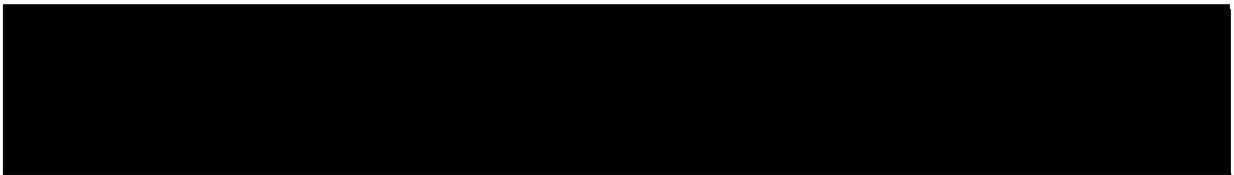




**A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED  
STUDY, TO CHARACTERIZE THE MECHANISM OF ACTION OF  
CRISABOROLE OINTMENT 2%, BY EVALUATION OF EFFICACY AND  
CHANGES IN SKIN BIOMARKERS, IN ADULT SUBJECTS WITH MILD TO  
MODERATE ATOPIC DERMATITIS, WITH A 4 WEEK OPEN-LABEL  
EXTENSION**

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## **PROTOCOL SUMMARY**

### **Background and Rationale:**

Atopic Dermatitis (AD) is an inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.<sup>1,6</sup> The majority of patients (up to 90%) with AD present with mild to moderate disease.<sup>7</sup> Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, and lichenification.<sup>8</sup> Continuous scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections. AD is often associated with significant morbidity, including asthma, allergic rhinitis, and food allergy. Currently, there is no cure for AD. AD is a chronic disease with treatment focused on the management of flares and maintenance of remissions.

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

Supporting evidence of the safety and efficacy of crisaborole in subjects 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 the two Phase 3 registration studies. Across the Phase 3 development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related Serious Adverse Events (SAEs) and with the majority of Adverse Events (AEs) being mild and deemed unlikely or not related to investigational product.

### **Objectives and Endpoints**

#### **Primary Objective(s):**

- To evaluate the efficacy of crisaborole ointment 2% vs vehicle in subjects with mild to moderate AD.
- To evaluate change in key skin biomarkers of AD in target lesions treated with crisaborole ointment 2% or vehicle.

#### **Secondary Objective(s):**

- To evaluate change in other skin biomarkers of atopic dermatitis in target lesions treated with crisaborole ointment 2% or vehicle.

- To evaluate normalization of biomarker and gene expression levels in lesional skin treated with crisaborole ointment 2% or vehicle.
- To evaluate changes in AD clinical sign and symptom severity in target lesions treated with crisaborole ointment 2% or vehicle.
- To assess the safety and local tolerability of crisaborole ointment 2% in subjects with mild to moderate AD.

CCI [REDACTED]

- [REDACTED]
- [REDACTED]

**Primary Endpoint(s):**

- Change from baseline in Total Sign Score (TSS) in target lesions treated with crisaborole ointment 2% or vehicle on Day 15.
- Change from baseline in key skin biomarkers of AD (S100A12, CCL17, CCL18, CCL22, K16, elafin/PI3 and IL-13 expression level) in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.

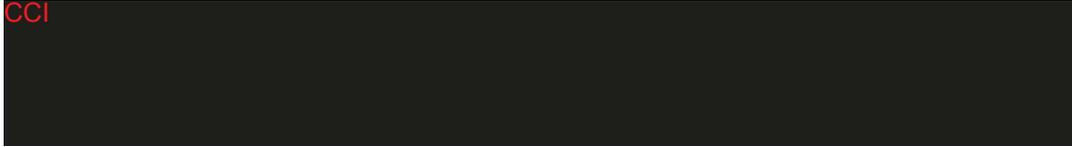
**Secondary Endpoint(s):**

- Change from baseline in other skin biomarkers in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.
- Biomarker and gene expression level in lesional skin treated with crisaborole ointment 2% or vehicle at Day 15 and levels in non-lesional skin at Baseline.
- Change from baseline in lesion severity as measured by TSS, Investigator Static Global Assessment (ISGA) and Pruritus Numerical Rating Scale at each visit up to Day 15.
- The incidence of treatment emergent AEs and SAEs.

CCI [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

CCI



## Study Design

This is a Phase 2a randomized, double-blind, vehicle-controlled study to characterize the mechanism of action, by evaluation of efficacy and changes in key skin biomarkers, of crisaborole ointment 2% in subjects with mild to moderate atopic dermatitis. After completing screening activities, including meeting eligibility criteria, approximately 40 subjects will be treated. In the double-blind treatment period, each subject will be randomly assigned to be treated with crisaborole ointment 2% for one target lesion. The other target lesion will receive vehicle.

The double-blind treatment period will last from Baseline/Day 1 to Day 15 skin biopsy collection and will include twice daily visits to the site for IP application and study assessments, where applicable. The open-label treatment period will start from the Day 15 skin biopsy collection and last until Day 43 (end of treatment/early termination); during this time, subjects will be able to treat all AD skin areas (except scalp), at home, with crisaborole ointment 2%.

In this study, skin biopsies will be collected to characterize the mechanism of action, by evaluation of efficacy and changes in skin biomarkers, of crisaborole ointment 2% over vehicle, applied twice a day in adult subjects with AD with maximum treatable BSA of 10%. The skin biopsy samples will be analyzed using immunohistochemistry (IHC) and gene expression, which will be done using Taqman Low Density Array (TLDA) polymerase chain reaction (PCR) for 48 genes including housekeeping genes as well as single gene PCR for a few genes that are below detection level on TLDA.

## Statistical Method

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The following is the statistical methods for the primary endpoints.

For the lesion TSS, the linear mixed model will be used to model the intra-subject change from baseline in TSS between crisaborole ointment 2% treated lesion and vehicle treated lesion. The model includes the fixed effect of visit as factor, and an unstructured variance and covariance matrix will be used to model the dependence among the same subjects across different visits.

Comparison of pre and post treatment of biomarker expression levels in skin treated with crisaborole ointment 2% or vehicle will be performed. A mixed effect model will be used to analyze the change from baseline in biomarkers from the target lesion treated with crisaborole ointment 2% or vehicle.

## 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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Study Day(s)/Visit Identifier/Visit Window	Double-Blind Period						Open-Label Period			
	-30 to -1 Screen	1 Baseline	2 to 7	8	9 to 14	Double-Blind Early Termination	15+1	16-42	43±3 End of Treatment/ Open-Label Early Termination	71+3 Follow-up Contact <sup>a</sup>
CRU Visit	X	X	X → X	X	X → X	X	X		X	
Informed consent	X									
Demographics	X									
Medical/surgical history	X	X								
Review prior/concomitant treatment	X	→	→	→	→	X	→		→	X
Vital signs	X									
Height and Weight	X									
Full physical examination	X <sup>b</sup>									
Limited physical examination		X <sup>b</sup>				X			X	
Safety Laboratory Tests	X					X			X	
Pregnancy test <sup>c</sup>	X	X				X	X		X	
FSH <sup>h</sup>	X									
Inclusion/exclusion criteria	X	X								
Randomization		X								
Investigational product application (BID) and record dosing <sup>d</sup>		X	X	X	X		X	X		
Train and Dispense investigational product for outpatient application							X			
Subject diary training & distribution <sup>e</sup>							X			
Subject diary completion							X <sup>i</sup>	X→X		
Subject diary collection & review <sup>e</sup>									X	

Study Day(s)/Visit Identifier/Visit Window	Double-Blind Period						Open-Label Period			
	-30 to -1 Screen	1 Baseline	2 to 7	8	9 to 14	Double-Blind Early Termination	15+1	16-42	43±3 End of Treatment/Open-Label Early Termination	71+3 Follow-up Contact <sup>a</sup>
Collect investigational product from outpatient administration									X	
% BSA for eligibility (excluding face, scalp, axilla, genitals, groin area, palms, back of the hands, and soles)	X	X								
ISGA	X	X				X	X <sup>k</sup>		X	
Lesion ISGA (for each target lesion)	X	X		X		X	X <sup>k</sup>			
Lesion TSS (for each target lesion)		X		X		X	X <sup>k</sup>			
CCI										
Skin biopsy <sup>f</sup>		X		X <sup>f</sup>		X	X <sup>k</sup>			
CCI										
Pruritus numerical rating scale (for each target lesion)		X	X→X	X	X→X	X	X <sup>k</sup>			
Pruritus numerical rating scale (global)		X				X	X <sup>k</sup>	X	X	
Contraception Check <sup>g</sup>	X	X	X	X	X	X	X		X	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	X	→	→	→	X

Abbreviations: → = ongoing/continuous event; AD = atopic dermatitis; BID = twice a day; % BSA = percent of body surface area; CRU = Clinical Research Unit; CCI [redacted]; ET = Early termination visit; FSH = follicle-stimulating hormone; ISGA = investigator's static global assessment; CCI [redacted]; TSS = Total Sign Score.

