thin layer of crisaborole ointment 2% BID to all treatable AD-involved areas identified at Baseline/Day 1. Investigational product will continue to be applied to all treatable AD-involved areas (excluding scalp) identified at Baseline/Day 1 regardless of whether they become clinically clear prior to Day 29.

Investigational product may also be applied to any new treatable AD-involved areas that appear following Baseline/Day 1 after consultation with the Investigator at the next scheduled visit. While lesions on the extremities (below wrists and below ankles) or within 2 cm of the mouth are exclusionary at the time of the Baseline/Day 1 visit for subjects in the CC cohort visit, new lesions developing in these areas may be treated as appropriate following completion of the Day 8 CC sample collections.

For all remaining visits post-Day 8, subjects will arrive at the clinic having had the morning dose applied at home, with the exception of Day 29/Early Termination visit. Dosing should continue up until the PM dose before that visit but no morning dose should be applied on Day 29/ET. The subject's parent(s)/legal guardian will be instructed to apply evening (PM) doses approximately 8–12 hours after the morning (AM) doses (eg, if an AM dose is completed at 8:00 AM, the PM dose can be applied anytime between 4:00 PM and 8:00 PM. In addition, the parent(s)/legal guardian will be provided with a dosing diary to be completed and brought to all study visits after Day 8.

5.9. Dosing Modifications

In the event a scheduled application is missed, the parent(s)/legal guardian will be instructed to apply it when they remember if it is at least 8 hours before the next scheduled application. Otherwise, they will be instructed to skip the missed application, perform the next application at the normally-scheduled time, indicate the missed dose in the dosing diary, and report the missed application to the Investigator at the next visit.

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

Criteria for study drug discontinuation are outlined in Section 6.12.

5.10. Investigational Product Accountability

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

Throughout the study, detailed investigational product accountability records, including tube weights for all dispensed tubes as well as all returned empty, partially used and unused tubes, will be maintained for each subject by study staff. For PK cohort subjects during the CC Phase, study staff will record the weight (in g) of all applied doses, along with the weight of any amount(s) dispensed in error and discarded as waste.

The subject's parent(s)/legal guardian will be asked to bring all dispensed investigational product (including empty, partially used and unused tubes) and the dosing diary to the clinic at every visit. Detailed drug accountability records, including weekly tube weights measured in the clinic, will be maintained by study staff for each subject.

The original investigational product accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the Sponsor) when the study is complete.

5.10.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

For all investigational product returned to the investigator by the parent(s)/legal guardian, the investigator will maintain the returned supply until destruction is authorized. The sponsor or designee will provide instructions as to the disposition of any unused investigational product.

5.11. Concomitant Treatment(s)

All treatments (including medications and non-medication therapies) used for the treatment of AD and all other medications and topical products (including bland emollients, diaper creams and wipes, sunscreen, over-the-counter drugs, vitamins, and antacids) used within 30 days prior to Screening will be recorded as a concomitant treatment 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 subject's medical history or to an AE, except for vitamins/nutritional supplements and routine immunizations.

Classes of medications and non-medication therapies that might alter the course of AD and that require washout prior to Baseline/Day 1 are summarized below. If a subject requires a medication washout, the Investigator will provide instructions on discontinuing the prohibited medication(s) at the Screening Visit.

5.11.1. Medications/Therapies Prohibited During the Study

During the Study (Day 1 through Day 29 Visit)

- Systemic corticosteroids.
- Systemic immunosuppressive agents (eg, methotrexate, ciclosporin, azathioprine, hydroxychloroquine, mycophenolate mofetil).
- Use of high-or-mid-potency topical corticosteroids or calcineurin inhibitors anywhere on the body.
- Systemic antihistamines.
- Light therapy (ultraviolet light therapy).
- Systemic antibiotics for the treatment of new onset infections that require use longer than 14 days.
- Systemic leukotriene receptor antagonist agents (eg, montelukast).
- Wet wrap therapy.
- Use of topical medications or products on AD lesions, including, but not limited to:
    - Antibacterial soaps (for bathing);
    - Bleach baths;
    - Topical sodium hypochlorite-based products;
    - Topical antihistamines;
    - Topical antibiotics (unless required for AE treatment);
    - Emollients;
    - Topical low potency corticosteroids (including hydrocortisone ≤1%);
    - Diaper rash creams, lotions, ointments, powders, etc. where lesions are present.

