



**A PHASE 3B/4, MULTICENTER, RANDOMIZED, ASSESSOR BLINDED,  
VEHICLE AND ACTIVE (TOPICAL CORTICOSTEROID AND CALCINEURIN  
INHIBITOR) CONTROLLED, PARALLEL GROUP STUDY OF THE EFFICACY,  
SAFETY, AND LOCAL TOLERABILITY OF CRISABOROLE OINTMENT, 2% IN  
PEDIATRIC AND ADULT SUBJECTS (AGES 2 YEARS AND OLDER) WITH MILD  
TO MODERATE ATOPIC DERMATITIS**

**Investigational Product Number:** PF-06930164  
**Investigational Product Name:** Crisaborole  
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Drug (IND) Number:** 77,537  
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### Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	16 Mar 2018	Not applicable (N/A)
Amendment 1	18 Oct 2018	Administrative changes following Swedish Medical Products Agency (MPA) review; a clearly defined benefit/risk assessment section, clarification on the break-blind methods and up-dates with regard to Regulatory compliance and Investigator reporting responsibilities.
Amendment 2	23 Jan 2019	Addition of investigational product withdrawal criteria for signs and symptoms of hypersensitivity as requested by the German Federal Institute for Drugs and Medical Devices (BfArM).
Amendment 3	12 Aug 2019	Addition of Appendix 4 detailing the Optical Coherence Tomography and biomarker sub-study; removal of telephone follow-up at Day 36; addition of a clinic visit at Day 43; addition of restrictions to concurrent medications during the follow-up phase; and changes to the pruritis scale descriptions, endpoints, and analysis.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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## PROTOCOL SUMMARY

### Background and Rationale:

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

Supporting evidence for the safety and efficacy of this product in patients 2 years and older represents a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the limitations of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in the two previous Phase 3 vehicle-controlled studies, AN2728-AD-301 and AN2728-AD-302. Across the development program, crisaborole demonstrated an acceptable safety profile; the majority of adverse events (AEs) were mild and deemed unlikely or not related to investigational product, with no crisaborole treatment related serious adverse events (SAEs) (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related).

This 4-week, randomized, assessor blinded, crisaborole ointment, 2%, vehicle and active (topical corticosteroid [TCS] and topical calcineurin inhibitor [TCI]) controlled study will determine the efficacy and safety of crisaborole ointment, 2% applied twice daily (BID) compared with vehicle in subjects ages 2 years and older with mild to moderate AD. The study will also evaluate the efficacy and safety of crisaborole ointment, 2% compared with the active controls; hydrocortisone butyrate cream, 0.1% [TCS] and pimecrolimus cream, 1% [TCI]. Hence, this study will, provide contextualization of the efficacy and safety of crisaborole ointment, 2% in the treatment of mild to moderate AD.

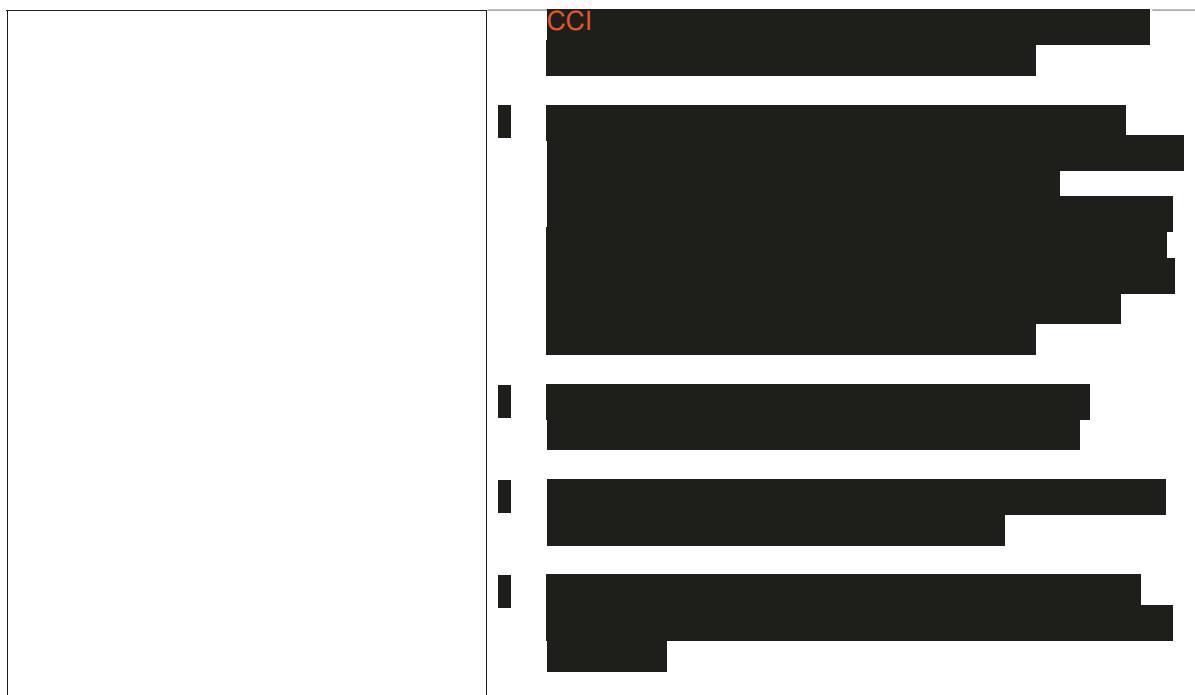
The crisaborole dose strength and regimen selected for this study has been demonstrated to be safe, well-tolerated and efficacious in subjects and healthy volunteers 2 years of age and older who participated in previous studies.

Hydrocortisone butyrate cream, 0.1% and pimecrolimus cream, 1% are approved products for the treatment of mild to moderate atopic dermatitis in subjects ages 2 years and older, and will be used as per their national approved label in this study.

## Objectives and Endpoints:

Primary Efficacy Objective	Primary Efficacy Endpoint
<ul style="list-style-type: none"><li>To compare the efficacy of crisaborole ointment, 2% applied BID versus vehicle in pediatric and adult subjects, aged 2 years and older, with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>Percent change from Baseline in the Eczema Area and Severity Index (EASI) total score at Day 29.</li></ul>
Primary Safety Objectives	Primary Safety Endpoints
<ul style="list-style-type: none"><li>To evaluate the safety and local tolerability of crisaborole ointment 2% applied BID versus vehicle in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li><li>To evaluate the safety and local tolerability of hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>AEs, SAEs, local tolerability, discontinuations and clinically significant changes in vital signs and clinical laboratory parameters.</li></ul>
Secondary Objectives	Secondary Endpoints
<ul style="list-style-type: none"><li>To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle on additional efficacy endpoints over time in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li><li>To evaluate the efficacy of crisaborole ointment, 2% BID versus hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>Efficacy endpoints<ul style="list-style-type: none"><li>Percent change from Baseline in EASI total score by scheduled time points except Day 29.</li><li>Achievement of success in the Investigator's Static Global Assessment (ISGA) (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline) by scheduled time points.</li><li>Achievement of ISGA score of clear (0) or almost clear (1) by scheduled time points.</li><li>Achievement of EASI75 (<math>\geq 75\%</math> improvement from Baseline) by scheduled time points.</li><li>Time to EASI75.</li><li>Change from Baseline in % BSA by scheduled time points.</li></ul></li></ul>
<ul style="list-style-type: none"><li>To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle, hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID on patient/observer</li></ul>	<ul style="list-style-type: none"><li>Patient/observer reported outcomes endpoints:<ul style="list-style-type: none"><li>Change from Baseline in Peak Pruritus Numerical Rating Scale (NRS) – for subjects <math>\geq 12</math> years by scheduled time points. Change from Baseline in Patient</li></ul></li></ul>

reported outcomes over time in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.	<p>Reported Itch Severity Scale - for subjects age 6-11 years Scale by scheduled time points.</p> <ul style="list-style-type: none"><li>• Change from Baseline in Observer Reported Itch Severity Scale – for subjects &lt;6 years by scheduled time points. Time to <math>\geq 2</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years. Time to <math>\geq 3</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years. Time <math>\geq 2</math> point to improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Time to <math>\geq 3</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Achievement of <math>\geq 2</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years. Achievement of <math>\geq 3</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years.</li><li>• Achievement of <math>\geq 2</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Achievement of <math>\geq 3</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years. Change from Baseline in Dermatology Life Quality Index (DLQI) (for Subjects 16 years and older), Children's Dermatology Life Quality Index (CDLQI) (for Subjects 4-15 years), and Dermatitis Family Impact Questionnaire (DFI) (Completed by parent/caregiver of Subjects 2-17 years) by scheduled time points.</li></ul>
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### **Study Design:**

This is a Phase 3b/4, multicenter, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study of the efficacy, safety and local tolerability of crisaborole ointment, 2% in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD involving at least 5% treatable body surface area (%BSA). Treatment will be clinical assessor-blinded for all treatment arms and double-blinded for crisaborole ointment, 2% and vehicle treatment arms.

A total of approximately 600 subjects will be enrolled in the study, of which at least 150 subjects aged 2-6; at least 140 subjects aged 7-11; at least 120 subjects aged 12-17 and up to 90 subjects will be adults. Following the screening period (up to 35 days prior to Baseline/Day 1), eligible subjects will be randomized at the Baseline/Day 1 visit.

Randomization will be stratified by eligibility for TCS or TCI treatment as per national approved labels. Cohort 1 will be for subjects who are eligible for TCS therapy, and Cohort 2 will be for subjects who are not eligible for TCS therapy but eligible for TCI therapy. The investigational products will be applied BID for 28 days to the Treatable body surface area (BSA) identified at Baseline/Day 1.

The primary efficacy endpoint is the percent change from baseline in the Eczema Area and Severity Index (EASI) total score at Day 29.

For the efficacy comparison of crisaborole versus vehicle, subjects from both Cohort 1 and Cohort 2 are included in the analysis, adjusted for cohort effect. For the efficacy comparison of crisaborole versus TCS, only subjects from Cohort 1 are included in the analysis. For the comparison of crisaborole versus TCI, only subjects from Cohort 2 are included in the analysis.

Safety and efficacy assessments will be conducted at the investigator site by a clinical assessor blinded to treatment assignment.

A sub-study will be conducted at selected investigator sites to evaluate differences of changes in epidermal skin thickness as measured by Optical Coherence Tomography (OCT) between treatment groups in Cohort 1. (see Appendix 4).

Scheduled study visits for all subjects will occur at Screening, Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (End of treatment/Early termination), Day 43 or 14 Days after last dose if subject is terminated early from treatment. A follow up telephone call will be made by site staff to the subjects/subject's legally acceptable guardian(s) on Day 60 or at least 28 days after last dose if subject is terminated early from treatment. The Day 60 visit will be completed in the clinic for subjects enrolled in the OCT sub-study. Refer to the [Schedule of Activities](#) for a complete list of assessments to be performed during the study.

### **Statistical Methods:**

The primary endpoint, EASI % change from baseline, as well as other change from baseline continuous endpoints, will be analyzed using a mixed-effect repeated measures model that includes the fixed effects of treatment, visit as class variable, treatment by visit interaction, and baseline value. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix.

Binary endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test.

Time to event endpoints will be analyzed by log rank test and duration of time to event will be estimated by the product limit method. A Kaplan-Meier plot will be provided.

Safety data will be descriptively summarized, and will be presented in tabular and/or graphical format.

### **Sample Size Determination**

A total of approximately 600 subjects will be enrolled into this study, of which approximately 300 subjects who are eligible to receive TCS therapy (Cohort 1) will be randomized to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or TCS with a randomization ratio of 1:1:2. Approximately 300 subjects who are ineligible to receive TCS therapy and eligible to receive TCI therapy (Cohort 2) will be randomized to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or pimecrolimus cream, 1% with randomization ratio 1:1:2.

A sample size of 150 subjects in the crisaborole treatment arm (combined from Cohort 1 and Cohort 2) and 150 subjects in vehicle treatment arm (combined from Cohort 1 and Cohort 2) will provide 86% power to detect a 12% difference in EASI percent reduction from baseline at Day 29 between crisaborole and vehicle at the 0.05 (2-sided) significance level (See [Figure 1](#)).

The sample size within each Cohort will also provide sufficient precision to enable contextualization of the efficacy of crisaborole in treating subjects with mild to moderate AD

relative to each active comparator. With a sample size of 75 subjects in the crisaborole group and 150 subjects in the TCS or TCI groups, the half width of the 95% confidence interval for the difference of EASI percent reduction from baseline at Day 29 between crisaborole and active comparator is 9.4%.

## 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.

Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43 <sup>b</sup>	Day 60 <sup>b</sup>
Window			±1 d	±3 d	±3 d	±3 d	±5 d	±3 d
Visit	Screening <sup>a</sup>	Baseline			End of Treatment/ Early Termination	Off Treatment Follow-up	Follow up telephone Contact <sup>t</sup>	
Informed consent, including assent	X							
Demographics	X							
Height	X							
Weight	X					X		
Review of Inclusion and Exclusion Criteria	X	X						
Medical history	X	X						
Prior and concomitant medications	X <sup>c</sup>	X	X	X	X	X	X	X
Vital signs <sup>d</sup>	X	X				X		
Detailed Physical examination	X <sup>e</sup>	X <sup>e</sup>				X <sup>e</sup>		
C SSRS <sup>f</sup>	X							
<b>CLINICAL EVALUATION OF AD</b>								
Serious and non serious adverse event monitoring <sup>g</sup>	X	X	X	X	X	X	X	X
ISGA <sup>h</sup>	X	X	X	X	X	X	X	
EASI <sup>h</sup>		X	X	X	X	X	X	
Body Surface Area for Investigational Product	X							

Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43 <sup>b</sup>	Day 60 <sup>b</sup>
Window			±1 d	±3 d	±3 d	±3 d	±5 d	±3 d
Visit	Screening <sup>a</sup>	Baseline				End of Treatment/ Early Termination	Off Treatment Follow-up	Follow up telephone Contact <sup>t</sup>
Record treatable AD areas (excluding scalp) in source and provide subjects and/or parent(s)/legal guardian with documentation of the designated treatment areas (body maps)		X						
Body Site checklist of treatable AD lesions <sup>b</sup>		X						
Photography of Representative treatable AD lesion(s) <sup>i</sup>		X		X		X		
<b>PATIENT/OBSERVER REPORTED OUTCOMES</b>								
Peak Pruritus Numerical Rating Scale (NRS) for subjects ≥12 years OR Patient Reported Itch Severity Scale - for subjects age 6-11 years OR Observer Reported Itch Severity Scale - for subjects <6 years	X <sup>j</sup>	To be captured QD from Day 1 to Day 29						
CCI								
CCI								
CCI CDLQI or DLQI <sup>m</sup>		X	X	X	X	X		
DFI <sup>n</sup>		X	X	X	X	X		
CCI								
<b>LABORATORY TESTING</b>								
Serum chemistry and hematology	X	X <sup>o</sup>				X		
Urine pregnancy test (in female subjects of	X	X				X		

Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43 <sup>b</sup>	Day 60 <sup>b</sup>
Window			±1 d	±3 d	±3 d	±3 d	±5 d	±3 d
Visit	Screening <sup>a</sup>	Baseline				End of Treatment/ Early Termination	Off Treatment Follow-up	Follow up telephone Contact <sup>t</sup>
childbearing potential only) <sup>p</sup>								
FSH (to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months)	X							
<b>OTHER ACTIVITIES</b>								
Register Subject with IRT to obtain a SSIN	X							
Randomization		X						
In-clinic dosing instruction		X	X	X	X			
In clinic dose application by study staff (1st dose [preferred AM]) <sup>q</sup>		X						
At home dosing, applied by subject or caregiver, as appropriate <sup>r</sup>		2 <sup>nd</sup> dose (PM) on Day 1, then BID through Day 28 <sup>q,r</sup>						
Dispense/Assess Dosing Diary and Instructions		X	X	X	X			
Obtain and review Dosing Diary data and assess compliance <sup>s</sup>			X	X	X	X		
Weigh new investigational product tube(s) and dispense for at-home dosing		X	X	X	X			
Collect and weigh returned investigational product tube(s)			X	X	X	X		
Contraception Check (for female subjects of childbearing potential only)	X	X	X	X	X	X	X	X
<b>Optical Coherence Tomography Sub-study (see Appendix 4) for participating sites and subjects only.</b>								

Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43 <sup>b</sup>	Day 60 <sup>b</sup>
Window		$\pm 1$ d	$\pm 3$ d	$\pm 3$ d	$\pm 3$ d	$\pm 5$ d	$\pm 3$ d	
Visit	Screening <sup>a</sup>	Baseline				End of Treatment/ Early Termination	Off Treatment Follow-up	Follow up telephone Contact <sup>t</sup>

AD=Atopic Dermatitis, CDLQI= Children's Dermatology Life Quality Index, C-SSRS=Columbia Suicide Severity Rating Scale, DLQI= Dermatology Life Quality Index, DFI= Dermatitis Family Impact Questionnaire, FSH=Follicle Stimulating Hormone, CCI= Interactive response technology, CCI SSIN= subject screening identification number, CCI IRT= Interactive response technology, CCI

- a. Peak Pruritus NRS for subjects  $\geq 12$  years or Patient Reported Itch Severity Scale - for subjects age 6-11 years or Observer Reported Itch Severity Scale - for subjects <6 years and ISGA will be collected at screening for all subjects scheduled for a Baseline Visit, regardless of whether the subject continues to randomization.
- b. Day 43 ( $\pm 5$  days) or 14 days ( $\pm 5$  days) after Early Termination. Day 60 ( $\pm 3$  d) or at least 28 days following the End of Treatment or Early Termination.
- c. Record all treatments (including medications and non-medication therapies) used for AD, as well as any biologic drugs used within 180 days prior to screening and all other medications (including bland [non-medicated] emollients, over-the-counter drugs, vitamins, and antacids) used within 30 days prior to Screening.
- d. Temperature, respiratory rate, pulse rate, and blood pressure taken in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes (when possible for younger children). Position of recording must be consistent within subject through-out the study. At Baseline/Day 1, and Day 29, assessment of vital signs should precede blood draw for clinical laboratory tests.
- e. Detailed physical examination includes, but is not limited to the following organ or body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, musculoskeletal, abdomen (liver, spleen), and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin. At screening confirm clinical diagnosis of AD per Hanifin and Rajka criteria.
- f. Investigator completed. Children's C-SSRS for subjects 7-11 years old, C-SSRS for subjects  $\geq 12$  years old.
- g. Completed by a clinical assessor blinded for treatment arms for AEs and SAEs. Other site personnel may also report and record AEs and SAEs reported to them spontaneously by the subject.
- h. Completed by a clinical assessor blinded for treatment arms.
- i. For subjects (optional) at a selected study site(s), photographs of treatable AD lesions will be obtained. Photographs will be utilized for illustrative purposes and not evaluated as an endpoint. (see Section 7.4).
- j. Peak Pruritus NRS for subjects  $\geq 12$  years will be completed by the subject (12 years and older) or the Patient Reported Itch Severity Scale - for subjects age 6-11 years will be completed by the subjects age 6-11 years or the Observer Reported Itch Severity Scale - for subjects <6 years will be completed by caregiver [parent/legal guardian/legally acceptable representative] during screening prior to Day 1, and once daily from Day 1 to Day 29 before IP morning dose application (as applicable) preferably at the same time of each day.

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Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43 <sup>b</sup>	Day 60 <sup>b</sup>
Window		$\pm 1$ d	$\pm 3$ d	$\pm 3$ d	$\pm 3$ d	$\pm 5$ d	$\pm 3$ d	
Visit	Screening <sup>a</sup>	Baseline				End of Treatment/ Early Termination	Off Treatment Follow-up	Follow up telephone Contact <sup>t</sup>

- C C
- m. The CDLQI will be completed by all subjects aged 4–15 years, based on the age at Screening Visit/time of informed consent/assent. The DLQI will be completed by all subjects aged 16 years and older, based on the age at Screening Visit/time of informed consent/assent. CCI [REDACTED] The DFI will be completed by the caregiver for subjects aged 2–17 years, based on the age at Screening Visit/time of informed consent/assent. CCI [REDACTED]
- C C
- o. Blood draw for clinical laboratory tests (serum chemistry and hematology) on Day 1 will be performed before the in-clinic investigational product application. If the screening serum chemistry and hematology tests are performed within 14 days prior to Day 1, whether the Day 1 serum chemistry and hematology tests are to be performed will be at the medical judgment of the investigator or his/her designee.
- p. Urine pregnancy testing ( $\beta$ -hCG) is required only for women of childbearing potential: test may be repeated as per request of IRB/IECs, if required by local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected or at the discretion of the investigator or his/her designee. Urine pregnancy testing will be performed at the site. For pediatric female subjects who have not experienced menarche, pregnancy testing is not required to be performed. If the pediatric female subject starts menarche during the study, pregnancy testing will be performed at the next visit and all visits according to the [schedule of activities](#).
- q. If the subject comes to the clinic in the afternoon, two doses ( $12 \pm 4$  hours apart) or single dose could be administered on Day 1.
- r. In the event the scheduled Day 29 (End-of-Treatment) Visit does not occur on Day 29, eg, due to an unavoidable scheduling conflict, the subject and/or caregiver will be instructed to continue investigational product application BID through the evening before the day that the rescheduled End-of-Treatment Visit is to occur.
- s. During study visits at Day 8, Day 15, and Day 22, re-educate subject and/or caregiver on the dosing instructions if any investigational product doses were missed during the interval since the previous study visit.
- t. A telephone call is not required for subjects enrolled in the OCT sub-study, as they are required to attend the clinic for this visit.

## 1. INTRODUCTION

### 1.1. Mechanism of Action/Indication (Crisaborole)

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

Crisaborole ointment, 2% is being developed for the topical treatment of patients with mild to moderate AD. On 14 December 2016, EUCRISA (crisaborole) 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.

### 1.2. Background

AD, also referred to as atopic eczema or, simply as eczema, is a chronic and relapsing disease affecting an increasing number of persons. Although AD affects patients of all ages, it is one of the most common, chronic, relapsing childhood dermatoses. The lifetime prevalence of AD is estimated to be 15-30% in children and 2-10% in adults while the incidence of AD has increased by 2- to 3-fold during the past 3 decades in industrialized countries.<sup>1</sup>

AD is a distinctive inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.<sup>2,3</sup> The majority of patients (up to 90%) with AD present with mild to moderate disease.<sup>4</sup> Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, lichenification, and bacterial colonization.<sup>5</sup> Continuous scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections. AD is often associated with other conditions including asthma, allergic rhinitis, and food allergy.<sup>6,7</sup>

AD is a condition associated with significant morbidity. The burden of the clinical symptoms of AD coupled with the stigma associated with highly visible skin lesions correlates with significant morbidity and extensive impairments on health related quality of life measures (HRQOL) for patients, especially in children, and caregivers.<sup>2,8,9,10</sup> Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.<sup>11</sup> The negative impact on HRQOL caused by childhood AD exceeds that in asthma, epilepsy, and diabetes, is comparable to that in renal disease or cystic fibrosis, and is equal (child) or exceeds (parents) that in psoriasis.<sup>9,12,13</sup> The hallmark symptom of itching causes scratching which is associated with sleep disturbance in greater than 60% of patients. Sleep deprivation leads to physical and mental exhaustion in patients and other family members resulting in loss of concentration and impaired performance at school or work.<sup>14,15</sup> AD is often associated with significant childhood behavioral problems and psychological disorders including depression, attention deficit hyperactivity disorder, anxiety, stress, and autism.<sup>11</sup>

Preschool children with AD show a significant increase in behavioral symptoms compared with matched controls.<sup>16</sup> Absolon et al<sup>17</sup> reported that the rate of psychological disturbance in school age children with AD doubled compared with matched controls. For older children with AD, in addition to problems associated with itching and sleep disturbance, their social and school life may be substantially affected. Social embarrassment, due to visible signs of the disease (crusted, excoriated, oozing, bleeding lesions), teasing, and bullying, often results in social isolation leading to depression.<sup>12</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; HRQOL; and psychosocial implications. In summary, AD is a disease with multiple comorbidities and significant impact on the health, day to day functioning, and HRQOL of AD patients, their caregivers, and family members.

AD may also be a source of significant economic burden<sup>18</sup> as this relapsing disease is often misdiagnosed, misunderstood, and ineffectively treated.<sup>3</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.

The objectives of AD management are to improve clinical signs and symptoms and quality of life, while minimizing potential medication side effects. The main treatment options targeted at the underlying disease process of mild to moderate AD are topical emollients. Topical corticosteroids (TCS) of varying potency, and the topical calcineurin inhibitor (TCI) pimecrolimus cream, 1% as second line therapy. Emollients, which are fundamental to basic skin care in AD, have limited efficacy. TCSs are limited in the treatment duration and body regions of treatment, due to risk of local and potentially irreversible skin toxicities such as atrophy, telangiectasia, and striae. Given the potential for inhibition of tumor surveillance in the skin and reports of malignancy (eg, skin and lymphoma), TCIs are designated as second line therapy for the short-term and non-continuous treatment of AD in non-immunocompromised patients.

Crisaborole ointment, 2% was developed by Anacor Pharmaceuticals, Inc. (Anacor), Palo Alto, California, United States of America (USA), which became a wholly owned subsidiary of Pfizer Inc. on 24 June 2016. Crisaborole is a novel, non-steroidal, topical anti-inflammatory PDE-4 inhibitor being developed for the topical treatment of patients with mild to moderate AD. Supporting evidence of the safety and efficacy of this product in patients 2 years and older represent a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the limitations on patient age, location, duration of use and line of therapy of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in favor of crisaborole ointment, 2% BID versus vehicle ointment BID in the two Phase 3 pivotal studies, AN2728-AD-301 and AN3728-302.<sup>19</sup> Across the development program, crisaborole demonstrated an acceptable safety profile; the majority of AEs were mild and deemed

unlikely or not related to investigational product, with no crisaborole treatment related SAEs (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related).

### **1.3. Drug Development**

Crisaborole ointment, 2% is a benzoxxaborole compound developed as a topical anti-inflammatory agent. Crisaborole has been formulated as a topical ointment. The formulation ingredients for crisaborole ointment, 2% are listed in [Section 5](#).

Crisaborole demonstrates in vitro inhibition of a wide range of pro-inflammatory cytokines implicated in the pathogenesis of AD and other inflammatory skin diseases, including TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-5, IL-6, IL-10, IL-12, and IL-23.<sup>20</sup> Crisaborole also inhibits the release of chemokines that are important inflammatory mediators. Crisaborole inhibits the enzymatic activity of PDE-4 through binding to the PDE-4 catalytic site in a manner that is competitive with cyclic adenosine monophosphate. Crisaborole formulated as ointment and cream formulations for topical use has demonstrated clinical benefit in nine psoriasis clinical studies and seven AD clinical studies. Safety has been evaluated in a total of 23 completed clinical studies.

#### **1.3.1. Nonclinical Studies**

Crisaborole demonstrated inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration ( $EC_{50}$ ) values ranging from high nanomolar to low micromolar concentrations. 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, which causes elevation of cAMP in leukocytes and subsequent protein kinase A (PKA)-mediated phosphorylation of transcription factors that are important for cytokine-, chemokine-, or prostaglandin-forming enzyme synthesis and release from cells. Crisaborole proved efficacious against an inflammatory challenge *in vivo* in a mouse phorbol 12-myristate 13-acetate (PMA)-induced ear edema model.

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

#### **1.3.2. Pharmacokinetics**

The efficacy of crisaborole for the treatment of AD is not dependent on systemic exposure. The development program evaluated systemic exposure to crisaborole and its main metabolites relative to establishing the safety of topically applied crisaborole. Systemic exposures to crisaborole following topical application were assessed in healthy volunteers and patients (atopic dermatitis and psoriasis). Based on a nonlinear regression analysis at a given ointment dose, patients will have 2.5 fold higher exposures compared to healthy volunteers.<sup>21</sup> In pediatric and adolescent subjects (2-17 years) with AD, and in adults with psoriasis, crisaborole demonstrated similar pharmacokinetic profiles and systemic exposure, irrespective of age and established that following topical application, crisaborole penetrated through the stratum corneum, epidermis, and dermis of human skin, as evidenced by the presence of crisaborole and its main metabolites in plasma.

Upon reaching the systemic circulation, biotransformation of crisaborole is rapid and extensive and primarily consists of oxidative deboronation/hydrolysis to produce AN7602 by CYP3A4 and CYP1A1/2, followed by subsequent downstream oxidation of this metabolite to form AN8323, without notable species-related qualitative differences. These two main metabolites of crisaborole observed in plasma following topical application to several species, including humans, were found to be inactive against PDE-4. Further, as a result of rapid biotransformation, systemic exposure of crisaborole is limited following topical application of crisaborole.

- In a clinical pharmacokinetic (PK) study conducted under maximal use conditions (maximal use systemic exposure [MUSE] study) in children and adolescents aged 2-17 years with extensive AD (mean treatable percent body surface area [Treatable % BSA] 48.7%; range 27%-92%), absorption across the skin was rapid, with a median time to reach maximum observed plasma concentration ( $T_{max}$ ) of 3.0 hours on both Day 1 and Day 8 (Study AN2728-AD-102). Steady state was achieved within the first 8 days of dosing, with a mean crisaborole maximum observed plasma concentration ( $C_{max}$ ) of 127 ng/mL. Minimal plasma accumulation of crisaborole and AN7602 was observed at steady state whereas AN8323 accumulated in plasma at a rate of 3-4 times that of crisaborole or AN7602, based on mean  $C_{max}$ .
- In a Thorough QT/QTc (TQT) study (Study AN2728-TQT-108) in which healthy subjects were treated with crisaborole ointment, 2% at a therapeutic dose (15 g using an approximate 30% BSA treatment area) or a supratherapeutic dose (45 g, using an approximate 60% BSA treatment area), mean  $C_{max}$  values of 36.9 ng/mL and 87.4 ng/mL were observed in therapeutic and supratherapeutic dose groups, respectively, at Day 9. Both therapeutic and supratherapeutic doses had no effect on cardiac repolarization based on results from the primary assessment and the pharmacokinetic-pharmacodynamic analysis.

### **1.3.3. Cutaneous Sensitization, Irritancy Potential and Tolerability**

#### **1.3.3.1. Local Tolerability in Sensitive Skin Areas**

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

### **1.3.3.2. Sensitizing and Cumulative Irritation Potential**

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

### **1.3.4. Clinical Experience**

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

- In a multicenter, maximal use, systemic exposure (MUSE) study in 34 pediatric subjects ranging in age from 2 to 17 years with mild-to-moderate AD who applied crisaborole ointment, 2% BID, subjects had overall blood levels of crisaborole that were low and similar to those previously observed in adults after adjusting for % BSA treated. Absorption across the skin was rapid, with a median  $T_{max}$  of 3.0 hours on both Day 1 and Day 8.
- In a 4-week, single arm, open-label safety, tolerability and PK trial in adolescents with mild-to-moderate AD involving 10-35% BSA, disease severity improved over the 28-day treatment period.
- In a 6-week bilateral comparison trial of subjects with mild-to-moderate AD, 68% of AD lesions treated with crisaborole ointment, 2% BID showed greater improvement in Atopic Dermatitis Severity Index (ADSI) than vehicle-treated lesions (20%) at 4 weeks (primary endpoint). These response rates were similar at Day 14 and Day 42 (end of treatment).
- In a 4-week bilateral comparison trial of 86 adolescent subjects with mild-to-moderate AD, crisaborole ointment, 2% BID showed greater improvement than the lower concentration of crisaborole ointment, 0.5% applied BID for 29 days, and was more efficacious than either concentration applied once daily (QD).