- Follow-up contact will be completed at least 28 calendar days after the last administration of the investigational product to capture any potential adverse events and to confirm appropriate contraception usage. Visit is planned to occur as a telephone contact.
- The Screening physical examination (full) may be performed at Baseline/Day 1 visit at the discretion of the Investigator. If full exam is completed at Screening, a limited exam should be collected at baseline. Target treatment areas must be identified at Screening and confirmed at Baseline.
- Women of childbearing potential only. Serum pregnancy test at Screening and urine pregnancy tests at all other visits.
- From Day 1 to Day 15 study treatment will be applied at the site (CRU), at regular intervals twice a day, approximately every 8 to 12 hours. From Day 15 through the end of treatment, subjects will apply open-label investigational product at home twice a day, approximately every 8-12 hours. During the open-label period, subjects will be required to complete the diary which will include dosing, adverse events and pruritus numerical rating scale information.
- On Day 15 study visit, a diary will be distributed to the subject. There will be a requirement to bring the subject diary to the subsequent visit(s) for collection and review.
- One 4.5 mm skin biopsy will be collected from each target treatment area prior to IP application on Day 1, Day 8 (optional for subjects) and Day 15. The biopsies on Day 8 and Day 15 will be collected in the vicinity, but at least 1 cm distant from where the biopsies were collected at Day 1, even if the target treatment area has cleared. One additional 4.5 mm skin biopsy will be collected from nonlesional skin on Day 1. If a subject has an early termination visit during the double-blind treatment period, every attempt should be made for the skin biopsy to be collected at this visit.
- The investigator or his/her designee will discuss with the subject the need to use contraception consistently and correctly according to contraception guidelines.

- h. Serum FSH concentration will be determined for all females who are amenorrheic for at least 12 consecutive months.
- i. Completion of initial subject diary entry of the open-label period IP with oversight and training by the study site.
- j. CCI [REDACTED]
- k. Assessment part of the double-blind period.

## 1. INTRODUCTION

### 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. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. The specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, but it is thought that crisaborole reduces the production of several pro-inflammatory cytokines implicated in the pathophysiology of atopic dermatitis (AD).

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

### 1.1. Background and Rationale

AD, also referred to as atopic eczema or in layperson terms as eczema, is a chronic and relapsing disease affecting an increasing number of patients and is of similar pathophysiology in adults and children of all ages. 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.<sup>1,2</sup> Adult-onset AD has been reported.<sup>3,4</sup> However, reliable estimates of the incidence of AD in adults are unavailable. Prevalence estimates among adults vary, but the condition may affect over 10% of adults in some regions. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US and Canada.<sup>5,6</sup>

The pathophysiology of AD is the product of a complex interaction between various susceptibility genes, host environments, infectious agents, defects in skin barrier function and immunologic responses. AD is an inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.<sup>1,6</sup> The majority of patients (up to 90%) with AD present with mild to moderate disease.<sup>7</sup> Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, and lichenification.<sup>8</sup> Continuous scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections.

AD is often associated with significant morbidity, including asthma, allergic rhinitis, and food allergy. Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.<sup>9</sup>

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, health-related quality of life (HRQoL), and psycho-social implications.

AD may also be a source of significant economic burden<sup>10</sup> as this relapsing disease is often misdiagnosed, misunderstood, and ineffectively treated.<sup>6</sup>

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

## **Drug Development**

Crisaborole is a novel, non-steroidal, topical anti-inflammatory PDE-4 inhibitor that will serve an unmet need in the treatment of AD. Supporting evidence of the safety and efficacy of this product in patients 2 years and older represent a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the treatment-limiting effects of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in the two Phase 3 registration studies. Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related SAEs and with the majority of AEs being mild and deemed unlikely or not related to investigational product.

The Investigator's Brochure (IB) contains summaries of nonclinical and clinical studies performed with crisaborole.<sup>14</sup> A brief summary as background to this study protocol is presented here.

## **Nonclinical Studies**

Crisaborole demonstrates inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration (EC<sub>50</sub>) values ranging from high nanomolar to low micromolar concentrations.<sup>15-21</sup> 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,<sup>22</sup> which causes elevation of cyclic adenosine monophosphate (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.<sup>23</sup> Crisaborole proved efficacious against an inflammatory challenge in vivo in a mouse phorbol 12-myristate 13-acetate phorbol 12-myristate 13-acetate (PMA)-induced ear edema model.<sup>24,25</sup> AN7602 and AN8323, major metabolites of crisaborole lack anti-inflammatory activities against PDE4<sup>26</sup> and a panel of cytokines.<sup>27</sup>

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

## **Effects in Humans**

Twenty-three (23) clinical trials of topical formulations of crisaborole have been completed to date, with a total of 2157 subjects exposed to one or more crisaborole formulations. Key study information is summarized below.

### Clinical pharmacology studies

- The pharmacokinetics (PK) of EUCRISA were investigated in 33 subjects 2 to 17 years of age with mild to moderate atopic dermatitis and a mean  $\pm$  standard deviation (SD) BSA involvement of  $49 \pm 20\%$  (range 27% to 92%). In this study, subjects applied approximately  $3 \text{ mg/cm}^2$  of EUCRISA ointment (dose range was approximately 6 g to 30 g per application) twice daily for 8 days. The mean  $\pm$  SD maximum plasma concentration ( $C_{\text{max}}$ ) and area under the concentration time curve from 0 to 12 hours post dose ( $\text{AUC}_{0-12}$ ) for crisaborole on Day 8 were  $127 \pm 196 \text{ ng/mL}$  and  $949 \pm 1240 \text{ ng}\cdot\text{h/mL}$ , respectively. Systemic concentrations of crisaborole were at steady state by Day 8. Based on the ratios of  $\text{AUC}_{0-12}$  between Day 8 and Day 1, the mean accumulation factor for crisaborole was 1.9.
- Healthy men who applied a single topical dose (9.5 g [approximately  $100 \mu\text{Ci}$ ]) of  $^{14}\text{C}$ -crisaborole ointment 2% had maximum mean blood and plasma radioactivity at 6 hours postdose; no radioactivity was observed in any subject by 96 hours postdose in blood and 144 hours postdose in plasma (AN2728-PSR-105). The major route of radioactive elimination was renal.
- In a thorough QT (TQT) study conducted in healthy adult subjects (AN2728-TQT-108), crisaborole ointment, 2%, at both therapeutic and suprathreshold doses had no effect on cardiac repolarization based on results from the primary assessment and the pharmacokinetic-pharmacodynamic analysis.
- A drug drug interaction (DDI) study evaluated the effect of multiple topical administrations of crisaborole ointment, 2% at a suprathreshold dose (covering approximately 60% BSA), on the single-dose pharmacokinetics of R- and S-warfarin, a CYP2C9 substrate, in healthy adult subjects. The study concluded that there was no drug-drug interaction when warfarin is co-administered with crisaborole ointment (AN2728-PK-101).
- In a randomized, single-center, controlled, within-subject comparison study of healthy volunteers, crisaborole ointment, 2% and crisaborole topical ointment, Vehicle showed no evidence of sensitization and only very minimal irritation (AN2728-RIPT-101).

### Clinical studies

- In a 6-week bilateral comparison trial of subjects with mild-to-moderate AD (AN2898-AD-202), 68% of AD lesions treated with crisaborole ointment E, 2% twice a day (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 dose selection trial of 86 adolescent subjects with mild-to-moderate AD (AN2728-AD-204), crisaborole ointment, 2% BID showed greater improvement than the lower concentration of crisaborole ointment, 0.5% applied BID for 29 days, and was more efficacious than either concentration applied once a day (QD).
- In two Phase 3 multicenter, randomized, double-blind, vehicle controlled studies in subjects  $\geq 2$  years of age and older with AD, crisaborole ointment, 2% BID outperformed the vehicle in the primary efficacy analysis and the difference between the treatment groups was statistically significant (AN2728-AD-301, AN2728-AD-302).
- An additional Phase 3 multicenter, open-label, long-term extension study (48 weeks duration) of crisaborole ointment, 2% BID for the treatment of mild to moderate AD in adults and children as young as 2 years of age affirmed the long-term safety of topical crisaborole (AN2728-AD-303). No clinically important safety signals were identified by this study.

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.

## **1.2. Study and Dose Rationale**

The specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined. In this study, skin biopsies will be collected to characterize the mechanism of action, by evaluation of efficacy and changes in key skin biomarkers, of crisaborole ointment 2% over vehicle, applied twice a day in adult subjects with AD with maximum treatable BSA of 10%. The skin biopsy samples will be analyzed using immunohistochemistry (IHC) and gene expression, which will be done using TLDA PCR for 48 genes including housekeeping genes as well as single gene PCR for a few genes that are below detection level on TLDA.

The safety and efficacy of crisaborole has been demonstrated in two phase 3 studies (AN2728-AD-301 and AN2728-AD-302) and one long term open-label study (AN2728-AD-303). The 2% dose strength of crisaborole ointment is approved in the US for the treatment of mild-moderate atopic dermatitis for subjects  $\geq 2$  years.