5.11.2. Medications/Therapies Allowed During the Study

During the Study (Day 1 through Day 29 Visit):

- Use of intranasal, ophthalmic and inhaled corticosteroids.
- Use of bland emollient(s) of choice to manage dry skin in areas surrounding, but not on or overlapping with treatable AD-involved areas.
- Use of bland emollient(s) of choice (not containing urea) in AD skin areas where crisaborole is not applied (eg, scalp).
- Use of sunscreen, but not on or overlapping with treatable AD-involved areas.

All topical products and treatments applied during the study (including emollients, diaper creams, diaper wipes, sunscreen, etc.), whether over-the-counter or prescription, should be recorded as a concomitant treatment. CCI [redacted]

6. STUDY PROCEDURES

6.1. Study Visits

Subjects will be required to visit the clinic for all scheduled visits. The timing of each study day is relative to the day of initial dosing (Baseline/Day 1).

6.2. Time Windows for Study Procedures

When multiple assessments are scheduled at the same nominal time, they are to be performed in the following order: vital signs, followed by CC [redacted] sampling, followed by clinical laboratory tests. Sampling for CC [redacted] should occur as close as possible to the scheduled nominal time.

Allowable time windows for other visits/contacts are as follows:

- Day 8 ±1 day;
- Day 15 ±3 days;
- Day 22 ±3 days;
- Day 29 ±3 days;
- Day 36 ±3 days;
- Day 57 +3 days.

CCI [redacted]

[redacted]

- Before AM dose on Day 8 (ie, 168 hours ±1 hour after recorded time of completion of the Day 1 AM dose application);
- 3 hours ±20 minutes after recorded time of completion of the Day 8 AM dose application;
- 12 hours ±1 hour after recorded time of completion of the Day 8 AM dose application.

Any CC sample collections and/or investigational product applications that occur outside of the specified windows will be reported as protocol deviations.

6.3. Screening Period

Screening procedures must be completed between 2 and 28 days (inclusive) prior to the Baseline/Day 1 Visit. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from the subject's parent(s)/legal guardian in accordance with the procedures described in the Subject Information and Consent section. If the time between Screening and dosing exceeds 28 days as a result of delays outside of the control of the study team (eg, delayed drug shipment), then subjects do not require re-screening if the laboratory results meet the eligibility criteria.

If necessary, the screening procedures may be completed over several days.

The following procedures will be performed at the Screening Visit:

- Obtain written informed consent before any study-specific evaluations or procedures are done;
- Collect demographic information;
- Review and record medical history (including immunizations, childhood illnesses, history of febrile convulsions);
- Confirm clinical diagnosis of AD including the date of onset (date of diagnosis, as specifically as known);
- Measure weight and height/length (see Section 7.1.2).
- Obtain vital signs (temperature, respiratory rate, pulse rate, and blood pressure [BP]) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes;
- Obtain a 12-lead ECG after the subject has been resting quietly (may be performed at Baseline/Day 1).

- Perform a full physical examination. If the full examination cannot be completed during screening, an unscheduled visit may be performed prior to Baseline/Day 1 to complete the full assessment.

[redacted]

- Review Inclusion Criteria and Exclusion Criteria.

- Draw blood for clinical laboratory tests (may be completed any time during the screening period Day -28 to Day -2), however the chemistry and hematology results must be available and reviewed by the PI prior to the Baseline/Day 1 visit and investigational product application. If the laboratory sample cannot be obtained due to an upset child, parent or other collections issues the subject cannot be enrolled into the study. Assessment of vital signs should precede blood draw for clinical laboratory tests whenever possible. Laboratory testing includes: (see Section 7.1.1).

  - Serum chemistry and hematology (see Section 7.1.1).

[redacted]

    - Note: The skin at the venous access area must be thoroughly cleansed prior to blood sample collection.

    - Note: Upon receipt of the Screening serum chemistry, and hematology results, if there are any clinically significant abnormalities that the PI or designee feels prohibit initiation of investigational product treatment, the PI or designee may contact the sponsor medical monitor to discuss the appropriate course of action.