- In two Phase 3 multicenter, randomized, double-blind, vehicle controlled studies in subjects ≥2 years of age and older with mild to moderate AD, crisaborole ointment, 2% outperformed the vehicle in the primary efficacy analysis, proportion of subjects achieving success in Investigator's Static Global Assessment (ISGA) at Day 29. Success was defined as an (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement over baseline. Proportion of success was 32.8% and 25.4% for crisaborole ointment, 2% and vehicle, respectively in AN2728-AD-301 and 31.4% and 18.0%, respectively in AN2728-AD-302. The primary efficacy endpoint was met; differences from vehicle were statistically significant in both studies.
- A Phase 3 multicenter, open-label, long-term extension study (AN2728-AD-303) of crisaborole ointment, 2% for the treatment of mild to moderate AD in adults and children as young as 2 years of age evaluated the long-term safety of topical crisaborole. Crisaborole ointment, 2% was well-tolerated and no clinically important safety signals were identified by this study.

In summary, crisaborole has been well-tolerated across completed clinical studies. No clinically important safety signals have been identified in adults and children as young as 2 years of age. Most AEs have been mild, and most considered unrelated or unlikely to be related to investigational product. The most common drug-related AEs was application site pain (eg, cutaneous stinging and or burning).

## **1.4. Rationale**

### **1.4.1. Study and Dose Rationale**

This 4-week, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study will determine the efficacy of crisaborole ointment, 2% applied BID compared with vehicle and evaluate the efficacy of crisaborole ointment, 2% applied BID compared with a TCS or TCI, in subjects ages 2 years and older with mild to moderate AD. The study will also evaluate the efficacy and safety of crisaborole ointment, 2% compared with the active controls; hydrocortisone butyrate cream, 0.1% [TCS] and pimecrolimus cream, 1% [TCI]. Hence, this study will, provide contextualization of the efficacy and safety of crisaborole ointment, 2% in the treatment of mild to moderate AD.

In the current treatment paradigm of mild to moderate AD there are only two main topical treatment options – TCS and the TCI pimecrolimus cream 1% (Elidel®). To fully inform the position of crisaborole ointment, 2% in relation to the available topical treatments for mild to moderate AD, both the TCS hydrocortisone butyrate cream 0.1% (a standard of care treatment) and pimecrolimus cream, 1% (a second line treatment) have been included as active comparators. The study will therefore provide contextualization of the efficacy of crisaborole ointment, 2% in the treatment of mild to moderate AD compared with hydrocortisone butyrate cream, 0.1% and pimecrolimus cream, 1%.

The dose strength and regimen of crisaborole for this study has been shown to be safe, well-tolerated and efficacious in subjects and healthy volunteers 2 years of age and older who participated in previously conducted studies. Crisaborole ointment, 2% applied BID was studied in two Phase 3, randomized, double-blind, vehicle-controlled studies, and a Phase 3 open-label long-term safety study. Data from the two controlled studies showed a statistically significant therapeutic effect compared to vehicle with no safety concerns in subjects 2 years and older. In the subsequent Phase 3 open-label extension study, crisaborole ointment, 2% applied BID, demonstrated that long-term use was well-tolerated and not associated with any systemic safety signals.

Dose selection for the previous Phase 3 clinical studies was based on the safety and efficacy results from Phase 2 studies. The Phase 2 Study AN2728-AD-204 compared two concentrations of crisaborole (2% and 0.5%) applied QD or BID in adolescents (12 to 17.9 years of age) with mild to moderate AD. The largest dose-related response and the greatest improvement in all 5 component signs and symptoms of AD occurred in the crisaborole 2% BID group, with a notable reduction from baseline in the pruritus score. The safety of the 2% dosage strength was confirmed in additional studies, including maximal use systemic exposure (MUSE) studies (pediatric subjects with AD and adult subjects with psoriasis) and with supra-therapeutic dosing in a TQT study (healthy adult subjects).

This study will evaluate crisaborole ointment, 2% applied BID, a dose strength and regimen that has been demonstrated to be safe, well-tolerated and efficacious.

Hydrocortisone butyrate cream, 0.1% and pimecrolimus cream, 1% are approved products for the treatment of mild to moderate atopic dermatitis in subjects ages 2 years and older, and will be used as per national approved label in this study.

#### **1.4.2. Benefit/Risk Assessment**

- This study will evaluate crisaborole at a dose strength and regimen that has been demonstrated to be well-tolerated and efficacious based on the completed Phase 3 development program data. Crisaborole ointment, 2% was applied BID in two Phase 3, randomized, double-blind, vehicle-controlled 4-week studies (AN2728-AD-301 and AN2728-AD-302) in subjects with mild to moderate AD aged 2 years and older. The pediatric population comprised approximately 86% of the pooled study population.
- This study also contains a vehicle arm that has important emollient properties and does not represent a true placebo. It is known that some vehicle excipients have a more pronounced beneficial effect on the skin than previously considered and can improve clinical appearance and skin barrier function. In particular, petrolatum the main excipient and base of crisaborole ointment, 2% was selected for its emollient properties and favorable tolerability profile. The use of topical emollients is an essential element of the treatment of AD recommended by published clinical guidelines.
- This study also contains two active comparator therapies, hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1%, that have been approved for the treatment of mild to

moderate AD in patients 2 years of age and older and will be used per the national approved labels in this study.

- The crisaborole dose strength and regimen of crisaborole for this study has been shown to have a favorable safety profile and to be well tolerated in subjects and healthy volunteers (adults only) of 2 years of age and older who participated in previously conducted studies. Crisaborole ointment, 2% applied BID was studied in two Phase 3, randomized, double-blind, vehicle-controlled studies (AN2728-AD-301 and AN2728-AD-302), and a Phase 3 open-label long-term safety study (AN2728-AD-303). Data from the two controlled studies showed no systemic safety concerns in subjects aged 2 years and older. In the open-label study, crisaborole ointment, 2% applied BID, demonstrated that long-term use was well tolerated and no clinically important systemic safety signals were identified in subjects aged 2 years and older.
- The most common drug related adverse events (AEs) from the two controlled studies were application site reactions (5.6% and 3.6% for crisaborole and vehicle groups, respectively) and most were classified as mild. Of these drug related application site reactions, application site pain (eg, burning or stinging) was the only treatment related AE that showed a clinically relevant difference in rates between the treatment groups (4.4% and 1.2% for crisaborole and vehicle groups, respectively). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.
- The safety profile from the open label long term clinical study in which crisaborole was applied intermittently for up to 48 weeks was consistent with that of the two controlled pivotal clinical studies.
- A review of the post-marketing safety data, to date, has shown that the type and occurrence of adverse event reports are consistent with the known safety profile of crisaborole. No new safety signals or unusual trends have been identified.
- Adequate and well-controlled clinical studies of pregnant women have not been performed for crisaborole and there is a limited amount of data from the use of crisaborole in pregnant women. As per protocol, women who are pregnant or intending to become pregnant are excluded from the study and women of child-bearing potential must use a highly effective method of contraception.
- Studies in renal or hepatic impaired patient populations have not been conducted. Studies to date did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.
- Hypersensitivity, including contact urticaria, has occurred in subjects treated with crisaborole. As per protocol, subjects with a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products are excluded.

- Hydrocortisone butyrate 0.1% cream is an approved treatment for AD and has a well-documented and established safety profile that is clearly described in the product label. The most common side effects (these may affect up to 1 in 10 people, or up to 10%) are application site reactions including skin infections, eczema, and redness.
- Pimecrolimus 1% cream is an approved treatment for mild to moderate AD and has a well-documented and established safety profile that is clearly described in the product label. In this study, pimecrolimus is used as a second-line treatment as per label. The most common side effects (these may affect up to 1 in 10 people, or up to 10%) are skin infections and application site reactions (irritation, redness, and itching).

In conclusion, the clinical experience obtained to date with crisaborole, support the continued development of crisaborole for the treatment of AD and support the initiation of this Phase 3b/4 clinical Study C3291037. Subjects will be monitored closely during the study for safety and local tolerability adverse events of the investigational products by the Investigators, Sponsor and External Data Monitoring Committee to ensure subject safety.

#### **1.4.3. Single Reference Safety Document**

Additional information for crisaborole may be found in the Single Reference Safety Document (SRSD), which for this study is the crisaborole Investigator's Brochure. The SRSD for hydrocortisone butyrate cream, 0.1% is the United States Prescribing Information and for pimecrolimus cream, 1% is the Summary of Product Characteristics. These SRSDs will serve to assess whether a serious adverse event related to the investigational products meets the criteria for a suspected unexpected serious adverse reaction (SUSAR).

## 2. STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Primary Efficacy Endpoint
<ul style="list-style-type: none"><li>To compare the efficacy of crisaborole ointment, 2% applied BID versus vehicle in pediatric and adult subjects, aged 2 years and older, with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>Percent change from Baseline in the Eczema Area and Severity Index (EASI) total score at Day 29.</li></ul>
Primary Safety Objectives	Primary Safety Endpoints
<ul style="list-style-type: none"><li>To evaluate the safety and local tolerability of crisaborole ointment 2% applied BID versus vehicle in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li><li>To evaluate the safety and local tolerability of hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>AEs, SAEs, local tolerability, discontinuations and clinically significant changes in vital signs and clinical laboratory parameters.</li></ul>
Secondary Objectives	Secondary Endpoints
<ul style="list-style-type: none"><li>To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle on additional efficacy endpoints over time in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li><li>To evaluate the efficacy of crisaborole ointment, 2% BID versus hydrocortisone butyrate cream 0.1% and pimecrolimus cream 1% applied BID in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.</li></ul>	<ul style="list-style-type: none"><li>Efficacy endpoints:<ul style="list-style-type: none"><li>Percent change from Baseline in EASI total score by scheduled time points except Day 29.</li><li>Achievement of success in the Investigator's Static Global Assessment (ISGA) (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from Baseline) by scheduled time points.</li><li>Achievement of ISGA score of clear (0) or almost clear (1) by scheduled time points.</li><li>Achievement of EASI75 (<math>\geq 75\%</math> improvement from Baseline) by scheduled time points.</li><li>Time to EASI75.</li><li>Change from Baseline in % BSA by scheduled time points.</li></ul></li></ul>
<ul style="list-style-type: none"><li>To evaluate the effect of crisaborole ointment, 2% applied BID versus vehicle, hydrocortisone butyrate cream 0.1% applied BID on patient/observer reported outcomes</li></ul>	<ul style="list-style-type: none"><li>Patient/observer reported outcomes endpoints:<ul style="list-style-type: none"><li>Change from Baseline in Peak Pruritus Numerical Rating Scale (NRS) for subjects <math>\geq 12</math> years by</li></ul></li></ul>

over time in pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.	scheduled time points
	<ul style="list-style-type: none"><li>• Change from Baseline in Patient Reported Itch Severity Scale - for subjects age 6-11 years by scheduled time points. Change from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years by scheduled time points.</li><li>• Time to <math>\geq 2</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years. Time to <math>\geq 3</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years. Time to <math>\geq 2</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Time to <math>\geq 3</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Achievement of <math>\geq 2</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years.</li><li>• Achievement of <math>\geq 3</math> point improvement from Baseline in Peak Pruritus NRS for subjects <math>\geq 12</math> years.</li><li>• Achievement of <math>\geq 2</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Achievement of <math>\geq 3</math> point improvement from Baseline in Observer Reported Itch Severity Scale - for subjects &lt;6 years.</li><li>• Change from Baseline in Dermatology Life Quality Index (DLQI) (for Subjects 16 years and older), Children's Dermatology Life Quality Index (CDLQI) (for Subjects 4-15 years), and Dermatitis Family Impact Questionnaire (DFI) (Completed by parent/caregiver of Subjects 2-17 years) by scheduled time points.</li></ul>
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### 3. STUDY DESIGN

This is a Phase 3b/4, multicenter, randomized, assessor blinded, vehicle and active (TCS and TCI) controlled study of the efficacy, safety and local tolerability of crisaborole ointment, 2% in pediatric and adult subjects, ages 2 years and older, with mild to moderate AD involving at least 5% treatable %BSA. Treatment will be clinical assessor-blinded for all treatment arms and double-blinded for crisaborole ointment, 2% and vehicle treatment arms.

A total of approximately 600 subjects will be enrolled in the study, of which at least 150 subjects aged 2-6; at least 140 subjects aged 7-11; at least 120 subjects aged 12-17 and up to 90 subjects will be adults. Following the screening period (up to 35 days prior to Baseline/Day 1), eligible subjects will be randomized at the Baseline/Day 1 visit.

Randomization will be stratified by eligibility for TCS or TCI treatment as per national approved labels and eligibility provided in [Section 4](#). Cohort 1 will be for subjects who are eligible for TCS therapy, and Cohort 2 will be for subjects who are not eligible for TCS therapy but eligible for TCI therapy. The investigational product will be applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1. Any new AD on treatment-eligible locations occurring following Baseline/Day 1 should also be treated with the study drug after consultation with the Investigator at the next visit.

The primary efficacy endpoint is the percent change from baseline in the EASI total score at Day 29.

For the efficacy comparison of crisaborole versus vehicle, subjects from both Cohort 1 and Cohort 2 are included in the analysis, adjusted for cohort effect. For the efficacy comparison of crisaborole versus TCS, only subjects from Cohort 1 are included in the analysis. For the comparison of crisaborole versus TCI, only subjects from Cohort 2 are included in the analysis.

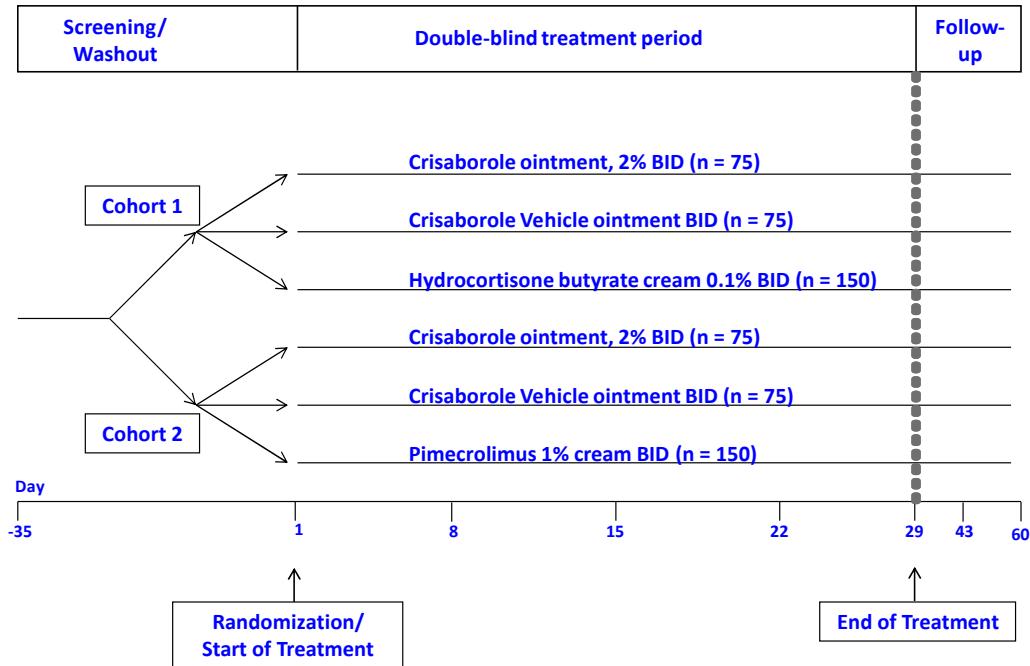
Safety and efficacy assessments will be conducted at the investigator site by a clinical assessor blinded for treatment arms.