## **1.3. 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.

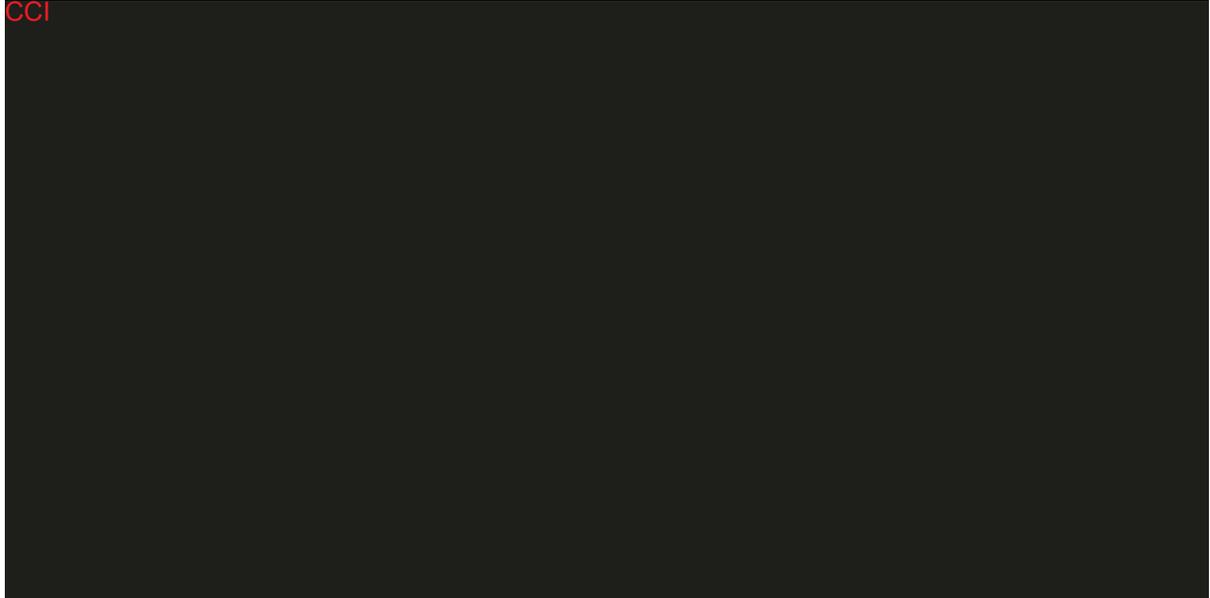
- The satisfactory safety and local tolerability demonstrated in non-clinical and clinical studies conducted with crisaborole ointment 2% to date.

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 for those subjects treated with crisaborole during the double-blind and/or open-label treatment period. Based on the favorable clinical safety profile as well as the projected low systemic availability of crisaborole, the risk to subjects treated with crisaborole is deemed to be minimal.

## 2. STUDY OBJECTIVES AND ENDPOINTS

<b>Primary Objective(s):</b>	<b>Primary Endpoint(s):</b>
<ul style="list-style-type: none"> <li>• To evaluate the efficacy of crisaborole ointment 2% vs vehicle in subjects with mild to moderate AD.</li> <li>• To evaluate change in key skin biomarkers of AD in target lesions treated with crisaborole ointment 2% or vehicle.</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline in TSS in target lesions treated with crisaborole ointment 2% or vehicle on Day 15.</li> <li>• Change from baseline in key skin biomarkers of AD (S100A12, CCL17, CCL18, CCL22, K16, elafin/PI3 and IL-13 expression level) in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.</li> </ul>
<b>Secondary Objective(s):</b>	<b>Secondary Endpoint(s):</b>
<ul style="list-style-type: none"> <li>• To evaluate change in other skin biomarkers of atopic dermatitis in target lesions treated with crisaborole ointment 2% or vehicle.</li> <li>• To evaluate normalization of biomarker and gene expression levels in lesional skin treated with crisaborole ointment 2% or vehicle.</li> <li>• To evaluate changes in AD clinical sign and symptom severity in target lesions treated with crisaborole ointment 2% or vehicle.</li> <li>• To assess the safety and local tolerability of crisaborole ointment 2% in subjects with mild to moderate AD.</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline in other skin biomarkers in target lesions treated with crisaborole ointment 2% or vehicle at Day 15.</li> <li>• Biomarker and gene expression level in lesional skin treated with crisaborole ointment 2% or vehicle at Day 15 and levels in non-lesional skin at Baseline.</li> <li>• Change from baseline in lesion severity as measured by TSS, ISGA, and Pruritus Numerical Rating Scale at each visit up to Day 15.</li> <li>• The incidence of treatment emergent AEs and SAEs.</li> </ul>

CCI



Abbreviations: AD = atopic dermatitis; AE = adverse event; CCI  
ISGA = Investigator's static global assessment; SAE = serious adverse event;  
TSS = total sign score.

### **3. STUDY DESIGN**

#### **Overview**

This is a Phase 2a randomized, double-blind, vehicle-controlled study to characterize the mechanism of action, by evaluation of efficacy and changes in key skin biomarkers, of crisaborole ointment 2% in subjects with mild to moderate atopic dermatitis. After completing screening activities, including meeting eligibility criteria, approximately 40 subjects will be treated. In the double-blind treatment period, each subject will be randomly assigned to be treated with crisaborole ointment 2% for one target lesion. The other target lesion will receive vehicle.

The double-blind treatment period will last from Baseline/Day 1 to Day 15 skin biopsy collection and will include twice daily visits to the site for IP application and study assessments, where applicable. The open-label treatment period will start from the Day 15 skin biopsy collection and last until Day 43 (end of treatment/early termination); during this time, subjects will be able to treat all AD skin areas (except scalp), at home, with crisaborole ointment 2%.

Scheduled (outpatient) study visits for all subjects will occur at Screening (up to 30 days prior to Day 1/Baseline), Days 1 to 14 (twice daily), Day 15, and Day 43 (end of treatment/early termination). On Day 71 (end of study), a follow-up telephone call will be made by site staff to assess for AEs that may have occurred since the last visit.

### Skin biopsy and biomarkers

For all subjects, one 4.5 mm skin biopsy will be collected from each target treatment area on Day 1, and Day 15. In addition, on Day 8, subjects will be offered one optional 4.5 mm skin biopsy collected from each target treatment area, to provide additional samples for analysis. The biopsies on Day 8 and Day 15 will be collected in the vicinity, but at least 1 cm distant from where the biopsies were collected at Day 1, even if the target treatment area has cleared. One additional 4.5 mm biopsy will be collected from nonlesional skin on Day 1. Each biopsy will be cut in half. One half will be used to perform reverse transcriptase (RT) PCR and gene arrays and the other half will be used for immunohistochemistry analysis and hematoxylin and eosin (H&E) staining.

Parameters studied using IHC will include epidermal thickness (performed on H&E sections), Ki-67+ cells, Keratin 16 (K16), CD3+ T-cells, CD11C+ dendritic cells (DCs), Fc Epsilon+ dendritic cells (DCs), langerin+ cells (for langerhans cells), filaggrin.

Gene expression by RT PCR panel (skin ribonucleic acid [RNA]) will include levels of the following established cytokines associated with AD: IL-13, IL-19, IL-22, IL-17A, IL-23 (p19), IL-12/23 p40.

Gene expression by TLDA RT PCR will include the levels of the following established cytokines associated with AD: IL-1B, IL-2, IL-2RA, IL-5, IL-6, IL-8, IL-9, IL-10, IL-12p35, IL-12/23p40, IL-13, IL-15, IL-15RA, IL-17A, IL-17F, IL-19, IL-22, IL-23 (p19), IL-31, IL-32, K16, PDE4A, PDE4B, PDE4D, filaggrin, loricrin, periplakin, S100A7, S100A9, S100A12, MMP12, IFN-gamma, CXCL1, CXCL2, CXCL9, CXCL10, CCL20, elafin/PI3, hBD2, CCL13, CCL17, CCL18, CCL22, CCL26, FOXP3 and TSLP receptor, of which the following are considered the key biomarkers associated with AD pathways:

**S100A12** (general inflammation); **Keratin 16** (epidermal hyperplasia; proliferation marker (barrier function)); **Elafin/PI3** (Th17); **CCL17** (Th2); **CCL18** (Th2); **CCL22** (Th2); **IL13** (Th2). PDE4 expression will be quantified in the tissue by TLDA.

Gene arrays using Affymetrix UPlus 2 arrays will also be performed to allow for more global analyses of genomic changes and normalization of lesional samples towards non-lesional samples with treatment.

### Efficacy outcomes:

Severity of AD will be characterized at baseline and throughout the study with the lesion ISGA, lesion TSS, percent of BSA with AD (%BSA), ISGA, CCI and pruritus numerical rating scale (NRS). Lesion ISGA and lesion TSS will be used to evaluate any correlation between change from baseline in biomarkers and AD severity.

### Safety Outcomes:

Safety will be assessed by physical exams, standard laboratory testing and collection of AEs.

Refer to the [Schedule of Activities](#) for a complete list of assessments to be performed during the study.