- Review and record prior and concomitant medications. This includes all medications and non-medication therapies used for the treatment of AD, including bland emollients, and all other medications (over-the-counter drugs, vitamins, antacids, etc.) used within 30 days of Screening.
    - If a subject is using a prohibited medication (or non-medication therapy) at the time of Screening, the Investigator will provide instructions on discontinuing the prohibited medication or therapy (ie, a "washout" period) at the Screening Visit.
- Record any AEs and SAEs that have occurred since the time the consent was signed.
- Review the Lifestyle Requirements with the parent(s)/legal guardian.
- Note: The results of all screening evaluations, including laboratory results, must be reviewed for clinical significance by the PI or designee prior to enrollment on Baseline/Day 1. Only subjects with no clinically significant screening evaluation findings (with the exception of AD) may be enrolled in the study.
- Schedule the Baseline/Day 1 Visit and all future study visits for the subject's study visit calendar, and review the calendar with the parent(s)/legal guardian.

6.3.1. Investigational Product Application Period

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

- Blood pressure/pulse rate should be obtained prior to blood specimen collection whenever possible;
- CCI [redacted]
- [redacted] procedures: all other procedures may be obtained before or after blood specimen collection.

When an intravenous catheter is utilized for blood sample collections, vital signs (pulse rate [PR], respiration rate [RR], BP and Temperature) should be collected prior to the insertion of the catheter whenever possible.

6.4. Baseline/Day 1

Subjects may return for the Baseline/Day 1 visit as soon as all Screening procedures are performed, prohibited medications have been discontinued for the required washout period, and the safety laboratory results have been reviewed by the PI and deemed acceptable.

The following procedures will be performed at the Baseline/Day 1 visit.

- Assess and record any changes in the subject's medical history since the Screening visit.
- Reconfirm diagnosis of AD and document in source.
- [redacted]
- Measure height/length and weight (see Section 7.1.2).
- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes; assessment of vital signs should precede blood draw for clinical laboratory tests whenever possible.
- Perform a limited physical examination.
- Obtain a 12-lead ECG after the subject has been resting quietly, if not performed at the Screening visit.
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Complete a Body Site checklist identifying the location of AD lesions.
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- Mark the subject's source documents to record the treatable AD areas, excluding the scalp, as identified by the PI or designee at Baseline/Day 1 and provide parent(s)/legal guardian with documentation of the designated treatment areas.

- Confirm subject's eligibility based on the Inclusion Criteria and Exclusion Criteria.
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.
- Assess and record any predose AEs and SAEs.
- Review the Lifestyle Requirements with the parent(s)/legal guardian.
- After PI's or designee's documented confirmation of eligibility, access IRT system to receive randomization number.

CCI [redacted]

- Dispense and weigh investigational product tube(s) before applying first dose; record tube weight(s) in subject's source documents.
- Wearing gloves, study staff will apply a layer of investigational product to all treatable AD lesions identified at Baseline/Day 1.

The following procedures will be performed at the Baseline/Day 1 Visit AFTER dosing with investigational product:

- Assess and record any post-dose AEs, including potential hypersensitivity and/or application site reactions, and SAEs.
- Provide to parent(s)/legal guardian a sufficient number of tubes of investigational product to allow for dosing until the next scheduled visit.
- Instruct the parent(s)/legal guardian regarding investigational product application (see Section 5.7) to begin with the evening (PM) dose on Day 1 followed by BID dosing up to the PM dose prior to the Day 29 visit.
- Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use (ie, each time study drug is applied).
- Review the schedule of upcoming study visits with parent(s)/legal guardian, and instruct them to return at the scheduled time for the Day 8 Visit.
- Remind the parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to their next visit.

6.5. Day 8 (±1 day) Study Visit

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes.
- Obtain a 12-lead ECG after the subject has been resting quietly.
- .
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.
- Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.
- Collect and weigh empty, partially used and unused investigational product tubes; record tube weight in subject's source documents. (Not applicable to subjects in CC cohort through Day 8).
- Mark the subject's source documents to record the treatable AD areas (including new areas to be treated), excluding the scalp, as identified by the PI or designee and provide parent(s)/legal guardian with documentation of the designated treatment areas.
- Dispense, and weigh new investigational product tube(s) for at-home dosing by parent(s)/legal guardian and record tube weight in source documents. Provide a sufficient number of tubes of investigational product to allow for dosing until the next scheduled visit.
- Review dosing diary; assess compliance; re-train parent(s)/legal guardian if doses missed.
- Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use.
- Review the Lifestyle Requirements with the parent(s)/legal guardian.
- Instruct the parent(s)/legal guardian regarding all procedures for at-home dosing BID dosing through Day 29 visit, including how to complete the dosing diary, which started at the Baseline/Day 1 visit and will continue BID through Day 29 visit (ie, each time investigational product is applied).
- Review the schedule of upcoming study visits with the parent(s)/legal guardian, and instruct them to return at the scheduled time for the Day 15 Visit.