A sub-study will be conducted at selected investigator sites to evaluate differences of changes in epidermal skin thickness as measured by Optical Coherence Tomography (OCT) between treatment groups in Cohort 1. (see Appendix 4).

Scheduled study visits for all subjects will occur at Screening, Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (End of treatment/Early termination) and Day 43 or 14 Days after last dose if subject is terminated early from treatment. A follow up telephone call will be made by site staff to the subjects/caregivers on Day 60 or at least 28 days after last dose if subject is terminated early from treatment. Subjects enrolled in the OCT sub-study will attend the clinic on Day 60 and do not require a telephone call on Day 60.

A schematic of the study design is shown in [Figure 1](#).

**Figure 1. Study Design Schematic**



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Treatment will be clinical assessor-blinded for all treatment arms and double-blinded for crisaborole ointment, 2% and vehicle treatment arms.

#### **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.

Subjects screening for the study prior to informed consent approval by IRB/EC for amendment 3 should complete the version of the study for which they consented. Subjects screening for the study after IRB/EC approval of the amendment 3 version of the protocol and consent should complete the amendment 3 version of the study.

Subject eligibility for the sub-study will be reviewed and documented according to additional criteria specified in Appendix 4. The sub-study informed consent process will be separate and in addition to the informed consent process for the main study.

#### **4.1. Inclusion Criteria**

##### **4.1.1. Inclusion Criteria – All Cohorts**

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

1. Is male or female 2 years and older at the Screening visit/time of informed consent/assent.
2. Has a clinical diagnosis of AD according to the criteria of Hanifin and Rajka (See [Appendix 2](#)).
3. Has AD involvement of  $\geq 5\%$  Treatable %BSA (excluding the scalp) at Baseline/Day 1.
4. Has an ISGA score of Mild (2) or Moderate (3) (excluding the scalp) at Baseline/Day 1.
5. Female subjects of childbearing potential who have a negative urine pregnancy test at the screening visit and negative urine pregnancy test at the baseline visit prior to randomization. A female is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children (includes any female who has experienced menarche and does not meet the criteria for females not of childbearing potential).
6. Female subjects of non-childbearing 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; have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
  - b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
  - c. Have medically confirmed ovarian failure.

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

7. Evidence of a personally signed and dated informed consent/assent document indicating that the subject [or parent(s)/legal guardian] has been informed of all pertinent aspects of the study.
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

#### **4.1.2. Inclusion Criteria – Cohort 1**

1. Subjects considered to be a candidate for hydrocortisone butyrate cream, 0.1% therapy according to the national approved labeling.

#### **4.1.3. Inclusion Criteria – Cohort 2**

1. Subjects who are not considered candidates for treatment with a topical corticosteroid because it is either inadvisable or not appropriate according to the national approved labeling. This may include:
  - Intolerance to topical corticosteroids;
  - Lack of effect of topical corticosteroids;
  - Use on the body regions where treatment with topical corticosteroids may be inappropriate.

### **4.2. Exclusion Criteria**

#### **4.2.1. Exclusion Criteria – All Cohorts**

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

1. Has any clinically significant medical disorder, condition, or disease (including active or potentially recurrent non-AD dermatological conditions and known genetic dermatological conditions that overlap with AD, such as Netherton syndrome) or clinically significant physical examination finding that in the PI's or designee's opinion may interfere with study objectives (eg, expose subject to unacceptable risk by study participation, confound evaluation of treatment response or AEs, or interfere with subject's ability to complete the study).
2. Has unstable AD or a history of requirement for high/strong potency or very high/very strong potency topical corticosteroids to manage AD signs and symptoms (See [Appendix 3](#)).
3. Has a significant active systemic or localized infection, including known actively infected AD.
4. History of or active suicidal ideation or behavior, or chronic psychiatric 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 including the following:

- For subjects 7-11 years of age, suicidal ideation associated with actual intent and a method or plan in the past 6 months: “Yes” answers on items 4 or 5 of the Children’s Columbia suicide severity rating scale (C-SSRS) or a previous history of suicidal behaviors in their lifetime: “Yes” answer to any of the suicidal behavior items of the Children’s C-SSRS.
  - For subjects ≥12 years of age, suicidal ideation associated with actual intent and a method or plan in the past year: “Yes” answers on items 4 or 5 of the C-SSRS or a previous history of suicidal behaviors in the past 5 years: “Yes” answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.
5. Pregnant female subjects; breastfeeding female subjects; and female of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
  6. Has received any of the prohibited medications/therapies that may alter the course of AD without the required minimum washout period (see [Section 5.8.1](#)) or anticipated concomitant use of any of the prohibited medications/therapy (see [Section 5.8.2](#)).
  7. Has any planned surgical or medical procedure that would overlap with study participation, from Screening through the end of study.
  8. Has a history of cancer within 5 years or 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).
  9. Has a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products.
  10. Has a known lack of efficacy to crisaborole.
  11. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.
  12. Other acute or chronic medical 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.
  13. 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.

#### **4.2.2. Exclusion Criteria – Cohort 1**

1. Has a contraindication for treatment with hydrocortisone butyrate cream 0.1% or meets warnings and precautions for use specifications in accordance with the national approved label or treatment with hydrocortisone butyrate cream, 0.1% is otherwise medically inadvisable.

#### **4.2.3. Exclusion Criteria – Cohort 2**

1. Has a contraindication for treatment with pimecrolimus cream, 1%, or meets warnings and precautions for use specifications in accordance with the national approved label or treatment with pimecrolimus cream, 1% is otherwise medically inadvisable.

### **4.3. Randomization Criteria**

Subjects will be randomized into the study provided that the subject or caregiver [parent/legal guardian/legally acceptable representative] has signed an informed consent (or assent, if applicable) document to participate in the study, and the subject has undergone all screening procedures, and satisfies all inclusion and exclusion criteria for participation in the study at the Baseline visit. A centralized computer-generated randomization schedule will be used to assign subjects to the treatment groups.

Subjects will be assigned to one of two cohorts prior to randomization. Subjects will be enrolled into Cohort 1 if eligible to receive TCS therapy; randomization will be 1:1:2 to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or hydrocortisone butyrate cream, 0.1%, respectively. Subjects will be enrolled into Cohort 2 if ineligible to receive TCS therapy and eligible to receive pimecrolimus cream, 1%; randomization will be 1:1:2 to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or pimecrolimus cream, 1%, respectively.

Subjects will be assigned a subject identification number in the order of their screening for the study. The identifying number will be retained throughout the study.

### **4.4. Lifestyle Requirements**

#### **4.4.1. 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 the screening period, 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 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 his/her 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 his/her 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:

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

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

#### **4.4.2. Other Lifestyle Requirements**

- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation.
- Subjects should avoid applying an occlusive dressing to the treated areas, not swim, bathe or be bathed or have treatment areas washed for at least 4 hours after application of investigational product.
- Use of sunscreen is permitted, but only on areas without AD involvement.
- Due to the potential to affect AD with ultraviolet light exposure, subjects must also avoid prolonged exposure to the sun and not use tanning booths, sun lamps or other ultraviolet light sources during the study.

- The subject and/or caregiver should avoid wiping the investigational product off the skin and investigational product should not be reapplied to areas that were inadvertently wiped until the next scheduled dose.
- When applying investigational product, the subject and/or caregiver will generally not be required to wear gloves. However, they must be instructed to wash their hands with mild soap and water before and after each application. Subjects with lesions on hands must take care not to wash off investigational product from the hands.
- Caregivers who are pregnant or women of childbearing potential, who are trying to become pregnant, should avoid accidental exposure by either avoiding applying investigational product or wearing gloves during its application. Care should also be taken when handling the child after investigational product has been applied.

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

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. 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 Council for 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 vehicle ointment, also referred to as vehicle;
- Hydrocortisone butyrate cream, 0.1% (eg. Locoid®), also referred to as TCS;
- Pimecrolimus cream, 1% (eg. Elidel®), also referred to as TCI.

Crisaborole ointment, 2%, is formulated to contain crisaborole (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.

For hydrocortisone butyrate cream, 0.1% and pimecrolimus cream, 1% the national approved label insert will be provided to each site for content information.

### **5.1. Allocation to Treatment**

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number(s) when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number(s) assigned. The confirmation report must be stored in the site's files.

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

### **5.2. Breaking the Blind**

- In this study treatment will be clinical assessor-blinded for all treatment arms and double-blinded for crisaborole ointment, 2% and vehicle treatment arms. Unblinded personnel will be required to manage subject treatment allocation, handle investigational products, review the Dosing Diary and participate in the Baseline/Day 1 investigational product application training. All study treatments will be masked by over-labeling with a tube label that will be applied over the entire body and crimp of the tube.
- At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The methods will be by an electronic or telephone process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject.  
Investigators are encouraged to discuss with a member of the study team if they believe

that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

### **5.3. Subject Compliance**

The subject and/or a caregiver will apply investigational product at home; compliance will be captured and completed by the subject/caregiver using a Dosing Diary and instructions provided by the site. The subject and/or caregiver will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1, then BID through Day 28 (ie, each time investigational product is applied) for the investigational product doses applied at home. If the subject comes to the clinic in the afternoon, two doses ( $12 \pm 4$  hours apart) or single dose could be administered on Day 1. Subjects and/or caregivers will be instructed to bring the Dosing Diary and all dispensed investigational product supplies in its original package (used as well as unused) to the clinic at Days 8, 15, 22, and 29.

A total of 56 doses are expected to be applied. A subject will be considered compliant with the dosing regimen if they receive at least 45 but no more than 67 investigational product doses (ie, 80–120%, inclusive, of the expected number of doses) administered in accordance with the protocol. This will be verified by the dosing records. Subjects and/or caregivers having missed doses of IP will be re-educated on the importance of compliance.

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

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

Crisaborole ointment, 2% and vehicle ointment will be supplied in 60 gram tubes for topical administration. The tubes will be provided in cartons and labeled in a blinded fashion.

Hydrocortisone butyrate cream, 0.1% will be supplied in either 30 gram or 45 gram tubes for topical administration. The tubes will be masked by a label and provided in cartons. The product will be labeled in a blinded fashion to mask contents.

Pimecrolimus cream, 1% will be supplied in either 30 gram or 60 gram tubes for topical administration. The tubes will be masked by a label and provided in cartons. The product will be labeled in a blinded fashion to mask contents.

The blinded labeling for all products will be according to local regulatory requirements.

The investigational products above are masked for appearance, and will be placed into identical cartons. Once removed from the product cartons, the investigational products could be discerned from each other based on commercial product tube shape/size and should only be handled by unblinded site personnel.

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

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a

healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

The investigational product will be dispensed in a blinded fashion using an IRT system at each visit from Baseline/Day 1 to the Day 22 visit. An unblinded qualified staff member will dispense the investigational product via unique container numbers on the cartons provided, in quantities appropriate for the study visit schedule and the treatable %BSA.

For doses to be administered at home, the subject or caregiver should be instructed to maintain the product in its original package provided throughout the course of dosing and return the product and its original package (including empty, partial used and unused tubes) to the site at the next study visit. All previously dispensed investigational product tubes will be retained by the site. Investigational product tubes will be weighed individually or collectively by the study site before dispensing and after return and the weights will be recorded. The sponsor will use the recorded weights to estimate usage (mg/cm<sup>2</sup>/day) by each subject. Note that the weight recorded on the investigational product label is a nominal weight and not an exact weight of the investigational product and tube.

## **5.5. Administration**

Before the Day 1 initial investigational product application is performed, the designated areas for treatment will be identified at the Baseline/Day 1 Visit and documented in the subject's source document study records (body maps). The subject and/or caregiver will be provided with documentation of the designated treatment areas.

**Regimen:** Investigational product will be applied BID (12 ±4 hours apart) to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28. Wearing gloves, unblinded personnel will apply a thin layer of investigational product to all treatable AD lesions identified at Baseline/Day 1. Subjects and/or caregivers will be encouraged to observe and participate in the initial investigational product application on Day 1. All subsequent doses, including the second dose on Day 1 (if applicable), will be applied at home. 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 investigational product application instructions.

Subjects and/or caregivers will be instructed to not wipe investigational product off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application.

In the event the scheduled Day 29 (End of Treatment) Visit does not occur on Day 29, eg, due to an unavoidable scheduling conflict, the subject and/or caregiver will be instructed to continue investigational product application BID through the evening before the day that the rescheduled End of Treatment Visit is to occur (see Subject Compliance [Section 5.3](#)). Investigational product will continue to be applied to all treatable AD involved areas (excluding scalp) identified at Baseline/Day 1 regardless of whether they become clinically

clear prior to Day 29. Investigational product will also be applied to any new AD on treatment eligible locations occurring following Baseline/Day 1 after consultation with the Investigator at the next visit. Therefore, the BSA for Investigational Product at subsequent visits should be equal to or greater than the value at Baseline/Day 1.

Subjects and/or caregivers will be instructed to apply evening (PM) doses approximately 8–16 hours after the morning (AM) doses (eg, if an AM dose is completed at 8:00 AM, the PM dose can be applied anytime between 4:00 PM and 12:00 AM). Caregivers or partners may also be ones to apply investigational product, especially for areas that a subject cannot reach, even in adults. The first dose is preferred to be administered in the morning on Day 1. If the subject comes to the clinic in the afternoon, two doses ( $12 \pm 4$  hours apart) or single dose could be administered on Day 1.

### **5.6. Investigational Product Storage**

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

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

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

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

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

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

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions. Site staff will instruct subjects and/or parents/legal guardians on the proper storage requirements for take home investigational products.

The Investigational Product Manual should be referenced for any additional guidance on storage conditions and actions to be taken when conditions are outside the specified range.

## **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.

Throughout the study, detailed investigational product accountability records, including tube weights, will be maintained for each subject by study staff.

The subjects and/or caregivers will be asked to bring all dispensed investigational product (including empty, partial used and unused tubes) and the dosing diary to the clinic at every visit. Detailed drug accountability records, including weekly tube weights measured in the clinic, will be maintained by unblinded personnel for each subject.

The original investigational product accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the Sponsor) when the study is complete. The accountability log will be an unblinded document until study completion and therefore should only be accessed by unblinded site personnel.

### **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.

For all investigational product returned to the investigator by subjects and/or the parents/legal guardians, the investigator will maintain the returned supply until destruction is authorized. Only unblinded personnel should have access or view any returned product. The sponsor or designee will provide instructions as to the disposition of any unused investigational product.

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

All prior medications, including all medications, non-medication therapies, as well as biologic drugs used for AD within 180 days prior to Screening and all other treatments, including bland (non-medicated) emollients, over the counter drugs, vitamins, and antacids, used within 30 days prior to Screening will be recorded at the screening visit. Any changes in concomitant medications or dosage will be recorded at Baseline/Day 1 and at each subsequent visit. Medication entries should provide the correctly spelled drug or therapy name and the dose, units, frequency, route of administration, start and stop date, and reason for use. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements and routine immunizations.

### **5.8.1. Medications Prohibited Prior to Baseline/Day 1**

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

#### Medications Prohibited 12 weeks or 5 half-lives (whichever is longer) Prior to Baseline/Day 1

- Biological drugs.

#### Medications Prohibited 28 Days Prior to Baseline/Day 1

- Use of systemic (oral, parenteral) corticosteroids, within 28 days prior to Baseline/Day 1.

Subjects with stable use (regular regimen) of intranasal/inhaled/ophthalmic corticosteroids with  $\geq 14$  days of consistent use prior to Baseline/Day 1 are permitted to continue use of intranasal/inhaled/ophthalmic corticosteroids but must not alter or stop their regimen during the study.