#### 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.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

##### 4.1. Inclusion Criteria

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

1. Subject is a male or female aged at least 18 years old at the time of consent.
2. Subject has confirmed clinical diagnosis of active atopic dermatitis (AD) according to Hanifin and Rajka criteria (see [Appendix 2](#)) with at least 6 month history prior to Screening visit and that has been clinically stable for  $\geq 1$  month.
3. Subject has a global ISGA of 2 or 3 at Baseline/Day 1 visit.
4. Subject has a BSA covered with atopic dermatitis of at least 0.5% and no more than 10% at Baseline/Day 1, excluding face, scalp, axilla, genitals, groin area, palms, back of the hands, and soles. The presence of AD on these areas (face, scalp, axilla, genitals, groin area, palms, back of the hands and soles) is not exclusionary, but will not be included in the calculation for coverage of BSA with AD.
5. Subject has two lesions of atopic dermatitis at least 3 cm x 3 cm with identical Lesion ISGA of  $\geq 3$ . These atopic dermatitis lesions must be at least 5 cm apart. The target lesions must not be on the face, scalp, axilla, genitals, groin area, palms, back of the hands, and soles.
6. Subjects who received any of the following AD treatment regimens are eligible if the following minimum washout criteria are observed:

**Must be discontinued for at least 12 Weeks or 5 half-lives (whichever is longer):**

- Biological drugs.

**Must be discontinued for at least 28 days prior to Baseline:**

- Systemic (oral/injectable) corticosteroids (Note: use of intranasal/inhaled or ophthalmic corticosteroids for stable medical conditions are allowed).

- Systemic immunosuppressive agents (eg, retinoids, calcineurin inhibitors, methotrexate, ciclosporin, hydroxycarbamide (hydroxyurea), azathioprine, hydroxychloroquine, mycophenolate mofetil).
- Nonbiological investigational product or device.
- Excessive sun exposure, light therapy (eg, ultraviolet light therapy) including phototherapy.

**Must be discontinued for at least 14 days prior to Baseline:**

- Topical products containing urea.
- Topical medicated treatments for atopic dermatitis (eg, tars, bleach, antimicrobials, medical devices (eg, Atopiclair), and bleach/bath oil.
- Topical corticosteroids (all potencies) and calcineurin inhibitors.
- Prescription skin barrier repair products.
- Systemic antibiotics.
- Doxepin.

**Must be discontinued for at least 7 days prior to Baseline:**

- Topical antibiotics.
- Use of antibacterial soaps (for bathing), or topical sodium hypochlorite-based products.
- Topical or oral antihistamines (eg, hydroxyzine or diphenhydramine or other sedating antihistamines).

**Must be discontinued at least 8 hours prior to Baseline:**

- Use of emollients.

7. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:
  - a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status must be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
  - b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

- c. Have medically confirmed ovarian failure.

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

- 8. Female subjects of childbearing potential who have a negative serum pregnancy test at the screening visit and negative urine pregnancy test at the baseline visit.
- 9. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
- 10. Subjects who are willing and able to comply with 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. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for at least 28 days prior to Day 1 and for the duration of the study and for at least 28 days after the last dose of investigational product.
- 2. Subject has clinically infected atopic dermatitis or subjects requiring high-potency topical corticosteroids (eg, clobetasol propionate 0.05% cream or ointment or bathamethasone dipropionate 0.05% cream or ointment) or systemic (oral/injectable) corticosteroids to manage AD.
- 3. History of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of crisaborole ointment 2% (listed in [Section 5](#)).
- 4. Subject had previous treatment with any topical or systemic PDE4 inhibitor, including apremilast unless stopped for the reason of lack of efficacy (in which case it is not exclusionary).
- 5. Subject is not willing to minimize or avoid natural and artificial sunlight exposure during the study.
- 6. Subject requires treatment with prohibited concomitant medication(s) as listed in [Section 5.8.2](#).
- 7. Subject who 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).

8. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
9. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
10. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets, novel oral anticoagulants (eg apixaban), antiplatelet medication (eg clopidogrel), or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs [NSAIDs] and low-dose aspirin  $\leq 81$  mg will not be considered antiplatelet therapy.
11. Subject with any planned surgical or medical procedure that would overlap with study participation from Screening through Day 71/end of study.
12. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
13. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
14. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

### **4.3. Lifestyle Requirements**

#### **4.3.1. General Care**

Subjects should avoid occluding the treated areas (with wraps, for example). Subjects must avoid exposing the target treatment areas to water (eg swimming, bathing or washing) and refrain from any activities that will induce sweating, for at least 4 hours after investigational product (IP) application during the double-blind treatment period and at least 4 hours after IP application during the open-label treatment period.

Subjects should avoid wiping the IP off the skin. In the case of any IP inadvertently being wiped off, it should not be reapplied until the next scheduled dose.

Subjects are recommended to use sunscreen products and protective apparel during the study, when sun exposure cannot be avoided. However these products must not be used on target treated areas during double-blind treatment period.

When applying IP at home, there is no expectation to wear gloves. However, subjects must be instructed to wash their hands with mild soap and water before and after each IP application. Those subjects applying IP at home and having difficulty reaching treatment-eligible atopic dermatitis areas (eg, back) may be assisted by another person who will need to apply the investigational product to the subject according to the above IP application instructions.

#### **4.3.2. Contraception**

All fertile female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for at least 28 days prior to Day 1 and for the duration of the active treatment period and for at least 28 days after the last dose of investigational product.

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use.

At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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

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

- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

#### **4.4. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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

### **5. STUDY TREATMENTS**

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or 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, investigational products are the following:

- Crisaborole ointment 2%, also referred to as active.
- Crisaborole placebo vehicle ointment, referred to as vehicle.

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

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

### **5.1. Randomization**

All subjects will receive active and vehicle investigational products during the double-blind treatment period.

Each target treatment area (1 and 2) will be assigned per the randomization schedule to one of the following:

- Crisaborole ointment 2%.
- Crisaborole placebo vehicle ointment.

All subjects will receive crisaborole ointment, 2% for the open-label treatment period (following the skin biopsy on Day 15).

### **5.2. Blinding and Maintenance of the Blind**

In an effort to ensure unbiased evaluation of the treatment groups, a randomization schedule will be created by the study statistician. The randomization schedule will be known only to the unblinded individual(s) at the site responsible for preparing the investigational product for the blinded doses for Days 1 through 14.

Two target treatment areas, meeting the inclusion criteria, will be identified on each subject by the Investigator. Upon randomization, the IP for that subject (for the double-blind treatment period) will be assigned to the respective target treatment area by the unblinded personnel at the site according to the randomization schedule. Blinded tubes (differentiated by label color), will be used to dispense treatment for the corresponding target treatment area throughout the double-blind period. The assessor and the subject will remain blind to treatment during this period. Only the unblinded staff members(s) dispensing the IP will be unblinded with respect to which target treatment area is receiving crisaborole and which is receiving vehicle. The unblinded dispenser(s) will not conduct any efficacy or safety assessments. The open-labeled investigational product will be under the control of the unblinded dispenser(s) and stored in a secure area that is not accessible to other blinded staff until dispensed.

In the event the Investigator and medical monitor agree that the blind should be broken for an individual subject during the double-blind period, the investigator will unseal the envelope and break the blind for that subject only. Since all subjects will receive both crisaborole and vehicle, the blinding is at the level of individual target treatment areas and not individual subjects.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be a manual process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely

essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented in the case report form (CRF).

### **5.3. Subject Compliance**

During the double-blind treatment period, subjects should not miss more than 6 IP applications in total, and have no missed IP applications the 2 days before Day 15 biopsy collection. If the above requirement is not met, the subject will be discontinued from the study. Similarly, subjects should not miss more than 3 IP applications in total, and have no missed IP applications the 2 days before Day 8 biopsy collection (if collected). If the subject missed a dose in those 2 days, the biopsy should not be performed at Day 8, but the subject should not be discontinued.

Compliance for the double-blind treatment period is expected to be at least 80%. This will be verified by the dosing records and visit schedule noted for each subject. Subjects having missed doses of IP will be re-educated on the importance of compliance. The Sponsor should be notified of any noncompliant subjects that are fulfilling above criteria for discontinuation. At discretion of the Sponsor, those subjects may be replaced, as discussed in [Section 9](#).

To facilitate compliance assessment during the open-label treatment period, subjects will be supplied with the subject diary and instructed to record the time for each daily dose of investigational product. Compliance for the open-blind treatment period will be collected and reviewed by the study site personnel at return to clinical research unit (CRU) visit(s). Subjects will be instructed to return this diary to the study staff at the scheduled visit, along with the investigational product carton(s) and tubes containing unused/partial/empty investigational product.

### **5.4. Investigational Product Supplies**

#### **5.4.1. Dosage Form(s) and Packaging**

Open-labeled crisaborole ointment 2% and vehicle ointment will be provided in 60 gram tubes for topical administration. The tubes will be provided in cartons and labeled in an open-label fashion according to local regulatory requirements. Crisaborole ointment 2% tubes/cartons and vehicle tubes/cartons will have different colored labels for clear differentiation of the products, as described in the IP manual.

#### **5.4.2. Preparation and Dispensing**

Investigational product should be prepared and dispensed by an appropriately qualified and experienced unblinded member of the study staff (eg, study coordinator, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

For IP application during the double-blind treatment period, one tube of crisaborole and one tube of vehicle will be dispensed for each subject and assigned, as per [Section 5.2](#), to the target treatment areas. Upon assignment, the unblinded staff will indicate subject number on

the product label(s) in the designated area. Each dose will be prepared by qualified unblinded site personnel. Each dose will be prepared by weighing the investigational products to ensure accurate application rate of 3 mg/cm<sup>2</sup> to an area of 10 cm x10 cm. The investigational product will be administered in blinded fashion to the subject by blinded site staff.