- Remind the parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to the next visit.

6.6. Day 15 (±3 days) Study Visit

[redacted]

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes.

[redacted]

[redacted]

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.

- Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.

- Collect and weigh empty, partially used and unused investigational product tubes; record tube weight in subject's source documents.

- Mark the subject's source documents to record the treatable AD areas (including new areas to be treated), excluding the scalp, as identified by the PI or designee and provide parent(s)/legal guardian with documentation of the designated treatment areas.

- Review dosing diary; assess compliance; re-train parent(s)/legal guardian if doses missed.

- Dispense and weigh new investigational product tube(s) for at-home dosing by parent(s)/legal guardian and record tube weight in source documents. Provide a sufficient number of tubes of investigational product to allow for dosing until the next scheduled visit.

- Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use.

- Review the Lifestyle Requirements with parent(s)/legal guardian.

- Instruct the parent(s)/legal guardian regarding all procedures for at-home dosing BID dosing through Day 29 visit, including how to complete the dosing diary, which started at the Baseline/Day 1 visit and will continue BID through Day 29 visit (ie, each time investigational product is applied).

- Review the schedule of upcoming study visits with the parent(s)/legal guardian, and schedule a time for the Day 22 telephone contact.

- Remind the parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to their next visit.

6.7. Day 22 (±3 days) Telephone Contact

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.

- Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.

    - If concerns are identified, the investigator may request the subject be brought to the site for an unscheduled visit for further assessment of AEs/SAEs.

- Review dosing diary by phone; assess compliance; re-train parent(s)/legal guardian if doses missed.

- Review the Lifestyle Requirements with the parent(s)/legal guardian.

- Review the schedule of upcoming study visits with the parent(s)/legal guardian, and instruct them to return at the scheduled time for the Day 29 visit.

- Remind the parent(s)/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the dosing diary to their next visit. Site staff should instruct the parent(s)/legal guardian that subject dosing should continue up until the PM dose prior to the Day 29 visit. No dose should be applied the morning of the Day 29 visit.

6.8. Day 29/End of Treatment (±3 days) Study Visit

In the event that the scheduled Day 29 visit does not fall exactly on Day 29, instruct the parent(s)/legal guardian to keep dosing BID until the evening dose prior to the Day 29 visit. No dose should be applied at home the morning of the Day 29 visit. Day 29 requires early morning scheduling as sample collection for assessment of CCI [redacted] systemic levels and lactate should be collected within 12 ±3 hours of the final Day 28 evening application.

[redacted]

- Measure height/length and weight.

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes.

- Obtain a 12-lead ECG after the subject has been resting quietly.
- Perform a full physical examination.
- [redacted]
- [redacted]
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.
- Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.
- Draw blood for clinical laboratory tests; assessment of vital signs should precede blood draw for clinical laboratory tests whenever possible. Laboratory testing includes:
  - Serum chemistry and hematology (see Section 7.1.1).
  - [redacted]
    - Note: The skin at the venous access area must be thoroughly cleansed prior to blood sample collection.
- Collect and weigh empty, partially used and unused investigational product tubes; record tube weight in subject's source documents.
- Collect the dosing diary and assess compliance.
- Review the Lifestyle Requirements with the parent(s)/legal guardian.
- Review the schedule of upcoming study visits with the parent(s)/legal guardian, and schedule a time for the Day 36 telephone contact.

6.9. Unscheduled Visit

The procedures performed at an Unscheduled Visit will depend on the reason for the visit (some procedures may not apply).

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.11.

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes.

- Ensure that the subject has adequate investigational product to support dosing until the next scheduled visit. If additional investigational product is needed, provide to parent(s)/legal guardian a sufficient number of tubes of investigational product to allow for dosing until the next scheduled visit. Ensure that all dispensed tubes are weighed and weight is recorded in subject's source documents.

- Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.

- Review the schedule of upcoming study visits with the parent(s)/legal guardian, and instruct them to return at the scheduled time.