- Use of systemic immunosuppressive agents, including but not limited to, methotrexate, cyclosporin, azathioprine, hydroxychloroquine, and mycophenolate mofetil (MMF), within 28 days prior to Baseline/Day 1.
- Use of sunbathing, tanning bed use, or light therapy Ultraviolet (UV), Ultraviolet B (UV-B), psoralen–UV-A [PUVA]), within 28 days prior to Baseline/Day 1.
- Escalating, decreasing, or as-needed (PRN) use of topical retinoids or benzoyl peroxide (BPO) on treatable AD lesions, within 28 days prior to Baseline/Day 1.

Subjects on a stable regimen of topical retinoids and/or BPO regimen with  $\geq 14$  days of consistent use prior to Baseline/Day 1 are permitted to continue the topical retinoids or BPO regimen (not on the AD lesions) but must not alter or stop their regimen during the study.

#### Medications Prohibited 14 Days Prior to Baseline/Day 1

- Use of systemic antibiotics, within 14 days prior to Baseline/Day 1.
- Use of TCS, or TCI, anywhere on the body, within 14 days prior to Baseline/Day 1.
- Use of crisaborole ointment, 2%, anywhere on the body, within 14 days prior to Baseline/Day 1.
- Use of topical antihistamines anywhere on the body, within 14 days prior to Baseline/Day 1.

#### Medications Prohibited 7 Days Prior to Baseline/Day 1

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body, within 7 days prior to Baseline/Day 1.
- Systemic sedating antihistamines (eg, hydroxyzine or diphenhydramine or other sedating antihistamines).
- Use of systemic non-sedating antihistamines in a nonstable (eg, escalating, decreasing, or PRN) regimen, within 7 days prior to Baseline/Day 1.
- Subjects on a stable non-sedating systemic antihistamine regimen with  $\geq 7$  days of consistent use prior to Baseline/Day 1 are permitted to continue but must not alter or stop their regimen during the study.

#### Medications Prohibited 1 Day Prior to Baseline/Day 1

- Use of bland (non-medicated) emollients on treatable AD lesions, within 1 day prior to Baseline/Day 1 (ie, during the 24-hour period before the Baseline/Day 1 Visit).

After the Baseline/Day 1 Visit, use of bland (non-medicated) emollient(s) is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD-involved areas (See [Section 5.8.2](#) and [Section 5.8.3](#)).

#### **5.8.2. Medications Prohibited During Treatment (Days 1–29)**

Classes of medications and non-medication therapies that may alter the course of AD and that are prohibited during the study (from Baseline/Day 1 through to the end of treatment visit on Day 29) are listed below.

- Use of systemic (oral, parenteral) corticosteroids.
- Subjects with a stable regimen of intranasal/inhaled/ophthalmic corticosteroids with ≥14 days of consistent use prior to Baseline/Day 1 are permitted to continue use of intranasal/inhaled corticosteroids but must not alter or stop their regimen during the study.
- Use of TCS, or TCI, anywhere on the body other than allocated investigational product.
- Use of systemic immunosuppressive agents, including but not limited to methotrexate, ciclosporin, azathioprine, hydroxychloroquine, or MMF.
- Escalating, decreasing, or PRN use of topical retinoids or BPO on treatable AD lesions.

Subjects on a stable topical retinoid and/or BPO regimen with ≥14 days of consistent use prior to Baseline/Day 1 are permitted to continue the topical retinoid or BPO regimen (not on AD lesions) but must not alter or stop their regimen during the study.

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

Subjects on a stable non-sedating systemic antihistamine regimen with ≥14 days of consistent use prior to Baseline/Day 1 are permitted to continue but must not alter or stop their regimen during the study.

- Use of systemic antibiotics for more than 14 consecutive days.

Short courses ( $\leq$ 14 days) of systemic antibiotics may be given during the study if clinically necessary for the treatment of new onset infections.

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body.
- Use of topical antihistamines anywhere on the body.
- Use of sunbathing, tanning bed use, light therapy (UV, UV-B, PUVA) anywhere on the body.
- Use of bland (non-medicated) emollients, moisturizers or sunscreen on AD lesions.
- Participation in another drug or device research study.

### **5.8.3. Medications Allowed During Treatment (Days 1–29)**

Classes of medications that are allowed during the study (from Baseline/Day 1 through the end of treatment visit on Day 29) are summarized below:

- After the Baseline/Day 1 Visit, use of bland (non-medicated) emollient(s) is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD-involved areas;
- Subjects on a stable regimen of inhaled, intranasal, or ocular corticosteroids, with ≥14 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study;
- Short courses ( $\leq$ 14 days) of systemic antibiotics may be given during the course of the study, if clinically necessary for the treatment of new onset infections;
- Subjects on a stable non-sedating systemic antihistamine regimen, with  $\geq$ 7 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study;
- Subjects on a stable topical retinoid and/or BPO regimen, with  $\geq$ 14 days of consistent use prior to Baseline/Day 1, are permitted to continue (not on AD lesions) but must not alter or stop their regimen during the study;
- Nonsteroidal anti-inflammatory drugs are allowed throughout the study;
- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation in study;
- Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception are permitted during the study, for female subjects of childbearing potential;
- Concomitant medications for other chronic medical conditions are permitted during the study unless the medication/therapy is specifically prohibited by the protocol.

### **5.8.4. Medications Allowed After the End of Treatment (Day 29 or after early termination from treatment until Day 43 visit)**

- In addition to medications allowed during the treatment phase, if the EASI score at the End of Treatment/Early Termination Visit is the same or higher than the EASI score at the Baseline Visit (ie, no improvement or worsening of AD severity), there are no restrictions to medications used to treat AD during this period.
- If the EASI score at the End of Treatment/Early Termination Visit is lower than the EASI score at the Baseline Visit (ie, improvement in AD severity), then medications prohibited

during treatment period (Day 1 to 29; see Section 5.8.2) are prohibited until the completion of the Day 43 Visit.

- After the end of treatment, and prior to the Day 43 visit, unscheduled clinic visits are available if subject's condition worsens, so that an assessment can be conducted in-clinic, and nonstudy treatment intervention prescribed as necessary. If the EASI score at this unscheduled visit is the same or higher than the EASI score at the Baseline Visit (ie no improvement or worsening of AD severity) there are no restrictions to medications used to treat AD. After the Day 43 visit, there are no restrictions to medications used to treat AD, except for subjects participating in the sub-study (Appendix 4).

## **6. STUDY PROCEDURES**

A number of tasks within the study procedures are completed by dedicated assigned roles at the site level; unblinded personnel and a clinical assessor blinded for treatment arms. The clinical assessor blinded for treatment arms should not have knowledge or access to the assigned subject's investigational product and should not participate in the Baseline/Day 1 investigational product application training and review of the Dosing Diary. The subject and/or caregiver must be instructed not to discuss any element of their study treatment (including study drug appearance) with the blinded clinical assessor.

### **6.1. Study Visits**

Subjects will be required to visit the clinic for all scheduled visits (Screening, Day 1, Day 8, Day 15, Day 22, Day 29/Early termination visit). The timing of each study day is relative to the day of initial dosing (Baseline/Day 1).

### **6.2. Time Windows for Study Procedures**

Allowable time windows for visits/contacts are as follows:

- Screening visit: up to 35 Days prior to Day 1/Baseline;
- Day 1 Visit: Day 1;
- Day 8 Visit: Day 8  $\pm$ 1 day;
- Day 15 Visit: Day 15  $\pm$ 3 days;
- Day 22 Visit: Day 22  $\pm$ 3 days;
- Day 29 End of Treatment Visit: Day 29  $\pm$ 3 days;
- Day 43 Off Treatment Follow Up Visit: Day 43  $\pm$ 5 days;
- Follow up telephone contact: Day 60  $\pm$ 3 days. Subjects enrolled in the OCT sub-study do not require a follow up telephone contact at Day 60 as this visit will occur in clinic.

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

### **6.3. Screening Period**

Screening procedures must be completed within 35 days (inclusive) before the Baseline/Day 1 Visit. If necessary, the screening procedures may be completed over several days.

The following procedures will be performed at the Screening Visit:

- Obtain written informed consent (from adult subject or parent/legal guardian of pediatric subjects) and assent (from pediatric subjects, as applicable) before any study procedures are performed;
- Only subjects that are enrolled after IRB/EC approval of an amendment should be consented to the study under that amendment. If a subject consents to the study prior to local approval of an amendment, they will consent and complete the study according to the version of the study currently approved by the IRB/EC at the time of their enrollment.
- Collect demographic information (sex, date of birth, race, and ethnicity);
- Measure height and weight;
- Measure and calculate the Body Surface Area for Investigational Product (per [Section 7.2](#));
- Register subject with IRT in order to obtain a subject screening identification number (SSIN);
- Perform a detailed physical examination and confirm clinical diagnosis of AD per Hanifin and Rajka criteria ([Appendix 2](#));
- Obtain vital signs (temperature, respiratory rate, pulse rate, and blood pressure [BP]) in the seated position or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes (when possible for younger children);
- Collect complete medical history, including onset of AD (date of diagnosis, as specifically as possible);
- Record treatments (including all medications and non-medication therapies) used for AD, as well as any biologic drugs used within 180 days prior to screening and all other medications, including bland (non-medicated) emollients, over-the-counter drugs, vitamins, and antacids, used within 30 days prior to Screening;

- If a subject is using a prohibited medication (or non-medication therapy) at the time of Screening, the investigator or his/her designee will provide instructions on discontinuing the prohibited medication or therapy (ie, a washout period) at Screening;
- Urine pregnancy test (female subjects of childbearing potential only);
- Contraception check: Confirm and document in source documents that proper contraception have been reviewed for a female subject of child bearing potential and their partner as appropriate, and the subject's agreement to use appropriate contraception methods throughout the study (see [Section 4.4.1](#));
- Serum chemistry and hematology;

Note: At the discretion of the investigator or his/her designee, a topical lidocaine-based anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject. However, the skin must be thoroughly cleansed prior to blood sample collection. Use of a topical lidocaine-based anesthetic must be recorded in the Concomitant Medication electronic case report form (eCRF);

- FSH (to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 months);
- Dispense daily diary (electronic patient reported outcome (ePRO) device or paper);
- Instruct subject and/or caregiver on the use of daily diary (ePRO device or paper);
- Peak Pruritus Numeric Rating Scale (NRS) for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects  $< 6$  years **CC1**

[REDACTED] will be completed by subject or caregiver when applicable during screening prior to Day 1 regardless of whether the subject continues to randomization;

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- Administer C-SSRS. Children's C-SSRS for subjects 7-11 years old, C-SSRS for subjects  $\geq 12$  years old. Subjects  $\geq 7$  years of age meeting any of the criteria specified in Exclusion Criterion 4 will be ineligible for participation (See [Section 4.2.1](#));
- Assess for AEs/SAEs, starting from the time of informed consent and assent, as applicable;
- ISGA completed by a clinical assessor blinded for treatment arms;
- Review subject's tentative eligibility according to the Inclusion and Exclusion Criteria;

Note: The results of all screening evaluations must be reviewed for clinical significance by the investigator or his/her designee prior to randomization of the subject on Baseline/Day 1;

- Schedule the Baseline/Day 1 Visit and all future study visits for the subject's study visit calendar and review the calendar with the subject and/or parent/legal guardian.

#### **6.4. Study Period/Treatment Period**

##### **6.4.1. Baseline/Day 1 Visit**

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

- Administer CCI [REDACTED] Dermatology Life Quality Index (DLQI) (completed by subjects ≥16 years old), Children's Dermatology Life Quality Index (CDLQI) (completed by subjects 4-15 years old), CCI [REDACTED]  
[REDACTED] Dermatitis Family Impact Questionnaire (DFI) (completed by caregivers of subject 2-17 years old) CCI [REDACTED]
- Confirm subject and/or caregiver has been instructed on the use of the diary (ePRO device or paper);
- Confirm subject and/or caregiver has completed Peak Pruritus NRS for subjects ≥12 years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects <6 years CCI [REDACTED] during screening prior to Day 1 to demonstrate understanding and compliance;
- If a subject was undergoing washout of a prohibited medication as directed by the investigator or his/her designee, confirm successful completion of the washout period;
- Perform a detailed physical examination;
- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes (when possible for younger children); assessment of vital signs should precede blood draw for clinical laboratory tests;
- Obtain and record medical history;

- Assess and record any changes in the subject's prior and concomitant medications since the Screening Visit; see [Section 5.8](#) for medications prohibited prior to Baseline/Day 1 and during the study;
- Ask the subject or caregiver (when applicable) to complete the Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects  $<6$  years CCI before investigational product (IP) morning dose applied starting at Baseline/Day 1 and continuing through Day 28 and at Day 29 (as applicable);
- Contraception check: Confirm and document that proper contraception is being used for the female subject of child bearing potential and their partner as appropriate;
- Perform a urine pregnancy test (female subjects of childbearing potential only) and confirm the subject has a negative urine pregnancy test result prior to randomization;
- Draw blood for clinical laboratory tests on Day 1 prior to initial dosing; assessment of vital signs should precede blood draw for clinical laboratory tests; testing includes serum chemistry and hematology;

Note: If the screening serum chemistry and hematology tests are performed within 14 days prior to Day 1, whether the Day 1 serum chemistry and hematology tests are to be performed will be at the medical judgment of Principle Investigator (PI) or designee;

At the discretion of the investigator or his/her designee, a topical lidocaine-based anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject. However, the skin must be thoroughly cleansed prior to blood sample collection. Use of a topical lidocaine-based anesthetic must be recorded in the Concomitant Medication electronic case report form (eCRF);

- ISGA completed by a clinical assessor blinded for treatment arms prior to the application of investigational product (Note: The ISGA score must be 2 or 3 at Baseline/Day 1 for subject to be eligible for the study);
- EASI assessment completed by a clinical assessor blinded for treatment arms prior to the application of investigational product;
- A checklist of body areas currently affected by AD will be completed at the Baseline/Day 1 visit by a clinical assessor blinded for treatment arms. Location of skin lesions will be selected from a prepopulated listing of body locations on the eCRF;
- Confirm subject's eligibility based on the Inclusion and Exclusion Criteria, including confirming acceptable methods of birth control for female subjects of childbearing potential;

- Assess and record any AEs/SAEs related to AD lesions by a clinical assessor blinded for treatment arms. Other site personnel may also report and record AE's and SAE's reported to them spontaneously by the subject;
- Mark the subject's source documents to record the treatable AD areas (excluding the scalp) as identified by a clinical assessor blinded for treatment arms at Baseline/Day 1 and provide subject and/or caregiver with documentation of the designated treatment areas (body maps);
- Photography of AD lesions (at selected sites – see [Section 7.4](#));
- After PI's or designee's documented confirmation of eligibility and Cohort assignment, access IRT system to randomize subject to receive randomization number and investigational product treatment;
- Dispense investigational product supply to subject and/or caregiver;
- Unblinded personnel to provide to subject and/or caregiver a sufficient number of tubes of investigational product for 1 week of dosing; ensure that all dispensed tubes are weighed and weight is recorded in subject's source documents;

Wearing gloves, unblinded study staff will apply a thin layer of investigational product (first dose) to all treatable AD lesions identified at Baseline/Day 1 (See Administration [Section 5.5](#)).

- Assess and record any post-dose AEs/SAEs including application site reactions.