Refer to the Investigational Product Manual (IP manual) for instructions on how to prepare the investigational product for administration.

Open-label crisaborole 2% ointment tubes and cartons will be dispensed at the Day 15 visit for self-application by the subject. A qualified staff member will dispense the investigational product in the cartons provided, in quantities appropriate for the study visit schedule and subjects' requirements. On Day 15, the site should dispense an adequate amount of investigational product used until the subject returns for the Day 43 visit (end of treatment/early termination).

The first dose of the open-label treatment period should be performed at the CRU after the Day 15 biopsy sample collection. The subject should be instructed how to apply the product, and maintain the subject diary. The subject should also be instructed to maintain the product in the tubes and cartons until dosing and return all dispensed supplies (unused/partial/empty) at the next study visit.

### **5.5. Administration**

Crisaborole ointment 2% is for external use on the skin only. Contact with mucous membranes (ie, inside of nostrils, mouth, vagina, urethra, and rectum), and the eyes should be avoided. Subjects should avoid ingestion of IP.

During the double-blind treatment period, the investigational product will be administered in blinded fashion, at the CRU, to the subject in the morning and evening (approximately 8-12 hours apart). To standardize the application, the investigational products (3 mg/cm<sup>2</sup>) will be applied on an area of 10 cm x10 cm for each of the two target treatment areas (designated '1' and '2') and applied at least 5 cm apart. The treatment areas will be mapped on a transparency using natural skin landmark to ensure they remain the same throughout the double-blind treatment period. If the target treatment area is smaller than 100 cm<sup>2</sup>, the application area will also include surrounding non-lesional skin. If the target treatment area is larger than 100 cm<sup>2</sup>, only a 100 cm<sup>2</sup> area will be treated.

During the double-blind treatment period, subjects will be permitted to use emollient on the remaining AD areas that are outside of targeted treatment areas.

Prior to initiation of the open-label treatment period, subjects will be provided appropriate training for IP application and will be instructed to apply a thin layer of crisaborole to all areas of the body with atopic dermatitis (except scalp), twice daily, from the Day 15 skin biopsy collection through Day 43 (end of treatment/early termination). The first IP application will occur in the CRU, with all subsequent applications occurring at home, approximately every 8-12 hours.

After Day 15 subjects will continue to apply the IP even if a lesion clears. Any new atopic dermatitis on treatment-eligible areas occurring following Day 15 may be also treated with investigational product.

During the open-label treatment period (home-based), if a subject misses a scheduled morning dose, that day's dose should be applied as soon as possible, but not later than 6 hours beyond the scheduled time of applications. If it is greater than 6 hours beyond the scheduled dose, the subject should be instructed to skip that dose and resume dosing the next regularly scheduled time. Missed doses and reasons for missed doses should be noted on the subject diary.

## **5.6. Investigational Product Storage**

The investigator or an approved representative, eg, unblinded dispenser, 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 single reference safety document (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 IP 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 in the IP Manual.

Temperature deviations outside of the labeled storage conditions for less than 20 minutes are not considered a temperature excursion, unless the recorded temperature is below 0°C.

Site staff will instruct subjects on the proper storage requirements for investigational products during the open-label treatment period.

### **5.7. 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. When IP is taken home by the subject, all used and unused products must be returned to the investigator by the subject at subsequent visit(s).

#### **5.7.1. Destruction of Investigational Product Supplies**

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

### **5.8. Concomitant Treatment(s)**

Treatments taken before the first application of IP will be documented as a prior treatment. Treatments taken after the first application of IP will be documented as concomitant treatments.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each CRU visit.

All treatments (including medications and non-medication therapies) used for the treatment of AD within 2 months prior to screening and all other treatments (including over-the-counter drugs, vitamins, and antacids) used within 28 days prior to Screening will be recorded at the Screening visit.

Any changes in concomitant medications or dosage will be recorded at Baseline/Day 1 and at each subsequent visit. All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Classes of medications and non-medication treatments that might alter the course of AD and that require washout prior to Baseline/Day 1 are described in the Inclusion criteria. If a subject requires a treatment washout, the Investigator will provide instructions on discontinuing the prohibited medication(s) at the Screening Visit.

#### **5.8.1. Permitted Concomitant Treatments - Day 1 through Day 43 (end of treatment/early termination)**

- Stable use of intranasal, inhaled, and ophthalmic corticosteroids.

- Bland emollient(s) of choice (not containing urea) in skin areas where crisaborole is not applied (therefore not on or overlapping with target lesions) during double-blind treatment period.
- Stable dose of non-sedating antihistamines (eg, fexofenadine, loratadine, desloratadine, cetirizine and levocetirizine).

**5.8.2. Prohibited Concomitant Treatments - Day 1 through Day 43 (end of treatment/early termination)**

- Systemic (oral/injectable) corticosteroids.
- Biological drugs.
- Systemic immunosuppressive agents that could affect atopic dermatitis (eg, retinoids, calcineurin inhibitors, methotrexate, ciclosporin, hydroxycarbamide (hydroxyurea), azathioprine, hydroxychloroquine, mycophenolate mofetil).
- Use of any potency topical corticosteroids or calcineurin inhibitors anywhere on the body.
- Investigational product(s).
- Systemic antibiotics for the treatment of new onset infections that require use longer than 14 days.
- Doxepine.
- Hydroxyzine and diphenhydramine.
- Use of topical medications or products including, but not limited to:
  - Topical products containing urea;
  - Prescription skin barrier repair products;
  - PDE4 products;
  - Antibacterial soaps (for bathing);
  - Bleach baths and bath oils;
  - Tars;
  - Antimicrobials;
  - Medical devices;

- Topical sodium hypochlorite-based products;
- Topical antihistamines;
- Emollients (use of emollients on non-target lesions is permitted).

## **6. STUDY PROCEDURES**

### **6.1. Screening**

Subjects will be screened within 30 days prior to Day 1 to confirm that they meet the subject eligibility criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in [Section 12.3](#).

The following procedures will be completed:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Obtain medical and surgical history.
- Obtain complete history of all treatments (including medications and non-medication therapies) used for the treatment of AD within 2 months prior to Screening and all other treatments (including over-the-counter drugs, vitamins, and antacids) used within 28 days prior to Screening.
- Conduct a full physical examination (may be performed at Baseline/Day 1 visit at the discretion of the investigator). Target treatment areas must be identified at Screening.
- Obtain demography information.
- Measure height and weight.
- Conduct vital signs (single sitting blood pressure [BP], pulse rate and respiratory rate).
- Collect blood specimens for the following:
  - Safety laboratory tests (as described in [Section 7.1.1, Table 1](#));
  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months;
  - Serum pregnancy test for any woman of childbearing potential.
- %BSA.

- ISGA.
- Lesion ISGA.
- Contraception verification.
- Begin AE collection with the signing of informed consent.

Rescreening may be permissible at investigator discretion and consultation with Sponsor.

## **6.2. Study Period**

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

- AD assessment scales.
- Laboratory collection.
- Biopsy collection (nonlesional skin and each target lesion).
- Obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When procedures are scheduled in addition to morning or evening dosing, the assessments are to be completed prior to the dose application.

During double-blind treatment period, any procedures not collected in the morning visit may be obtained during the evening CRU visit.

## **6.3. Day 1 (Baseline)**

Subjects will come to the CRU on Day 1 as scheduled by the site. The following procedures will be completed:

- Conduct limited physical examination (unless the full Screening PE was deferred to Day 1 visit). Target treatment areas must be confirmed at Baseline.
- Urine pregnancy test for women of childbearing potential.
- Review inclusion and exclusion criteria.
- Confirm and document that appropriate contraception is in place for the subject and their partner.
- Assess symptoms by spontaneous reporting of AEs.

- Review changes in the subject's medical history including medication history since Screening.
- Review prior and concomitant treatments.
- Confirmation of the target treatment areas.
- % BSA for eligibility.
- CCI [REDACTED]
- ISGA.
- Lesion ISGA.
- Lesion TSS.
- CCI [REDACTED]
- Pruritus numerical rating scale (global and for each target lesion).
- Randomization number assigned after verification of eligibility.
- Skin biopsy collection.
- Application of the investigational product to target treatment areas '1' and '2' per the randomized assignment.

**After morning dosing**, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of AEs/AE monitoring.
- Subject is to return to the CRU approximately 8-12 hours after morning dose application for a second dose application of investigational product to target treatment areas '1' and '2'.
- Subjects will be asked about concomitant treatment.

#### **6.4. Days 2 through 14**

Subjects will come to the CRU as scheduled by the site. The following procedures will be completed:

- Confirm and document that proper contraception is being used for the subject and their partner as appropriate.
- Assess symptoms by spontaneous reporting of AEs.

- Review concomitant treatments.
- CCI [REDACTED]
- Lesion ISGA (Day 8 only).
- Lesion TSS (Day 8 only).
- Pruritus Numerical Rating Scale (for each target lesion).
- Optional skin biopsy collection (Day 8 only).
- Application of the investigational product to target treatment areas '1' and '2'.