6.10. Post-treatment Follow-up Period

6.10.1. Day 36 (±3 days) Telephone Contact

- Assess and record any changes in concomitant medications, (see the Time Period for Collecting AE/SAE Information section). Assess and record any AEs, including potential hypersensitivity and/or application site reactions, and SAEs.

    - If concerns are identified, the investigator may request the subject be brought to the site for an unscheduled visit for further assessment of AEs/SAEs.

- Schedule the Day 57 follow up phone contact.

6.10.2. Follow-up Contact (Day 57 (+3 days) End of Study)

Follow-up contact will be completed 28 +3 calendar days after the last administration of the investigational product to capture any adverse events including ongoing potential hypersensitivity and/or application site reactions and to review and record concomitant medications (see the Time Period for Collecting AE/SAE Information section). Contact with the subject may be done via a phone call. Any subject with a new or ongoing adverse event at the time of the Day 57 visit should however be seen in the clinic for evaluation of that adverse event.

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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- [redacted]
- [redacted]
- [redacted]
- [redacted]


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[redacted]

6.12. Subject Withdrawal/Early Termination

The following criteria will be considered for the subjects' discontinuation or withdrawal from the study:

- The occurrence of adverse events that require the subject to stop participation in the study, due to availability for, or intolerance to, the study procedures.
- Adverse effects of the study active ingredient that are considered to be clinically significant by the physician in charge, and/or might be harmful to the subjects' health.
- Abnormal laboratory tests considered to be clinically relevant.
- Concurrent diseases that require use of a prohibited medication.
- CCI [redacted]
- Clinically significant hypersensitivity reactions.

Subjects may be withdrawn from the study at any time at their parent(s)/legal guardian's request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or, behavioral reasons, or the inability of the subject's parent(s)/legal guardian to comply with the protocol required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are enrolled and then are prematurely withdrawn from the study.

Subjects should return to the clinic for the early termination visit as early as practically feasible following the decision to withdraw from the study. Subject's parent(s)/legal guardian should be questioned regarding their reason for withdrawal. Every effort must be made to complete the assessments outlined in the Day 29/End of Treatment visit (Section 6.8). Subjects will in addition be requested to be available for the follow-up contacts at 1 week and 4 weeks after last dose of study treatment.

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

Withdrawal of consent:

Subjects for whom it has been requested to discontinue receipt of study treatment by the parent(s)/legal guardian must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject's parent(s)/legal guardian specifically withdraws consent for the subject for any further contact with him or her or persons previously authorized to provide this information. The subject's parent(s)/legal

guardian should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate case report form (CRF) page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects who are withdrawn from the study may be replaced at the discretion of the investigator upon consultation with the sponsor. In the CC cohort, subjects discontinuing for reasons other than TEAE may be replaced at the discretion of the sponsor to ensure 16 subjects complete the CC assessments.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject's parent(s)/legal guardian as noted above. Lost to follow-up is defined by the inability to reach the subject's parent(s)/legal guardian after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's parent(s)/legal guardian contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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

7. ASSESSMENTS

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

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

7.1. Safety

7.1.1. Clinical Laboratory Evaluations

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

The clinical laboratory test parameters that will be reviewed for safety evaluation are presented in Table 2.

Table 2. Clinical Laboratory Test Parameters

Hematology	Chemistry	Other Bioanalytical Laboratory Assessment
Hemoglobin Hematocrit Red blood cell count Platelet count White blood cell count (% and absolute) • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes	Blood urea nitrogen Glucose (non-fasting) Creatinine Sodium Potassium Chloride Bicarbonate Alanine aminotransferase Aspartate aminotransferase Total bilirubin Alkaline phosphatase Albumin Total protein Lactate Calculation of osmolal gap Calculation of anion gap	CCI [redacted]

Baseline clinical laboratory tests will be drawn during the Screening visit, after assessment of vital signs and prior to the first investigational product application.

At the discretion of the Investigator, a lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject provided the anesthetic CCI [redacted] The skin must be thoroughly cleansed prior to blood sample collection.

The Investigator will review all clinical laboratory test results for safety evaluation upon receipt. After reviewing the laboratory reports and evaluating the results for clinical significance, the Investigator or designee must sign and date the laboratory report. Clinically significant laboratory abnormalities are defined as abnormal values that have clinical manifestations or require medical intervention. Clinically significant laboratory abnormalities noted from the Screening Visit will be recorded in the medical history. Note: Upon receipt of the Screening serum chemistry, and hematology results, if there are any clinically significant abnormalities that the PI or designee considers prohibit initiation of investigational product treatment, the PI or designee may contact the sponsor medical monitor to discuss the appropriate course of action.