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

- Unblinded personnel to instruct the subject and/or caregiver that investigational product should not be wiped off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application;
- Dispense subject dosing instructions and Dosing Diary and instruct the subject and/or caregiver on use (ie, each time investigational product is applied). Instruct the subject and/or caregiver regarding all procedures for at home dosing beginning with the evening (PM) dose on Day 1 followed by BID dosing through Day 28, including how to complete the Dosing Diary, which will start at the Baseline/Day 1 Visit and continue BID through the evening before Day 28 or End of Treatment Visit (ie, each time investigational product is applied);
- The subject or caregiver must be instructed to avoid discussing treatment details (eg, ointment or cream) with the clinical assessor blinded for treatment arms;

- Review the schedule of upcoming study visits with the subject and/or caregiver, and instruct them to return at the scheduled time for the Day 8 Visit. Advise subject and/or caregiver that the investigational product should be applied at least 4 hours prior to the clinic visit to ensure that there are no visible residues left on the lesions so as to not unblind the blinded clinical assessor;
- Remind the subject and/or caregiver to bring all investigational product tubes (empty, partially used and unused) in their original packages and the Dosing Diary to their next visit.

#### **6.4.2. Day 8 ( $\pm 1$ day), Day 15 ( $\pm 3$ days) and Day 22 ( $\pm 3$ days) Study Visit**

The following procedures will be performed:

- Remind the subject or caregiver (when applicable) to complete the Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects  $< 6$  years CCI (QD before investigational product is applied);
- Administer CCI [REDACTED] DLQI (completed by subjects  $\geq 16$  years old), CDLQI (completed by subjects 4-15 years old), CCI [REDACTED]  
[REDACTED]
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications;
- Contraception check: Confirm and document that proper contraception is being used for the female subject of child bearing potential and their partner as appropriate;
- Unblinded personnel to review Dosing Diary and assess compliance; re-educate the subject and/or caregiver if any missed doses have occurred;
- Unblinded personnel to weigh returned investigational product tubes (including empty, partial used and unused tubes); record investigational product tubes weight in subject's source documents and eCRF;
- Dispense new tube(s) of investigational product (enough for 1 week of dosing) and weigh them prior to dispensing the tube(s) to subject and/or caregiver. Weights will be recorded in the subject's source documents;

- Remind the subject and/or caregiver that investigational product must continue to be applied at home twice each day (am and pm), as instructed, to all treatable AD involved areas (excluding scalp) identified at Baseline/Day 1 regardless of whether they become clinically clear prior to Day 29. Investigational product should also be applied to any new treatable AD involved areas that appear following Baseline/Day 1 after consultation with the Investigator;
- Re-educate subject and/or caregiver on the dosing instructions if any investigational product doses were missed during the interval since the previous study visit;
- Re-dispense dosing instructions and new Dosing Diary;
- Unblinded personnel to instruct the subject and/or caregiver that investigational product should not be wiped off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application;
- Unblinded personnel must remind the subject and/or caregiver not to discuss any element of the Investigational product with the blinded assessor, including study drug appearance;
- Unblinded personnel should check for any residue of investigational product. If any investigational product is visible, it is permissible to gently remove it prior to the assessments performed by the clinical assessor blinded to treatment arms to avoid potential unblinding;.
- Photography of AD lesions (at selected sites - see [Section 7.4](#)) (only Day 15 visit, not scheduled for Day 8 and Day 22 visit);
- Review the schedule of upcoming study visits with the subject and/or caregiver, and instruct them to return at the scheduled time for the next visit;
- Remind subject and/or caregiver to bring all investigational product tubes (empty, partially used and unused) in their original packages and the Dosing Diary to their next visit. Advise subject and/or caregiver that the investigational product should be applied at least 4 hours prior to the clinic visit to ensure that there are no visible residues left on the lesions as to unblind the blinded assessor;
- Assess and record any AEs and SAEs by a clinical assessor blinded for treatment arms. Other site personnel may also report and record AEs and SAEs reported to them spontaneously by the subject;
- ISGA completed by a clinical assessor blinded for treatment arms;
- EASI assessment, including treatable BSA, completed by a clinical assessor blinded for treatment arms.

#### **6.4.3. Day 29 ( $\pm 3$ days) (End-of-Treatment)/Early Termination Study Visit**

The following procedures will be performed at the Day 29/Early Termination Visit:

- Ask the subject or caregiver (when applicable) to complete Day 29 Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects  $< 6$  years [REDACTED] if not already completed;
- Administer [REDACTED]  
[REDACTED] DLQI (completed by subjects  $\geq 16$  years old), CDLQI (completed by subjects 4-15 years old), [REDACTED] CCI [REDACTED] DFI (completed by caregivers of subject 2-17 years old [REDACTED]  
[REDACTED]
- Perform a detailed physical examination, evaluate any current or reported symptoms for clinically significant changes and report relevant AE if applicable;
- Measure weight;
- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated position, after the subject has been sitting calmly for a minimum of 5 minutes (when possible for younger children); assessment of vital signs should precede blood draw for clinical laboratory tests;
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications;
- Urine pregnancy test (female subjects of childbearing potential only);
- Contraception check: Confirm and document that proper contraception is being used for the female subject of child bearing potential and their partner as appropriate;
- Draw blood for clinical laboratory tests (testing includes serum chemistry and hematology); (after having assessed vital signs);

Note: At the discretion of the investigator or his/her designee, a topical lidocaine-based anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject. However, the skin must be thoroughly cleansed prior to blood sample collection. Use of a topical lidocaine-based anesthetic must be recorded in the Concomitant Medication eCRF;

- Photography of AD lesions (at selected site(s) – see [Section 7.4](#));

- Unblinded personnel to collect and review Dosing Diary and assess compliance;
- Unblinded personnel to weigh returned investigational product tubes (including empty, partial used and unused tubes); record investigational product tubes weight in subject's source documents and eCRF;
- Unblinded personnel must remind the subject not to discuss any element of the Investigational product with the blinded assessor, including study drug appearance;
- Unblinded personnel should check for any residue of Investigational product. If any Investigational product is visible, it is permissible to gently remove it prior to the assessments performed by the clinical assessor blinded to treatment arms to avoid potential unblinding;
- Assess and record any AEs and SAEs by a clinical assessor blinded for treatment arms. Other site personnel may also report and record AEs and SAEs reported to them spontaneously by the subject;
- ISGA completed by a clinical assessor blinded for treatment arms;
- EASI assessment, including treatable BSA, completed by a clinical assessor blinded for treatment arms.

#### **6.4.4. Day 43 ( $\pm 5$ days), or 14 days ( $\pm 5$ days) after Early Termination, Off Treatment Study Visit**

This visit will occur at Day 43 ( $\pm 5$  days) or 14 days ( $\pm 5$  days) after last dose if subject is terminated early from treatment. The following procedures will be performed at the Day 43 Study Visit:

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications (see Section 5.8.4);
- Assess and record any AEs and SAEs by a clinical assessor blinded for treatment arms. Other site personnel may also report and record AEs and SAEs reported to them spontaneously by the subject;
- ISGA completed by a clinical assessor blinded for treatment arms;
- EASI assessment completed by a clinical assessor blinded for treatment arms including treatable BSA calculation.
- Contraception check: Confirm and document that proper contraception is being used for the female subject of child bearing potential and their partner as appropriate.

#### **6.4.5. Unscheduled Visit**

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

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes (when possible for younger children);
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in [Section 5.8.3](#);
- Unblinded personnel to instruct the subject and/or caregiver regarding all procedures for at home dosing beginning BID dosing through Day 29 visit, including how to complete the dosing diary;
- Unblinded personnel must remind the subject not to discuss any element of the Investigational product with the blinded assessor, including study drug appearance;
- Unblinded personnel should check for any residue of Investigational product. If any Investigational product is visible, it is permissible to gently remove it prior to the assessments performed by the clinical assessor blinded to treatment arms to avoid potential unblinding;
- Review the schedule of upcoming study visits with the subject and/or caregiver, and instruct them to return at the scheduled time;
- Assess and record any AEs and SAEs by a clinical assessor blinded for treatment arms. Other site personnel may also report and record AEs and SAEs reported to them spontaneously by the subject.
- After the end of treatment, unscheduled clinic visits are available if subject's condition worsens, so that an assessment can be conducted in-clinic, and nonstudy treatment for AD may be prescribed if the subject qualified for this treatment. At this visit, an EASI assessment completed by a clinical assessor blinded for treatment arms will be completed to determine if treatment is allowed per the protocol. If a subject is participating in the sub-study, all efforts should be made not to treat the sub-study target skin sites until after the end of the follow up phase (Day 60).

#### **6.4.6. Follow-up Contact**

Follow-up contact will be done via a phone call on Day 60 (or at least 28 days after End of Treatment/Early Termination) to capture any potential adverse events (see the [Time Period for Collecting AE/SAE Information](#) section 8.1.4), to review and record concomitant medications and to confirm appropriate contraception usage (see the [Contraception](#) section 4.4.1). For subjects participating in the sub-study, this visit will occur in the clinic.

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

### **Withdrawal of Investigational Product:**

- If signs and symptoms of hypersensitivity are attributable to the investigational product, including contact urticaria, it must be discontinued immediately and appropriate therapy initiated.

The subject will remain in the study and continue to be followed for protocol specified follow-up procedures, unless they have withdrawn consent. If consent is withdrawn for the follow-up period, the procedures for withdrawal of consent will be followed.

### **Withdrawal of consent:**

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

### **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, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (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. Efficacy Assessments

#### 7.1.1. Investigator's Static Global Assessment

The Investigator's Static Global Assessment (ISGA), a five point global assessment of AD severity ([Table 1](#)), will be assessed at times specified in the **STUDY PROCEDURES** section of this protocol to characterize subjects' overall disease severity across all treatable AD lesions (excluding the scalp).

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

ISGA assessment during the study must be completed by a clinical assessor blinded for treatment arms. Every effort should be made to ensure that all ISGA assessments for a given subject are done by the same qualified individual throughout the study.

**Table 1. Investigator's Static Global Assessment**

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

\* The ISGA will exclude scalp from the assessment/scoring

### 7.1.2. Eczema Area and Severity Index (EASI)

The EASI<sup>22</sup> quantifies the severity of a subject's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

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

**Table 2. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)**

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

\* The EASI will exclude scalp from the assessment/scoring

**Percent BSA with Treatable AD:** The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 3 and [Table 4](#)).

**Table 3. Handprint Determination of Body Region Surface Area for Subjects aged  $\geq 8$  years old**

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

**Table 4. Handprint Determination of Body Region Surface Area for Subjects aged < 8 years old**

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

The extent (%) to which each of the four body regions is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 5).

**Table 5. Eczema Area and Severity Index (EASI) Area Score Criteria**

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

**Body Region Weighting:** Each body region is weighted according to its approximate percentage of the whole body (Table 6).

**Table 6. Eczema Area and Severity Index (EASI) Body Region Weighting**

Body Region	Body Region Weighting for ≥8 years old subjects	Body Region Weighting for <8 years old subjects
Head and Neck	0.1	0.2
Upper Limbs	0.2	0.2
Trunk (including axillae)	0.3	0.3
Lower Limbs (including buttocks)	0.4	0.3

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

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

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

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

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

### 7.1.3. Patient/Observer Reported Outcomes

The Patient/Observer Reported Outcomes questionnaires in this study include: Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects <6 years [REDACTED] CCI [REDACTED] CCI [REDACTED] CCI [REDACTED] CCI [REDACTED]. They will be performed at the time points defined in the [Schedule of Activities](#).

On study visit days, subjects or caregiver as instructed should complete the patient/observer reported outcomes at the clinic prior to any procedures being performed. It is preferred that all observer reported outcomes for a given subject are completed by same individual throughout the study. The one who completes the questionnaires should be captured and stored in database and available for analysis.

#### 7.1.3.1. Peak Pruritus Numerical Rating Scale (NRS) for subjects $\geq 12$ years, Patient Reported Itch Severity Scale - for subjects age 6-11 years, and Observer Reported Itch Severity Scale - for subjects <6 years.

The severity of itch (pruritus) due to atopic dermatitis will be assessed using the Peak Pruritus Numerical Rating Scale (NRS) for subjects  $\geq 12$  years, an 11-category numeric rating scale from 0 to 10,<sup>23, 24</sup> which is subject (12 years and older) reported. A five-category Patient Reported Itch Severity Scale - for subjects age 6-11 years has been developed for subjects  $\geq 6$  and <12 years of age. The Observer Reported Itch Severity Scale - for subjects <6 years will be completed by a caregiver for subjects <6 years old. It is preferred that all observer reported outcomes for a given subject are completed by same individual throughout the study.

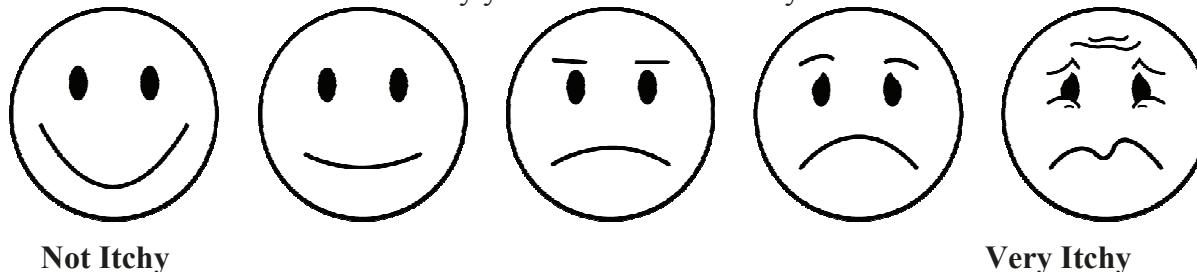
The Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects <6 years will be completed during screening prior to Day 1 and completed once daily every day from Day 1 to Day 29 before IP morning dose is applied preferably at the same time of each day, as noted in the [Schedule of Activities](#).

Subjects will be asked to assess their worst itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10). The Peak Pruritus NRS for subjects  $\geq 12$  years is presented in Figure 2. The Patient Reported Itch Severity Scale - for subjects age 6-11 years is presented in Figure 3. The Observer Reported Itch Severity Scale - for subjects  $<6$  years is presented in Figure 4. These scales are designed to capture a similar concept.

**Figure 2. Peak Pruritus NRS [©Regeneron Pharmaceuticals, Inc. and Sanofi (2017)] for subjects  $\geq 12$  years**

**Figure 3.** Patient Reported Itch Severity Scale - for subjects age 6-11 years

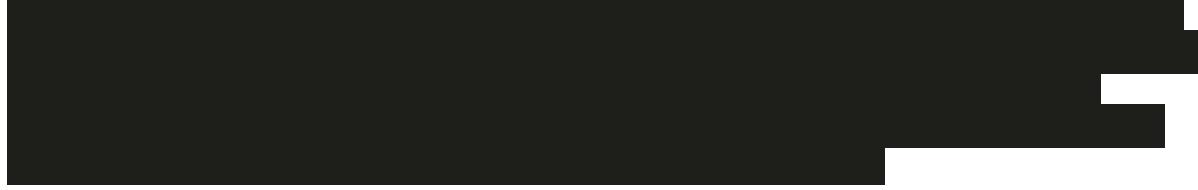
Circle the face that shows how itchy your skin has been today:



**Figure 4.** Observer Reported Itch Severity Scale - for subjects <6 years

CC1

CCI



CCI



CCI



CCI



CCI



CCI



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

#### 7.1.3.5. Dermatology related Quality of Life Questionnaires

Dermatology related quality of life (QoL) scores will be descriptively summarized by treatment group for each collection time point defined in the [Schedule of Activities](#). It is preferred that all observer reported outcomes for a given subject are completed by same individual throughout the study.

- The DLQI will be completed by all subjects aged 16 years and older, based on the age at Screening Visit/time of informed consent/assent.
- The CDLQI will be completed by all subjects aged 4–15 years with the help of the caregiver as needed, based on the age at Screening Visit/time of informed consent/assent.