**After morning dosing**, the following procedures will be completed:

- Assess symptoms by spontaneous reporting of AEs/AE monitoring.
- Subject is to return to the CRU approximately 8-12 hours after morning dose application for a second dose application. Any procedures not collected in the morning visit may be obtained during the evening CRU visit. The subject may be discharged from CRU immediately post-dose application.
- Subjects will be asked about concomitant treatment.

### **6.5. Day 15 (+1 day)**

Subjects will return to CRU on Day 15 and the following procedures will be completed:

- Review concomitant treatments.
- Assess symptoms by spontaneous reporting of AEs.
- Confirm and document that proper contraception is being used for the subject and their partner, as appropriate.
- Collect Urine pregnancy test.
- ISGA.
- Lesion ISGA.
- CCI [REDACTED]
- Lesion TSS.
- CCI [REDACTED]

- Pruritus Numerical rating scale (global and for each target lesion).
- Skin biopsy collection.
- Dispense open-label investigational product for outpatient administration.
- Train subject on correct application of IP.
- Subject diary training & distribution.
- Subject application of the open-label IP to all AD lesions with oversight of the study site.
- Completion of initial subject diary entry of the open-label IP with oversight and training by the study site.

**After Day 15 dosing**, the following procedures will be completed:

- AE collection.
- The subject may be discharged from CRU immediately post-dose application.

#### **6.6. Double-Blind Early Termination**

If a subject has an early termination during the double-blind treatment period, every attempt should be made for the skin biopsy to be collected.

All study procedures are identical as for Day 43 (end of treatment/early termination) [Section 6.8](#). In addition lesion ISGA, lesion TSS, skin biopsy, CCI, and pruritus for target lesion should be collected.

#### **6.7. Days 16 to 42 Outpatient/Home based Dosing**

Approximately every 8-12 hours until Day 43 (end of treatment/early termination) visit, the subjects will apply open-label IP at home to all AD lesions (excluding scalp), complete the subject diary and maintain all IP supplies. The subjects will be instructed how to complete the diary, which will include dosing, AEs and pruritus numerical rating scale information.

#### **6.8. Day 43 ( $\pm 3$ days) - End of treatment/Open-label Early Termination**

Subjects will return to the CRU on Day 43 (end of treatment/early termination) for an outpatient visit and the following procedures will be completed:

- Collection and review of subject diary.
- Confirm and document that proper contraception is being used for the subject and their partner as appropriate.
- Perform a limited physical examination.

- Collect urine pregnancy test.
- Collect all IP tubes and cartons (full/partial/empty) returned by the subject.
- Collect safety laboratory tests.
- ISGA.
- CCI [REDACTED]
- Pruritus Numerical Rating Scale (global only).
- Review concomitant treatments.
- AE collection.

### **6.9. Day 71 (+3 days) - Follow-up Contact**

The subject is to have the follow-up contact at least 28 days after the last administration of the IP to capture any potential AEs (see the [Time Period for Collecting AE/SAE Information](#) section), confirm appropriate contraception usage (see the [Contraception](#) section), and review concomitant treatments. This visit is planned to occur as a telephone contact.

### **6.10. Subject Withdrawal/Early Termination**

**Withdrawal of consent:** Subjects who request to discontinue receipt of investigational product will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

**Lost to follow-up:** All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject 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 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.

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

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

## **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. Laboratory Tests**

The following safety laboratory tests in [Table 1](#) will be performed at times defined in the Schedule of Activities 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 laboratories may be obtained at any time during the study to assess any perceived safety concerns.

**Table 1. Laboratory Tests**

<b>Hematology</b>	<b>Chemistry</b>	<b>Other</b>
Hemoglobin	Blood urea nitrogen	FSH <sup>a</sup>
Hematocrit	Glucose (random)	Pregnancy test in all females of childbearing potential as defined by the protocol <sup>b</sup>
RBC count	Creatinine	
Platelet count	Sodium	
WBC count	Potassium	
Total neutrophils (abs)	Aspartate aminotransferase	
Eosinophils (abs)	Alanine aminotransferase	
Monocytes (abs)	Total bilirubin	
Basophils (abs)	Alkaline phosphatase	
Lymphocytes (abs)	Albumin	
	Total protein	

Abbreviations: abs=absolute, FSH=follicle-stimulating hormone, RBC=red blood cell, WBC=white blood cell.

- a At Screening only, in females who are amenorrheic for at least 12 consecutive months.
- b Serum pregnancy test at Screening and urine pregnancy test at Day 1, 15 and 43 or at Final Visit/Early Withdrawal/Termination.

### 7.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test with sensitivity of at least 25 mIU/mL will be performed at Screening, and urine pregnancy test on Day 1, 15 and Day 43 to confirm the subject has not become pregnant during the study, and at the early-termination visit, if applicable.

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

Urine pregnancy tests will be conducted with the test kit approved by the sponsor in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

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

### 7.1.3. Physical Examinations

Physical examinations (PE) will be performed at times specified in the [Schedule of Activities](#) of this protocol.

PEs may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full PE 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), and neurological systems. The limited PE will be focused on general appearance, skin, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

Any changes to or worsening of existing physical examination findings, or new abnormal physical examination findings after dosing will be recorded as AEs, per the investigator's judgment.

Identification of the target treatment areas will be included with the Screening PE with confirmation at Baseline.

#### **7.1.4. Vital Signs**

Vital signs (single sitting blood pressure, pulse rate and respiratory rate) will be assessed, at Screening only, prior to blood sample collection.

Additional collection times, or changes to collection times of vital signs will be permitted, as necessary, to ensure appropriate collection of safety data.

Vital signs will be measured in subjects in a sitting position with feet flat on the floor after 5 minutes of rest.

Blood pressure: For blood pressure, the subject's arm is to be supported at the level of the heart, with the same arm (preferably the dominant arm, unless contraindicated) used throughout the study. Subjects should be instructed not to speak during measurements.

Pulse rate: The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

Respiratory rate: Measure the respiratory rate after at least 5 minutes at rest and accurately document.

#### **7.2. Skin Biopsy Samples**

One 4.5 mm skin biopsy (punch biopsy) will be collected from each target treatment area on Day 1 and Day 15. In addition, on Day 8, subjects will be offered to have one optional 4.5 mm skin biopsy collected from each target treatment area. Subjects should not miss more than 3 IP applications in total, and have no missed IP applications the 2 days before Day 8 or Day 15 biopsy collection.

The biopsies on Day 8 and Day 15 will be collected in the vicinity, but at least 1 cm distant from where the biopsies were collected at Day 1, even if the target treatment area has cleared. One additional 4.5 mm biopsy will be collected from nonlesional skin on Day 1. Each

biopsy will be cut in half. One half will be used to perform RT PCR and gene array and the other half will be used for immunohistochemistry analysis.

Details of the biopsies sampling and handling will be described in a separate manual.

Tissue and derived material left over from the biopsy already being performed in this study may be used for potential further testing (eg, RNA-Seq analysis) provided material is available. Each sample will be labeled with a code so that the laboratory personnel (including biomarker laboratory personnel) testing the samples will not know the subject's identity. Any tissue or derived material left over may be stored long term for further research purposes at a Sponsor-designated facility. The samples will be used for the purposes described in the protocol and in the informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, the samples may be stored for up to 15 years after the end of the study and then destroyed.

### 7.3. Investigator Static Global Assessment (ISGA)

The clinical evaluator of atopic dermatitis will perform an assessment of the overall severity of atopic dermatitis and assign ISGA score and category as described in Table 2. The assessment will be a static evaluation without regard to the score at a previous visit.

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

#### Investigator's Static Global Assessment

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

### 7.4. Lesion ISGA

The clinical evaluator of atopic dermatitis will perform an assessment of each target lesion severity of atopic dermatitis and assign a lesion ISGA score and category as described in Table 2.