A clinically significant laboratory abnormality detected after the Screening Visit may reflect the development of an AE. Whenever possible, Investigators should report the clinical diagnosis suggested by the laboratory abnormality rather than listing individual abnormal test results as AEs. If no diagnosis has been found to explain the abnormal laboratory result, the clinically significant lab result should be recorded as an AE, reflecting the lack of a diagnosis (see Section 8.2.2).

7.1.2. Physical Examination, including Height/Length, and Weight

Physical examinations, including height/length, and weight will be performed at times specified in the STUDY PROCEDURES section of this protocol.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include, but is not limited to the following organ or body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, abdomen (liver, spleen), cardiovascular, and neurological systems. In addition, an assessment will be made of the condition of all AD-involved skin.

The limited or abbreviated physical examination will be focused on general appearance, the respiratory, cardiovascular, and neurological systems, as well as towards symptoms reported by the subject's parent(s)/legal guardian. In addition, symptoms and signs of diarrhea and vomiting should be assessed to monitor for evidence of dehydration.

The neurological examination component of all physical examinations should include evaluation of clinical signs that have been associated, in published reports, with [redacted] toxicity[21] including central nervous system depression, seizure activity, ataxia, as well as somnolence, poor feeding and irritability which are considered newly emergent and independent of the subject's AD related signs.

Results from blood pressure and prior ECG assessments should be referred to when performing the cardiovascular component of all physical examinations in order to actively monitor for clinical signs that have been associated, in published reports, with [redacted] toxicity including hypotension and cardiac arrhythmia.

For both weight and height/length measurements, the investigator or examiner should be trained in measuring height/length and weight as well as in calibration procedures. Ideally, the same person should measure the subject at every visit. Attempts should be made to schedule visits, so that measurements can be taken at approximately the same time throughout the study. The parent / caregiver is needed to help with measurement and to soothe and comfort the child. Explain to the parent/ caregiver the steps in the procedures and that it is important to keep the child still and calm to obtain good measurements.

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

For measuring length, a length board (infantometer) must be used and be placed on a flat, stable surface, such as a table.

For both weight and height/length, three reproducible measurements of both the child's weight and height/length should be recorded and the average of the 3 recordings will be entered onto the eCRF.

7.1.3. Electrocardiogram

A single standard supine 12-lead ECG will be performed at times defined in the STUDY PROCEDURES section of this protocol. In the event of a 12-lead ECG cannot be obtained due to technical reasons (eg, pediatric patient with small chest), a 6-lead ECG should be obtained instead. Assessment should be performed after the subject has been resting quietly and precede measurement of vital signs and blood draws whenever possible. An ECG collection device will be provided by a central vendor and ECG data will be submitted to the central laboratory for measurement. ECG interpretation will be provided directly to the site indicating central reader assessed relevance of abnormal findings. It is the responsibility of the investigator to assess the findings based on the subject's clinical presentation and determine clinical significance for a given subject. Any clinically significant changes from the Baseline/Day 1 ECG should be recorded as AEs and evaluated further as clinically warranted.

7.1.4. Vital Signs (temperature, respiratory rate, pulse rate, and BP

Vital signs will be measured at times specified in the STUDY PROCEDURES section of this protocol. Vital sign measurements (temperature, respiratory rate, pulse rate, and BP) should be performed with the subject in the seated or supine position and after the subject has been sitting or lying face up for a minimum of 5 minutes. Eating or drinking should be avoided for 15 minutes prior to the measurements.

On study day visits when clinical laboratory tests are performed, assessment of vital signs should precede blood draw whenever possible.