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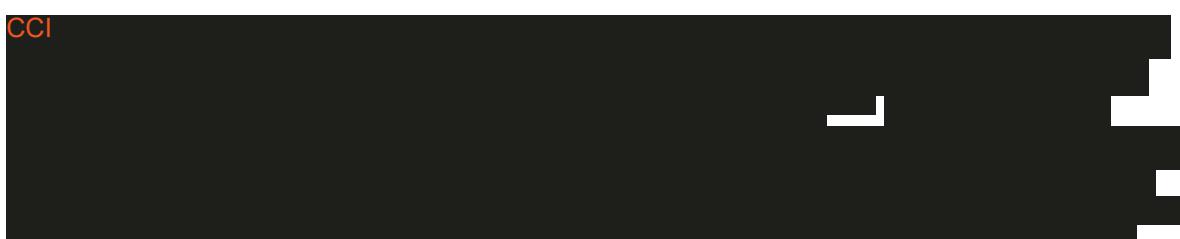


- The DFI will be completed by the caregiver for subjects aged 2–17 years, based on the age at Screening Visit/time of informed consent/assent.

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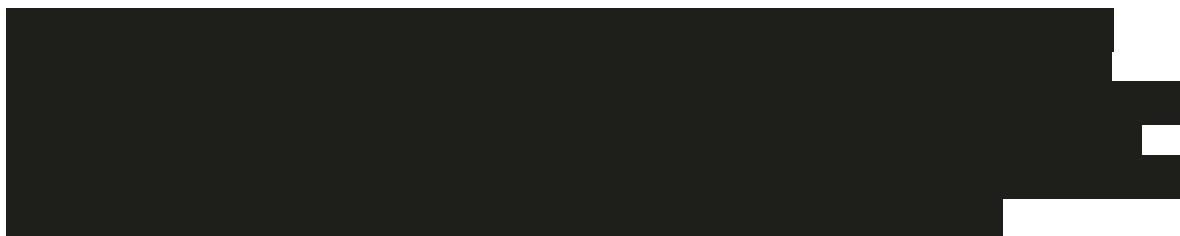
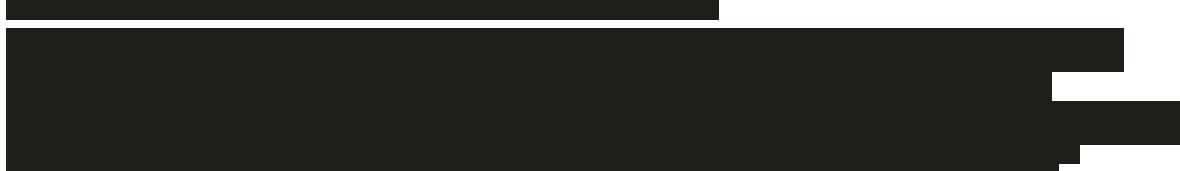
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## **7.2. Body Surface Area for Investigational Product**

Evaluation of BSA for Investigational Product is the percent BSA across all body locations being treated with the study drug. Percent BSA for Investigational Product evaluation method will be the same as described in [Section 7.1.2](#), except that it will exclude AD on the scalp.

Study drug should be applied at Baseline/Day 1 throughout the treatment period regardless of clearing or improvement of AD. Any new AD on treatment-eligible locations occurring following Baseline/Day 1 should also be treated with the study drug after consultation with the Investigator at the next visit. Therefore, the BSA for Investigational Product at subsequent visits should be equal to or greater than the value at Baseline/Day 1.

## **7.3. Body Site Checklist for Atopic Dermatitis**

A checklist of body areas currently affected by AD will be completed at the Baseline/Day 1. Location of skin lesions will be selected from a prepopulated listing of body locations. Treatable AD areas (excluding the scalp) as identified by a clinical assessor blinded for treatment arms will be recorded in the subject's source documents at Baseline/Day 1 and will be provided to the subject and/or caregiver with documentation of the designated treatment areas (body maps).

## **7.4. Photography of Representative AD Lesion (Selected Study Sites Only)**

For subjects (optional) at a selected study sites, photographs of treatable AD lesions will be obtained (according to the separately provided Photography Instructions) at Baseline/Day 1, Day 15 and Day 29. Areas photographed should be recorded in study documents so that the same AD body region(s) will be photographed at Day 15 and Day 29. Photographs will be utilized for illustrative purposes and not evaluated as an endpoint.

Photographic services will be provided through a central photography laboratory selected by the sponsor. Detailed procedures to assure consistency will be provided separately in a central photography laboratory instruction manual.

## **7.5. Columbia Suicide Severity Rating Scale (C-SSRS)**

The Columbia Suicide Severity Rating Scale (C-SSRS) is a validated tool for investigative staff to use to evaluate suicidal ideation and behaviour and will be completed at the Screening for subjects  $\geq 7$  years of age. The children's C-SSRS will be administered for subjects 7-11 years old and the C-SSRS for subjects  $\geq 12$  years old. This is investigator completed.

## **7.6. Safety Assessments**

### **7.6.1. Clinical Laboratory Evaluations**

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

The clinical laboratory test parameters that will be reviewed for safety evaluation are presented in [Table 7](#). Hematology, Chemistry and FSH will be done at a central laboratory.

**Table 7. Clinical Laboratory Test Parameters**

Hematology	Chemistry	Pregnancy	FSH <sup>a</sup>
Hemoglobin	Blood urea nitrogen/Urea	At Screening,	
Hematocrit	Glucose (non-fasting)	Baseline/Day 1, and	
Red blood cell count	Creatinine	Day 29 (End of	
Platelet count	Sodium	treatment)/Early	
White blood cell count (% and absolute)	Potassium	termination visit: Urine	
• Neutrophils	Chloride	pregnancy test <sup>b</sup> (female	
• Eosinophils	Bicarbonate or Total CO <sub>2</sub>	subjects of childbearing	
• Monocytes	Alanine aminotransferase	potential only)	
• Basophils	Aspartate aminotransferase		
• Lymphocytes	Total bilirubin		
	Alkaline phosphatase		
	Albumin		
	Total protein		

- a. At Screening only, to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months.
- b. 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 urine β-hCG test during the treatment period, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study; if the serum β-hCG test is negative and investigator judged that the subject is not pregnant, the subject may resume investigational product.

Clinical laboratory tests will be drawn at the Screening visit and Baseline/Day 1, after assessment of vital signs and prior to the first investigational product application and on Day 29.

If the screening serum chemistry and hematology tests are performed within 14 days prior to Baseline/Day 1, whether the Baseline/Day 1 serum chemistry and hematology tests are to be performed will be at the medical judgment of the investigator.

At the discretion of the investigator or his/her designee, a lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject. However, the skin must be thoroughly cleansed prior to blood sample collection. This must be recorded in the eCRF.

The blinded clinical assessor will review all clinical laboratory test results for safety evaluation upon receipt. After reviewing the laboratory reports and evaluating the results for clinical significance, the blinded clinical assessor must sign and date the laboratory report. Clinically significant laboratory abnormalities are defined as abnormal values that have

clinical manifestations or require medical intervention. Clinically significant laboratory abnormalities noted from the Screening Visit will be recorded in the medical history.

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

#### **7.6.2. Physical Examination, Height, and Weight**

Physical examinations, height, and weight will be performed at times specified in the [Schedules of Activities](#) section of this protocol.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

A detailed physical examination will be performed at Screening, Baseline/ Day 1 and Day 29 (End of treatment)/Early termination visit which 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, musculoskeletal, abdomen (liver, spleen), and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin.

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

#### **7.6.3. Vital Signs**

Vital sign measurements (temperature, respiratory rate, pulse rate, and BP) will be performed at Screening, Baseline/Day 1 and Day 29. Vital sign measurements should be performed with the subject in the seated or lying position and after the subject has been sitting or lying calmly for a minimum of 5 minutes. The position of recording must be consistent within subject through-out the study. On study day visits when clinical laboratory tests are performed, assessment of vital signs should precede blood draw.

### **7.7. Pregnancy Testing**

For female subjects of childbearing potential, a urine pregnancy test (beta-human chorionic gonadotropin ( $\beta$ -hCG), with sensitivity of at least 25 mIU/mL, will be performed at screening, prior to dosing with investigational product on Day 1 and at the end-of-treatment (Day 29) visit, to confirm the subject has not become pregnant during the study.

A negative pregnancy test result is required before the subject can receive investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy

tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations or at the discretion of the investigator or his/her designee.

A pediatric female subject who has not experienced menarche is not required to perform pregnancy testing. If the pediatric female subject starts menarche during the study, pregnancy testing will be performed at the next visit and all visits according to the [Schedule of Activities](#).

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted at site with the test kit provided by the central laboratory 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 urine  $\beta$ -hCG test during the treatment period, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for  $\beta$ -hCG testing. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study; if the serum  $\beta$ -hCG test is negative and investigator judges that the subject is not pregnant, the subject may resume investigational product.

## 7.8. Rater Qualifications

Clinical evaluations of atopic dermatitis will be performed by an experienced and qualified dermatologist (board certified or equivalent) who is **treatment blinded**. An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of AD clinical trials who is **treatment blinded** may be permitted to perform the clinical evaluations of atopic dermatitis when designated by the primary site Investigator and with Sponsor approval. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible;** a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

Study personnel administering the C-SSRS must have completed the appropriate training and have valid certification.

## 8. ADVERSE EVENT REPORTING

### 8.1. Requirements

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), <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/[parent(s)/legal guardian]. In addition, each study subject/[parent(s)/legal guardian/] will be questioned about the occurrence of AEs in a non-leading manner.

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

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

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

### **8.1.4. Time Period for Collecting AE/SAE Information**

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

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

#### **8.1.4.1. Reporting SAEs to Pfizer Safety**

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

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

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

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

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

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

#### **8.1.4.3. 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.

#### **8.1.4.4. Reporting Requirements Regarding SUSARs**

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

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

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

## **8.2. Definitions**

### **8.2.1. Adverse Events**

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

### **8.2.2. Abnormal Test Findings**

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

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

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

#### **8.2.3. Serious Adverse Events**

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

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

Or that is considered to be:

- An important medical event.

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

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

#### **8.2.4. Hospitalization**

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

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

Hospitalization does not include the following:

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

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

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

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

### 8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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

### 8.4. Special Situations

#### 8.4.1. Protocol-Specified Serious Adverse Events

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

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

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

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  $>3 \times$  ULN AND a TBili value  $>2 \times$  ULN with no evidence of hemolysis and an alkaline phosphatase value  $<2 \times$  ULN or not available;
- For 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  $>3 \times$  ULN; or  $>8 \times$  ULN (whichever is smaller).
  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least  $1 \times$  ULN or if the value reaches  $>3 \times$  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 tests (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability**

**of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

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

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

**8.4.3.1. Exposure During Pregnancy**

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.
  - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.
- If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural

integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

#### **8.4.3.2. Exposure During Breastfeeding**

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

#### **8.4.3.3. Occupational Exposure**

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

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

#### **8.4.4. Medication Errors**

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

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

##### **8.4.4.1. Medication Errors**

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

Medication errors include:

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

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

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

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

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

### **9. DATA ANALYSIS/STATISTICAL METHODS**

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

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

A total of approximately 600 subjects will be enrolled into this study. Approximately 300 subjects who are eligible to receive TCS therapy (Cohort 1) will be randomized to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or TCS with a

randomization ratio of 1:1:2. Approximately 300 subjects who are ineligible to receive TCS therapy and eligible to receive TCI therapy (Cohort 2) will be randomized to crisaborole ointment, 2%, the matching vehicle ointment for crisaborole, or pimecrolimus cream 1% with randomization ratio 1:1:2.

A sample size of 150 subjects in the crisaborole group combined from Cohort 1 and Cohort 2 and 150 subjects in vehicle group combined from Cohort 1 and Cohort 2 will provide 86% power to detect a 12% difference of EASI percent reduction from baseline at Day 29 between crisaborole and vehicle at the 0.05 (2-sided) significance level, assuming the common standard deviation of EASI percent reduction from baseline at Day 29 is 34%.

EASI was not collected in previous crisaborole studies. The 12% treatment effect in EASI percent improvement was converted from the ISGA response in the Phase 3 studies using a linear regression equation that evaluated the relationship between ISGA response rate and EASI percentage improvement from historical trial data of other topical products. From the crisaborole Phase 3 pooled data, the ISGA response rate is 32.1 % for crisaborole ointment, 2%, and 21.8% for vehicle. The converted EASI percent improvement is 38.9% and 26.8% respectively. The difference of EASI percent improvement between crisaborole ointment, 2% and vehicle is approximately 12%.

With sample size of 75 subjects in the crisaborole group and 150 subjects in the TCS or TCI groups, the half width of the 95% confidence interval for the difference of EASI percent reduction from baseline at Day 29 between crisaborole and active comparator is 9.4%. The sample size within each Cohort will also provide sufficient precision to enable contextualization of the efficacy of crisaborole in treating subjects with mild to moderate AD relative to each active comparator.

## **9.2. Efficacy Analysis**

### **9.2.1. Analysis Sets**

The primary analysis population for efficacy data will be the Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of investigational product. The primary efficacy endpoint will also be analyzed for the Per-Protocol Analysis Set (PPAS) defined as a subset of FAS who had no protocol violations affecting the efficacy endpoints. The subjects excluded from the PPAS will be determined and documented before the study is unblinded. For all analyses, baseline value will be based on observations collected pre-dose.

For the comparison of crisaborole versus vehicle, subjects from both Cohort 1 and Cohort 2 are included in the analysis, and effect of Cohort will be adjusted. For the comparison of crisaborole versus TCS, only subjects from Cohort 1 are included in the analysis. For the comparison of crisaborole versus TCI, only subjects from Cohort 2 are included in the analysis.

### **9.2.2. Analysis of the Primary Endpoint**

The primary endpoint, EASI % change from baseline, will be analyzed using a mixed-effect repeated measures model that includes the fixed effects of treatment, visit as class variable,

treatment by visit interaction. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix. For the comparison of crisaborole versus vehicle, the model will also include factor of Cohort.

### **9.2.3. Analysis of the Secondary Endpoints**

Binary endpoints such as ISGA success (defined as an ISGA score of Clear ([0]) or Almost Clear ([1]) with at least a 2 grade improvement from baseline), ISGA score of clear ([0]) or almost clear ([1]), improvement in Peak Pruritus NRS for subjects  $\geq 12$  years and Observer Reported Itch Severity Scale - for subjects  $< 6$  years (defined as achieving  $\geq 2$  points reduction in NRS from baseline), improvement in Peak Pruritus NRS for subjects  $\geq 12$  years and Observer Reported Itch Severity Scale - for subjects  $< 6$  years (defined as achieving  $\geq 3$  points reduction in NRS from baseline), and achievement of EASI75 at each time point will be analyzed using the CMH test. The comparison of crisaborole versus vehicle will be stratified by Cohort. The evaluation of efficacy of crisaborole versus active comparator (TCS, TCI) will be performed within each Cohort.

Continuous endpoints such as change from baseline in Peak Pruritus NRS for subjects  $\geq 12$  years/Patient Reported Itch Severity Scale - for subjects age 6-11 years/Observer Reported Itch Severity Scale - for subjects  $< 6$  years, % BSA, DLQI, CDLQI, and DFI will be analyzed using the same method as proposed in [Section 9.2.2](#). Baseline value will be used as an additional covariate when modeling the change from baseline.

For peak pruritus NRS for subjects  $\geq 12$  years, Patient Reported Itch Severity Scale - for subjects age 6-11 years, and Observer Reported Itch Severity Scale - for subjects  $< 6$  years, weekly average score will be used in the analyses of binary endpoint improvement in peak pruritus/itch and continuous endpoint change from baseline in peak pruritus/itch. There will be no pooling of data from the pruritus/itch scales from different age groups. Data from each instrument will be analyzed separately.