### 7.5. Lesion Total Sign Score (TSS)

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

**Table 3. Lesion Total Sign Score**  
**Signs of Atopic Dermatitis**

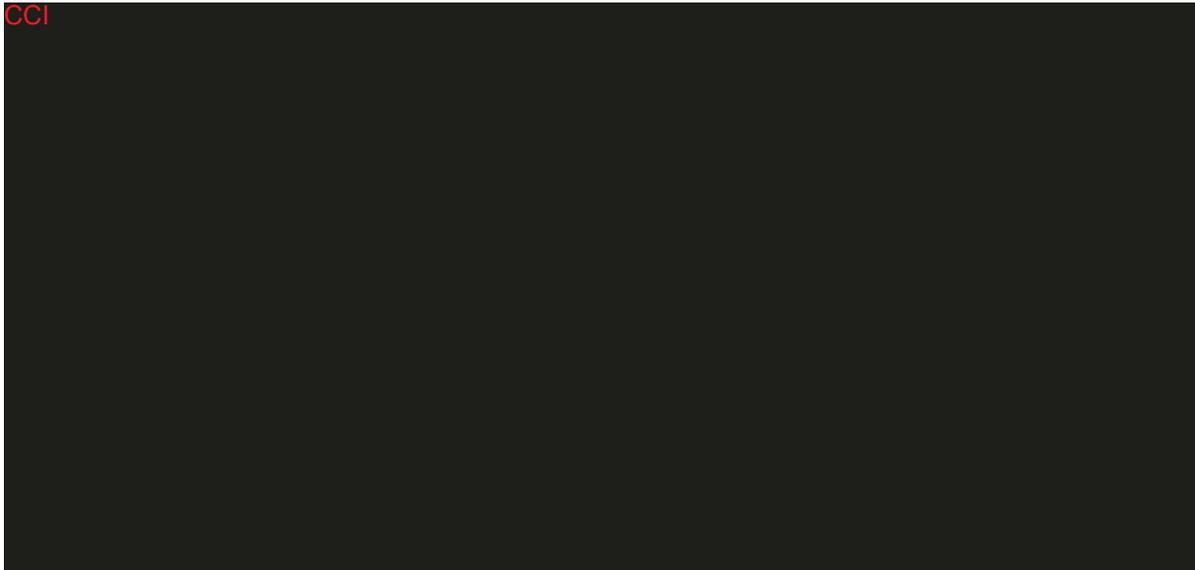
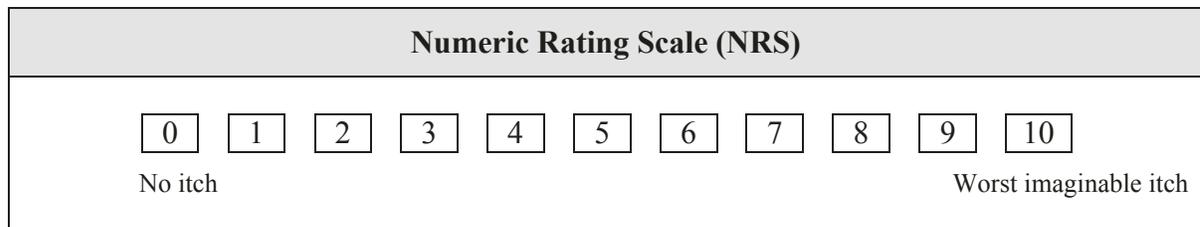
<b>Erythema (Redness)</b>		
<b>Score</b>	<b>Grade</b>	<b>Description</b>
0	None	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
<b>Induration/Papulation</b>		
<b>Score</b>	<b>Grade</b>	<b>Description</b>
0	None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

### 7.6. Pruritus Numerical Rating Scale (NRS)

The intensity of pruritus will be assessed by a numerical rating scale (NRS),<sup>12,10</sup> an eleven-point numeric rating scale from 0 to 10, to be completed for each target lesion and global, before IP morning dose is applied, at the time noted in the Schedule of Activities. During the open-label treatment period, the pruritus NRS scale should be recorded consistently, once daily, before IP application.

This will be evaluated by asking subjects to assign a numerical score representing the current intensity/intensity over the last 24 hours of their pruritus on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pruritus is presented in Figure 1.<sup>14</sup>

**Figure 1. Pruritus Numerical Rating Scale**



CCI



CCI



CCI



CCI

### 7.8. %BSA with Atopic Dermatitis

The overall BSA affected by AD will be evaluated (from 0% to 100%) at the visits specified in [Schedule of Activities](#). The Investigator may use the “handprint method” by which the area represented by the palmar (ie, outstretched) surface of the subject’s hand with all five digits adducted together is approximately 1% of the subject’s BSA, In addition, at the Screening and Baseline visit, the BSA will be evaluated to verify each subject’s eligibility using the same method as previously described, but excluding face, scalp, axilla, genitals, groin area, palms, back of the hands, and soles.

**Percent BSA with Atopic Dermatitis (BSA Efficacy):** The number of handprints of atopic dermatitis skin in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 6).

**Table 6. Handprint Determination of Body Region Surface Area**

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

\* The number of handprints are for the entire body region; these values are not adjusted for exclusion of scalp, palms, soles, groin, and genitals from the BSA Efficacy assessment

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 7).

CCI

CCI

## 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 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), <b>except occupational exposure</b>	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

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

within 24 hours after learning of it and document the time of his/her first awareness of the event.

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

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

#### **8.1.1. Additional Details on Recording Adverse Events on the CRF**

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

#### **8.1.2. Eliciting Adverse Event Information**

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

#### **8.1.3. Withdrawal from the Study Due to Adverse Events (see also the [Subject Withdrawal/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 (SAE) 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 SAEs, listed above.

#### 8.3.1. 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.

#### 8.3.2. Potential Cases of Drug-Induced Liver Injury

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

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

considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values  $>3 \times \text{ULN}$  AND a TBili value  $>2 \times \text{ULN}$  with no evidence of hemolysis and an alkaline phosphatase value  $<2 \times \text{ULN}$  or not available;
- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at Baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values  $>2$  times the baseline values AND  $>3 \times \text{ULN}$ ; or  $>8 \times \text{ULN}$  (whichever is smaller).
  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least  $1 \times \text{ULN}$  **or** if the value reaches  $>3 \times \text{ULN}$  (whichever is smaller).

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

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

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the 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.

### **8.3.3. 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.

#### **8.3.3.1. 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).

If a subject 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.

### **8.3.3.2. 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.

### **8.3.3.3. 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.

### 8.3.4. 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

#### 8.3.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

## 9. DATA ANALYSIS/STATISTICAL METHODS

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

### **9.1. Sample Size Determination**

The sample size of this study is based on the objective to demonstrate crisaborole ointment 2% is more efficacious than vehicle in the target lesion in subjects with mild to moderate AD as measured by the change from baseline in target lesion severity score (TSS) between crisaborole treated lesion and vehicle treated lesion.

Approximately 40 subjects will be enrolled in the study to ensure approximately 30 subjects who will have skin biopsy done at Day 15 during the double-blind treatment period to have the precision described below (considering the non-compliance during the double-blind treatment period is ~20%).

A sample size of 40 will have 90% power to establish the superiority of crisaborole to vehicle as measured by the change from baseline in TSS between crisaborole treated lesion and vehicle treated lesion at Day 15 using paired t-test at 0.05 (one-sided) significance level, assuming the difference is 1.4 and standard deviation 3. With sample size of 30, the power becomes 80%.

A sample size of 30 also provides the following precision to estimate the change in the key skin biomarkers S100A12, CCL17, CCL18, CCL22, elafin/PI3, K16, or IL-13 in the target lesion treated with crisaborole 2% ointment or vehicle. The expression level of biomarkers at Baseline or Day 15 will be expressed as log<sub>2</sub> transformed fold change (FCH) relative to house-keeping gene human acidic ribosomal protein gene (hARP), ie, the ratio between expression level of each biomarker and the expression level of hARP for each RT PCR sample. The margin of error for the estimates, ie, the half width of the 95% confidence intervals (CIs) for the change from baseline in FCH, is less than 1.1 under the assumption that the maximal standard deviations for the change in FCH is 3 based on unpublished data.

### **9.2. Analysis of Primary Efficacy Endpoints**

The population for the analysis is the full analysis set (FAS), which includes any subject randomized and receiving  $\geq 1$  dose of investigational product.

For the lesion TSS, the linear mixed model will be used to model the intra-subject change from baseline in TSS between the crisaborole ointment 2% treated lesion and vehicle treated lesion. The model includes the fixed effect of visit as factor, and an unstructured variance and covariance matrix will be used to model the dependence among the same subjects across different visits.

### **9.3. Analysis of Biomarker Endpoints**

In addition to the key biomarkers, the other biomarkers endpoints in this study include (but may not be limited to) the following:

Parameters studied using immunohistochemistry (IHC) will include epidermal thickness (H&E staining), Ki-67<sup>+</sup> cells, CD3<sup>+</sup> T-cells, CD11c<sup>+</sup> dendritic cells (DCs), FcEpsilonRI<sup>+</sup> DCs, langerin<sup>+</sup> cells, and FLG<sup>+</sup> (filaggrin) cells. Gene expression endpoints from RT PCR or Gene array will include MMP12, IL-1B, IL-2, IL-2RA, IL-5, IL-6, IL-8, IL-9, IL-10,

IL-12p35, IL-15, IL-15RA, IL-17A, IL-17F, IL-19, IL-22, IL-31, IL-32, IL-23p19, IL-12/23p40, INF- $\gamma$ , CXCL1, CXCL2, CXCL9, CXCL10, CCL13, CCL20, CCL26, S100A7, S100A9, hBD2 (human  $\beta$  Defensive 2), FLG (filaggrin), LOR (loricrin), periplakin, FOXP3, and thymic stromal lymphopoietin (TSLP) receptor. PDE4A, PDE4B, and PDE4D expression will also be quantified.

The population for the analysis of the biomarkers will be ‘per protocol’ (PP) population, which includes any subject receiving  $\geq 1$  dose of investigational product, with both Day 1 and Day 15 biopsies done, and without protocol violations that were thought to impact the biomarker expression during the vehicle controlled period. All protocol deviations will be reviewed and assessed by the study team prior to database release. In general, all data will be summarized using descriptive statistics. No imputation will be made for missing data.

Comparison of pre- and post- treatment of skin treated with crisaborole ointment 2% or vehicle will be performed. Expression levels from RT PCR will be normalized to the housekeeping gene hARP (validated in other studies<sup>31</sup>) and log<sub>2</sub>-transformed prior to analysis (reporting unit: Expression/hARP). Microarray data will be preprocessed using standard pipeline and log<sub>2</sub> transformed expressions. Adjustments by batch effect and clinical variables will be carried out using ComBat, if needed. Mixed effect model will be used and p-values will be adjusted by Benjamini-Hochberg procedure.