7.2. Efficacy

[redacted]

[redacted]

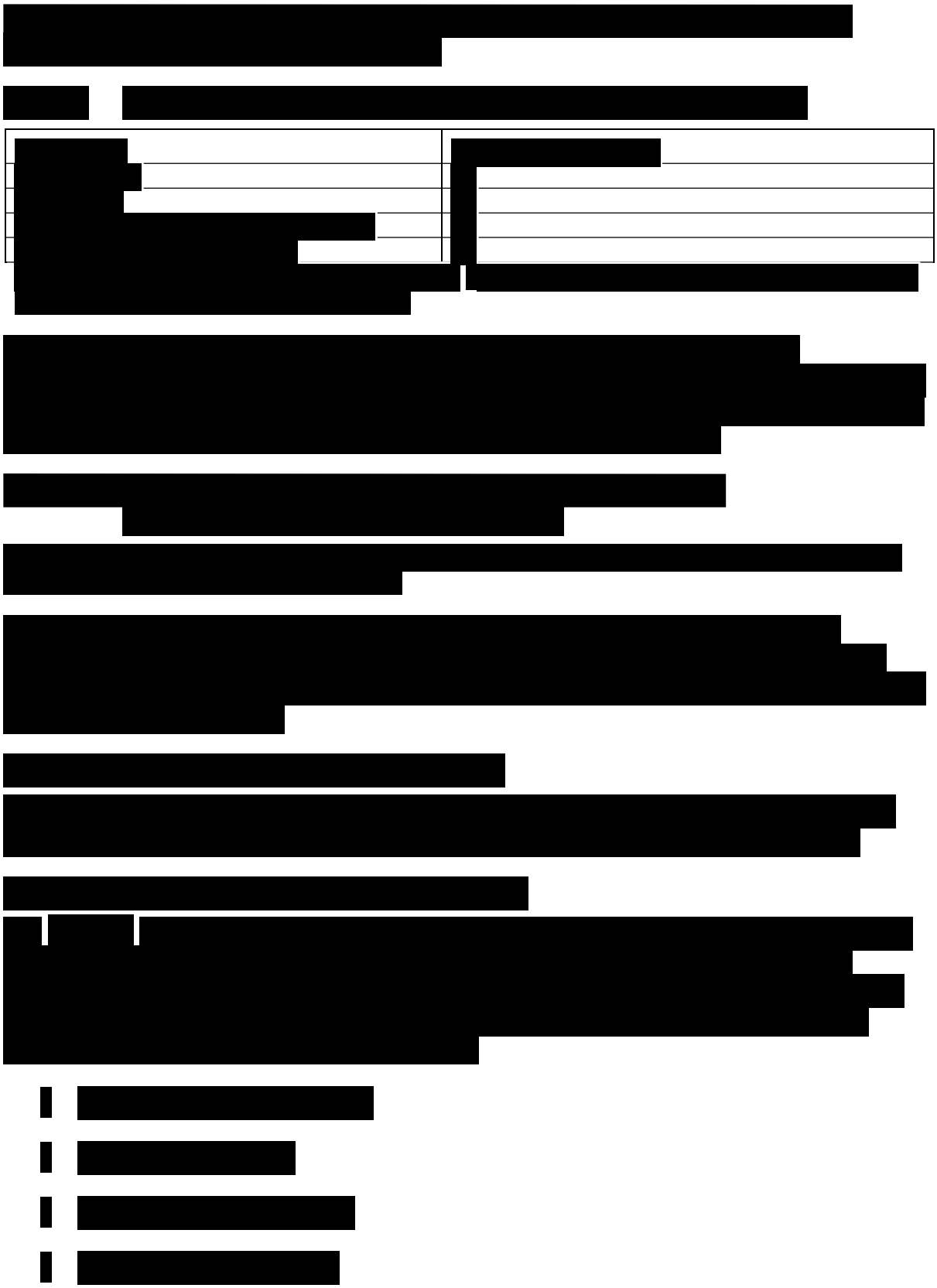
[redacted]

[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]



- 25 to 28 = Very severe eczema.

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[redacted]

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)
Abbreviations: CRF=case report form; CT=clinical trial; SAE=serious adverse event; AE=adverse event.		

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

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

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

In this protocol, in which the 3 month to less than 24 month old subjects are receiving investigational product via topical application by the parent/legal guardian, an EDP may occur to the parent/legal guardian via environmental exposure.

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

This is a multi-center, open-label, safety study of subjects with AD. To ensure 100 completers, 125 subjects will be enrolled assuming a 20% drop out rate. Of the 125 subjects enrolled, at least 16 subjects with moderate AD and [redacted] excluding scalp, who have completed all CC assessments will be included in a subgroup for CC assessment. The sample size was determined by clinical judgment based on

Sponsor experience with other clinical studies with the investigational product and was not based on statistical power.

CCI

[redacted]

[redacted]

9.2. Analysis of the Primary Endpoint

Any subject receiving ≥1 dose of investigational product will be included in safety analysis set.