Additionally, extensive bioinformatics tools will be employed to gain insights into the mechanism of action of crisaborole.

Correlation analysis will be performed to assess if change from baseline in biomarkers correlates with change in the lesion TSS.

#### 9.4. Analysis of Other Efficacy Endpoints

The lesion TSS, lesion ISGA, and lesion Pruritus Numerical Rating Scale will be summarized descriptively by visit and treatment during the vehicle-controlled period. The difference of the improvement from baseline between crisaborole treated target treatment area and vehicle treated target treatment area will be derived.

CCI

The overall (global) efficacy of treatment with crisaborole ointment 2% during the open label-period will include CCI Pruritus Numerical Rating Scale and ISGA response of clear or almost clear and at least a 2 grade improvement from baseline, which will be summarized descriptively by visit.

No imputation will be made for missing data.

## **9.5. Safety Analysis**

The Safety population will include any subject receiving  $\geq 1$  dose of investigational product. All safety data will be summarized using descriptive statistics. No imputation will be made for missing safety data.

All AE(s) that occur during the study after signing the informed consent through the final study visit will be recorded, classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology and listed. Treatment emergent adverse events (TEAEs) are defined as 1) AEs where the onset is on or after the first administration or, 2) AEs that occur prior to the first investigational product administration and there is an increase of severity 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, system organ class (SOC), preferred term, severity, relationship to investigational product, and seriousness.

Serious adverse events (SAEs) will be summarized by severity and relationship to investigational product, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinued from the study due to an AE will be provided.

## **9.6. Interim Analysis**

No formal interim analysis will be conducted for this study.

## **9.7. Data Monitoring Committee**

This study will not use a Data Monitoring Committee.

## **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 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.

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

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

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

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

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

### **13. DEFINITION OF END OF TRIAL**

#### **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 (PF-06930164) 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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer-sponsored interventional studies (conducted in subjects) 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.

[www.pfizer.com](http://www.pfizer.com)

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

## 16. REFERENCES

1. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358(14):1483–94.
2. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract*. 2006 Aug;60(8):984-92.
3. Ozkaya E. Adult-onset atopic dermatitis. *J Am Acad Dermatol* 2005; 52(4):579-82.
4. Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol* 2000; 41(4):225–8.
5. Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. *Semin Cutan Med Surg* 2012;31(3 Suppl):S3-5.
6. Leicht S, Hanggi M. Atopic dermatitis. How to incorporate advances in management. *Postgrad Med* 2001;109(6):119–27.
7. Arkwright PD, Motala C, Subramanian H, et al. Management of difficult-to-treat atopic dermatitis, 2013. *J Allergy Clin Immunol Pract*. 2013 Mar;1(2):142-51.
8. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. *Allergol Int*. 2013 Jun;62(2):151-61.
9. Halvorsen J, Lien L, Dalgard F, et al. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population-based study. *J Invest Dermatol*. 2014 Jul;134(7):1847-54.
10. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol*. 2011 Nov 10;7 Suppl 1:S4.
11. Simpson EL, Bieber T, Guttman-Yussky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis *N Engl J Med* 2016; 375:2335-2348.
12. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 subjects with chronic pruritus. *Acta dermato-venereologica*. 2012;92(5):502-7.
13. Hamilton JD, Suarez-Farinas M, Nikhil D, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *JACI* 2014;134 (6): 1293–1300.
14. Pfizer Crisaborole IB February 2017.
15. Anacor Pharmaceuticals Report No. 003-NCL PP-002-01, Effect of AN2728 on the Inhibition of Cytokine Release from THP-1 Cells Stimulated with LPS.

16. Anacor Pharmaceuticals Report No. 003-NCL PP-010-01, Effect of AN2728 on Inhibition of IL-12 and IL-23 Production in THP-1 Cells Stimulated with Interferon- $\gamma$  and Lipopolysaccharide.
17. 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- $\gamma$  and Lipopolysaccharide.
18. 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.
19. Anacor Pharmaceuticals Report No. 003-NCL PP-007-01, Effect of AN2728 in Inhibition of IL-1 $\beta$ , IL-4, TNF $\alpha$ , and IFN $\gamma$  from PBMCs Challenged with PHA for 24 h.
20. Anacor Pharmaceuticals Report No. 003-NCL PP-008-01, Effect of AN2728 in Inhibition of IL-1 $\beta$ , IL-4, TNF $\alpha$ , and IFN $\gamma$  from PBMCs Challenged with PHA for 24 or 48 h.
21. Anacor Pharmaceuticals Report No. 003-NCL PP-006-01, Effect of AN2728 on Inhibition of IL-2 and IL-5 Cytokine Release from PBMCs.
22. Anacor Pharmaceuticals Report No. 003-NCL PP-013-01, PDE Isoform Profiling (Percent Inhibition).
23. Houslay MD, Adams DR. PDE4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling cross-talk, desensitization and compartmentalization. *Biochem J.* 2003;370(Pt 1):1-18.
24. Anacor Pharmaceuticals Report No. 003-NCL PP-022-01, Pharmacology Data Report: Evaluation of Anti-Inflammatory Activity of AN2728 in the Topical Inflammation, Phorbol Ester Assay.
25. Anacor Pharmaceuticals Report No. 003-NCL PP-023-01, Pharmacology Data Report: Evaluation of Anti-Inflammatory Activity of AN2728 in the Topical Inflammation, Phorbol Ester Assay.
26. Anacor Pharmaceuticals Report No. 003-NCL PP-024-01, Pharmacology Data report: AN7602 and AN8323 IC50 Against PDE4.
27. Anacor Pharmaceuticals Report No. 003-NCL PP-025-01, Effect of AN7602 and AN8323 on Cytokine Release from Human Peripheral Blood Mononuclear Cells Stimulated with Lipopolysaccharide or Phytohemagglutinin-L.
28. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, Wang C, Purohit V, Mamolo C, Papacharalambous J, Ports WC. *Br J Dermatol.* 2016

- Nov;175(5):902-911. doi: 10.1111/bjd.14871. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial.
29. Hanifin JM and Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980;92(suppl):44-7.
  30. E Guttman-Yassky et al. A model to evaluate intra-patient differential effects of topical agents in atopic dermatitis. Icahn School of Medicine Mount Sinai 2016; Abstract.
  31. Imhof et al. TEWL, Closed-Chamber Methods: AquaFlux and VapoMeter (Springer 2013).

## 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
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BBS	biospecimen banking system
BP	blood pressure
BID	twice a day
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CI	confidence interval
CK	creatin kinase
C <sub>max</sub>	maximum plasma concentration
CRF	case report form
CRU	Clinical Research Unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Clinical Trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DCs	dendritic cells
DDI	drug drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
CCI	
EC	ethics committee
EC <sub>50</sub>	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
FLG	filaggrin
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

<b>Abbreviation</b>	<b>Term</b>
GSVA	Gene Set Variation Analysis
H&E	hematoxylin and eosin
hARP	human acidic ribosomal protein gene
HIV	human immunodeficiency virus
HRQL	health-related quality of life
HRQoL	health-related quality of life
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IGA	Investigator's global assessment
IgE	immunoglobulin E
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISGA	investigator static global assessment
IUD	intrauterine device
IWR	interactive web response
K <sub>2</sub> EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LMW	low molecular weight
LOR	loricrin
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
MnB	meningitidis serogroup B
N/A	not applicable
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PCD	primary completion date
PCR	polymerase chain reaction
PD	Pharmacodynamics(s)
PDE-4	phosphodiesterase-4
PE	physical examination
PFS	prefilled syringe
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	pharmacokinetic
PKA	protein kinase A
PMA	phorbol 12-myristate 13-acetate
PT	prothrombin time

<b>Abbreviation</b>	<b>Term</b>
QD	once a day
RNA	ribonucleic acid
RT	reverse transcriptase
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment emergent adverse events
CCI	
TLDA	Taqman Low Density Array
TQT	thorough QT
TSLP	thymic stromal lymphopoietin
TSS	total sign score
ULN	upper limit of normal
US	United States
UV	ultraviolet

## **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<sup>19</sup> or at least 6 months prior to Screening visit and that has been clinically stable for  $\geq 1$  month.

**Table 4: Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis**

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### **Major Criteria (must have at least three)**

Pruritus

Typical morphology and distribution:

Adults: flexural lichenification or linearity

Children and infants: involvement of facial and extensor surfaces

Chronic or relapsing dermatitis

Personal or family history of atopy

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### **Minor Criteria (must have at least three)**

Xerosis

Icthyosis/keratosis pilaris/palmer hyperlinearity

Immediate (type 1) skin test reactivity

Elevated serum immunoglobulin E (IgE)

Early age at onset

Tendency to skin infections (Staphylococcus aureus, herpes simplex)/impaired cellular immunity

Hand/foot dermatitis

Nipple eczema

Conjunctivitis

Dennie-Morgan fold

Keratoconus

Anterior subcapsular cataracts

Orbital darkening

Facial pallor/erythema

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool and lipid solvents

Perifollicular accentuation

Food intolerance

Course influenced by environmental/emotional factors

White demographic/delayed blanch

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