9.2.1. Safety

Safety data will be descriptively summarized (including extent of exposure), and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data.

All AE(s) that occur after signing of the informed consent through the final study visit will be recorded, classified and listed on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AE(s) (TEAEs) are defined as, 1) AEs where the onset is on or after the first investigational product administration or, 2) there is a worsening of a pre-existing condition on or after the time of the first dose of investigational product administration. TEAEs will be summarized by the number of subjects reporting any TEAE, SOC, PT, severity, relationship to investigational treatment, and seriousness. When summarizing TEAEs by relationship and severity, each subject will be counted only once

within a SOC or a preferred term by using the event with the greatest relationship and highest severity within each classification.

Serious adverse events (SAEs) will be summarized by SOC and PT, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinue from the study due to an AE will be provided.

Clinically significant changes in height, weight, vital signs, ECG and safety laboratory parameters will be summarized.

[redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

9.4. Extent of Exposure

The extent of exposure to investigational product will be summarized by the total number of days of dosing, total number of applications, total amount of investigational product applied, and number and percentage of subjects who are compliant with the dosing regimen.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment facilitating CCI [redacted] pharmacodynamic (PD) modeling, and/or to support clinical development.

9.6. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for a final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

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

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

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

All subjects enrolled in this study will be 3 months to less than 24 months of age at the time of their enrollment in this study. The maximum duration of this study is 88 days and therefore no subjects will reach an age where they are able to provide informed consent/assent during their participation. As such, informed consent must be obtained from their parent(s)/legal guardian.

The investigator must ensure that each study subject's parent(s)/legal guardian is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's parent(s)/legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

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25. Anacor Pharmaceuticals Report No. 003-NCL PP-017-01, Effect of AN2728 on Inhibition of IL-23 Production in THP-1 Cells Stimulated with Interferon-γ and Lipopolysaccharide.

26. Anacor Pharmaceuticals Report No. 003-NCL PP-001-01, Effect of AN2728 on the Inhibition of Cytokine Release from Human Peripheral Blood Mononuclear Cells Challenged with LPS or PHA.

27. Anacor Pharmaceuticals Report No. 003-NCL PP-007-01, Effect of AN2728 in Inhibition of IL-1β, IL-4, TNFα, and IFNγ from PBMCs Challenged with PHA for 24 h.

28. Anacor Pharmaceuticals Report No. 003-NCL PP-008-01, Effect of AN2728 in Inhibition of IL-1β, IL-4, TNFα, and IFNγ from PBMCs Challenged with PHA for 24 or 48 h.

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Appendix 1. Abbreviations

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

Abbreviation	Term
AD	atopic dermatitis
ADSI	atopic dermatitis severity index
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BP	blood pressure
[redacted]	[redacted]
cAMP	cyclic adenosine monophosphate
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed plasma concentration
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
DILI	drug-induced liver injury
DU	dispensable unit
[redacted]	[redacted]
EC	ethics committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GRAS	generally recognized as safe
HRQL	health-related quality of life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	investigational new drug application
INR	international normalized ratio

Abbreviation	Term
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
[redacted]	[redacted]
IVIG	intravenous immunoglobulin
IWR	interactive web response
LFT	liver function test
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MUSE	maximal use, systemic exposure
N/A	not applicable
NOAEL	no observed-adverse-effect level
NOEL	no observed-effect level
PCD	primary completion date
PD	pharmacodynamics(s)
PDE4	phosphodiesterase-4
CC[redacted]	[redacted]
PI	principal investigator
CC[redacted]	[redacted]
PKA	protein kinase a
PMA	phorbol 12-myristate 13-acetate
[redacted]	[redacted]
PT	prothrombin time
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal phase half-life
TEAE	treatment emergent adverse event
TBili	total bilirubin
T_{max}	time to reach maximum observed plasma concentration
ULN	upper limit of normal
US	United States

Appendix 2. Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[45]

Table 8. Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Major Criteria (must have at least three)
Pruritus
Typical morphology and distribution:
Adults: flexural lichenification or linearity
Children and infants: facial and extensor involvement
Chronic or chronically-relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Minor Criteria (must have at least three)
Xerosis
Ichthyosis/keratosis pilaris/palmar hyperlinearity
Immediate (type 1) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (esp. staphylococcus aureus and herpes simplex), impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor, facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Periofollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors
White demographism, delayed blanch