Time to event endpoints such as time to EASI75 and time to improvement in peak pruritus/itch will be analyzed by log rank test and duration of time to event will be estimated by the product limit method. A Kaplan-Meier plot will be provided. Log rank test will be stratified by cohort for comparison of crisaborole versus vehicle. The evaluation of efficacy of crisaborole versus active treatment will be performed within each cohort. For Peak Pruritus NRS for subjects  $\geq 12$  years, Patient Reported Itch Severity Scale - for subjects age 6-11 years, and Observer Reported Itch Severity Scale - for subjects  $< 6$  years, daily peak pruritus/itch assessment value will be used for the analysis of time to improvement in peak pruritus/itch.

All secondary endpoints will be evaluated at the 5% level of significance, without adjustments for multiple comparisons.

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### **9.3. Safety Analysis**

The safety data will be summarized in accordance with Pfizer Reporting Standards. All subjects who receive investigational product (safety population) will be included in the safety analyses. Safety data will be descriptively summarized, and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data. The following safety data will be summarized:

- AEs, including SAEs, local tolerability AEs/SAEs and discontinuations;
- Clinically significant changes in vital signs;
- Clinically significant changes in clinical laboratory parameters.

### **9.4. Interim Analysis**

No formal interim analysis will be conducted for this study.

### **9.5. Data Monitoring Committee**

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

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

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

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

During study conduct and/or after study completion, the investigator site may be subject to review by the 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 shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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[/assent] 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.

The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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 [/assent] 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).

In addition, this study will be conducted in accordance with the following:

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

### **12.3. Subject Information and Consent**

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. 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 the Clinical Study Agreement and applicable privacy laws.

The informed consent [/assent] 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 [/assent] 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, or parent(s) or legal guardian if a minor is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject [or the subject's parent(s) or legal guardian and the subject's assent, when applicable,] before any study-specific activity is performed [unless a waiver of informed consent has been granted by an IRB/EC]. The investigator will retain the original of each subject's signed consent [/assent] document.

Crisaborole will not be provided to subjects after the study is over.

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

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

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

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

### **13.1. End of Trial in All Participating Countries**

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

## **14. SPONSOR DISCONTINUATION CRITERIA**

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

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

## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), 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 patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

#### EudraCT

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

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#### **15.2. Publications by Investigators**

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

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

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

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

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

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

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

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CC1

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## Appendix 1. Abbreviations

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

Abbreviation	Term
AD	Atopic Dermatitis
AR	Autoregressive
ADSI	Atopic Dermatitis Severity Index
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Morning
AST	Aspartate Aminotransferase
BID	Twice Daily
β-hCG	Beta Human Chorionic Gonadotrophin
BP	Blood Pressure
BPO	Benzoyl Peroxide
BSA	Body Surface Area
%BSA	Percent Body Surface Area
cAMP	Cyclic Adenosine Monophosphate
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Science
CK	Creatine Kinase
Cmax	Maximum Observed Plasma Concentration
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel test
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CTA	Clinical Trial Application
DFI	Dermatitis Family Impact Questionnaire
DILI	Drug-Induced Liver Injury
DLQI	Dermatology Life Quality Index
DU	Dispensable Unit
EASI	Eczema Area And Severity Index
EASI75	Eczema Area And Severity Index ≥75% improvement from Baseline
EC	Ethics Committee
EC50	Half Maximal Effective Concentration
eCRF	Electronic Case Report Form
E-DMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy
ePRO	Electronic patient reported outcome

Abbreviation	Term
EU	European Union
EudraCT	European Clinical Trials Database
CCI	[REDACTED]
FAS	Full Analysis Set
FDA	Food And Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HRQOL	Health-Related Quality Of Life
HTA	health technologies assessment
CCI	[REDACTED]
IB	Investigator's Brochure
ID	Identification
ICH	International Council For Harmonisation
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWR	Interactive Web Response
ISGA	Investigator'S Static Global Assessment
IUD	Intrauterine Devicem
LFT	Liver Function Test
LSLV	Last Subject Last Visit
MMF	Mycophenolate Mofetil
MMRM	mixed model repeated measure
CCI	[REDACTED]
MUSE	Maximal Use Systemic Exposure
N/A	Not Applicable
NRI	Non Responder Imputation
NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
CCI	[REDACTED]
PCD	Primary Completion Date
PD	Pharmacodynamics(S)
PDE-4	Phosphodiesterase-4
CCI	[REDACTED]
PI	Principal Investigator
PK	Pharmacokinetic
PKA	Protein Kinase A

Abbreviation	Term
PM	Evening
PMA	Phorbol 12-myristate 13-acetate
CCI	[REDACTED]
PKA	Protein Kinase A
PPAS	Per Protocol Analysis Set
PRO	Patient Reported Outcome
PRN	As Needed
PT	Prothrombin Time
PUVA	Psoralen–UV-A
QD	Once Daily
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	stratum corneum
SRSD	Single Reference Safety Document
SSIN	Subject Screening Identification Number
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TBili	Total Bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEWL	Transepidermal Water Loss
Tmax	Time to Reach Maximum Observed Plasma Concentration
TQT	Thorough QT/QTc
TSS	Total Severity Score
ULN	Upper Limit of Normal
US	United States
USA	United States of America
UV	Ultraviolet
UV-B	Ultraviolet B
VAS	Visual Analog Scale

## 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>31</sup>

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

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

### **Appendix 3. Very High/Very Strong and High/Strong Potency Topical Corticosteroids**

Per [Exclusion Criterion 2](#). Based upon the World Health Organization classification where topical corticosteroids have been ranked in terms of potency into four groups consisting of seven classes.

Including but not limited to;

#### Very high potency topical corticosteroids

##### Group 1

- Clobetasol propionate cream (0.05%);
- Diflorasone diacetate ointment (0.05%).

#### High potency topical corticosteroids

##### Group II

- Amcinonide ointment (0.1%);
- Betamethasone dipropionate ointment (0.05%);
- Desoximetasone (cream or ointment) (0.025%);
- Fluocinonide (cream, ointment, or gel) (0.05%);
- Halcinonide cream (0.1%).

##### Group III

- Betamethasone dipropionate cream (0.05%);
- Betamethasone valerate ointment (0.1%);
- Diflorasone diacetate cream (0.05%);
- Triamcinolone acetonide ointment (0.1%).

**Appendix 4. Optical Coherence Tomography Sub-Study – A Study of Optical Coherence Tomography and Biomarkers in Subjects ages 2 to <18 years old, with Mild to Moderate Atopic Dermatitis, treated with Crisaborole Ointment, 2% or Crisaborole Vehicle Ointment or Hydrocortisone Butyrate 0.1% Cream applied BID.**

## **1. Introduction**

Skin atrophy, characterized by whole skin thinning and damage to the skin barrier, is a common problem in the treatment of AD with TCS.<sup>1</sup> Often, effective treatment with TCS must be limited because of the risk of skin atrophy.<sup>1</sup> To further explore the benefit/risk of crisaborole ointment, 2%, this sub-study aims to evaluate differences in atrophic skin changes across study treatment groups in Cohort 1.

Optical coherence tomography (OCT) is a non-invasive imaging modality conceptually similar to ultrasound but uses near-infrared radiation rather than sound. It has a 2-10 micron depth resolution compared with 100-1,000 micron typical for clinical US; and 1-2 mm imaging depth vs. 10-100 mm for clinical US. It is thus ideal for imaging the surface layers of accessible tissues such as the skin.<sup>2</sup> OCT imaging will be obtained using the VivoSight OCT scanner, by Michelson Diagnostics, Ltd. in this sub-study to evaluate atrophic changes in epidermal thickness during and after treatment with study investigational product in Cohort 1.

This sub-study also provides an opportunity to explore differences in Transepidermal Water Loss (TEWL) and cutaneous inflammatory and barrier biomarkers associated with AD within the stratum corneum (SC) across treatment groups in Cohort 1.

The Aquaflux device is an evaporimeter that measures water exchange through human skin using the condenser-chamber method. The condenser-chamber method uses a humidity gradient to determine the amount of water diffusing through the SC<sup>3</sup>. This device will be used in this sub-study to evaluate TEWL during and after treatment at select sub-study centers.

Tape-strips are a minimally invasive method that captures cutaneous inflammatory and barrier biomarkers within the SC, circumventing the need for skin biopsies, especially in the pediatric population. Studies have used proteomic immune assays and messenger ribonucleic acid analyses to evaluate SC biomarkers in tape-strips from AD lesional and non-lesional skin from patients with AD. Expression of AD-associated biomarkers in AD tape-striped skin have been significantly correlated with disease severity (EASI/pruritus) and the functional barrier measure TEWL. Tape-strips will be used in this sub-study to evaluate SC biomarkers from AD lesional and non-lesional skin.

## **2. Objectives and Endpoints**

The primary objective of this sub-study is to evaluate the differences in atrophic changes in epidermal thickness by structural OCT after treatment with crisaborole ointment, 2% or

crisaborole vehicle ointment, or hydrocortisone butyrate 0.1% cream applied BID for 28 days.

The secondary objectives of this sub-study are to evaluate the differences in atrophic change in epidermal thickness, skin biomarkers of AD, and TEWL during the course of treatment and following treatment with crisaborole ointment, 2% or crisaborole vehicle ointment, or hydrocortisone butyrate 0.1% cream applied BID for 28 days.

This sub-study is expected to provide OCT, TEWL, and skin biomarker evidence of the effects of crisaborole ointment and vehicle ointment compared to TCS.

**Primary Sub-Study Endpoint:**

- Change in epidermal thickness from Baseline/Day 1 to Day 29

**Secondary Sub-Study Endpoints:**

- Change in epidermal thickness from Baseline/Day 1 to all sub-study time points except Day 29 (Days 8, 15, 22, and 60)
- Intrasubject difference of change in epidermal thickness between the non-lesional target skin site and the OCT AD lesional target skin site from baseline to Days 8, 15, 22, 29 and 60
- Percentage change from Baseline/Day 1 in TEWL at Days 8, 15, 22, 29 and 60
- Change from Baseline/Day 1 in skin biomarkers of AD at Day 15 and Day 29

### **3. Sub-Study Design**

This sub-study will be conducted in selected centers in the United States, the United Kingdom, and in Germany. This sub-study will include approximately 60 subjects from Cohort 1 that are enrolled in the main study (C3291037) from the selected study centers. Subjects may only enroll in the sub-study during the screening phase or at the baseline visit of the main study prior to any sub-study evaluations or procedure. Subjects that do not qualify for the main study may not participate in the sub-study. Based on the randomization schema from the main study, it is expected that the sample size for this sub-study will include approximately 15 subjects in the crisaborole ointment, 2% arm, 15 subjects in the crisaborole vehicle ointment arm, and 30 subjects in the hydrocortisone butyrate 0.1% cream arm. Subjects will follow the main study assessments and visits as per the schedule of activities for the main study but will also follow additional procedures as described in this appendix. Subjects that are in the main study (C3291037) that are not enrolled in the sub-study will not participate in sub-study procedures or evaluations.

The telephone call at Day 60 in the main study is replaced with an in-clinic visit for sub-study participants.

## Sub-study Schedule of Activities

The following activities are to be performed in addition to the activities specified for the main study.

Day [relative to start of study treatment (Day 1)]	Within 35 days prior to Day 1	Baseline/ Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 60 <sup>a</sup>
Window			±1 d	±3 d	±3 d	±3 d	±5 d	±3 d
Visit	Screening	Baseline			End of Treatment/ Early Termination			
Sub-study Informed consent, including assent <sup>b</sup>	X	X						
Review of Sub-study Inclusion Criteria	X	X						
Identify and document sub-study target skin sites.		X						
<b>CLINICAL EVALUATION OF AD</b>								
Target skin sites local ISGA		X	X	X	X	X		X
EASI (global) <sup>c</sup>								X
<b>SKIN IMAGING</b>								
OCT images in triplicate at OCT lesional and non-lesional target skin sites		X	X	X	X	X		X
Transepidermal Water Loss <sup>d</sup> at OCT lesional and non-lesional target skin sites		X	X	X	X	X		X
<b>TAPE STRIP BIOMARKER COLLECTION</b>								
Tape strips at tape strips lesional target skin site		X		X		X		
Tape strips at non-lesional target skin site		X						
<b>PHOTOGRAPHY</b>								
Photography of all sub-study target skin sites <sup>e</sup>		X		X		X		

<sup>a</sup> Sub-study subjects will be evaluated in clinic.

<sup>b</sup> Sub-study subjects may consent during the Screening Phase or at the Baseline visit, prior to any sub-study evaluations or procedures.

<sup>c</sup> An EASI assessment will be performed on Day 60 in addition to Days specified in the main protocol (Days 1, 8, 15, 22, 29, and 43)

<sup>d</sup> TEWL will be performed only at selected sub-study investigative centers.

<sup>e</sup> In addition to photography for the main study, the sub-study target skin sites will be photographed.

## 5. Subject Eligibility Criteria

Subjects will be enrolled in the sub-study after meeting the eligibility criteria of the main study during the screening phase. Subjects must sign a separate informed consent document for the sub-study and meet the following Inclusion Criteria:

- A. Subject who is enrolled in Cohort 1.
- B. Subject is between the ages of 2 to <18 years.
- C. Subject is able to sit or lie still during the collection of images for approximately 30 minutes per visit for OCT imaging and photography, additional 30 minutes for TEWL (if applicable) measurements and additional 10 minutes for the tape-strips procedure.
- D. Subject has an AD lesional target skin site with a local ISGA score of 2 or 3 at the cubital fossa, that is accessible with the OCT probe head. This target skin site should be a minimum of 3 cm in each diameter. The target skin site must not include the area from which blood is drawn. This site is the OCT AD lesional target skin site.
- E. Subject has a non-lesional target skin site at the left or right volar forearm with a circumference clear of AD at screening and at Baseline/Day 1 that is accessible with the OCT probe head. This target skin site will have a local ISGA score of 0. The target skin site must not include the area from which blood is drawn. This site is the non-lesional target skin site.
- F. Subject has an AD lesional target skin site separate, but preferably adjacent to the AD lesional target skin site area for tape-strips procedure. This area will also have a local ISGA score of 2 or 3 and will be a minimum of 3 cm in each diameter. If there are not two adjacent lesional target skin sites for OCT and tape-strips, an alternate location for tape strips may be located at an AD lesional target skin site bilateral to the OCT lesional target skin site. The target skin site should not include the area from which blood is drawn. This site is the tape strips AD lesional target skin site.
- G. Evidence of a personally signed and dated informed consent/assent document indicating that the subject or parent(s)/legal guardian has been informed of all pertinent aspects of the sub-study.

## 6. Sub-Study Procedures

While the Day 60 visit for non-sub-study participants is completed via telephone, the Day 60 visit for subjects enrolled in the sub-study will be completed by a clinic visit to accommodate sub-study procedures.

### Identification of target skin sites for OCT and biomarker tape strips

Target skin sites for all sub-study procedures will be identified prior to any sub-study evaluations by the blinded assessor that will also perform the assessments. Target skin sites

will not have striae or other signs of prior TCS treatment. They must not involve the area from which blood is drawn.

1. The **OCT AD lesional target skin site** at the cubital fossa will have a local ISGA score of 2 or 3 and will be accessible with the OCT probe head. The same target skin site will be used for all evaluations throughout the duration of the sub-study. This target skin site will be recorded on a sub-study body map for reference so that the location is used consistently for all subsequent evaluations. This area should be  $\geq 3$  cm in each diameter.
2. The **non-lesional target skin site** will be at the left or right volar forearm and will be accessible with the OCT probe head. This target skin site must not include the area from which blood is drawn. This target skin site will have a local ISGA score of 0. In choosing between the right and left volar forearm, the side furthest away from any signs of AD should be selected. The same target skin site will be used for all evaluations throughout the duration of the sub-study. This target skin site will be recorded on a sub-study body map for reference so that the location is used consistently for all subsequent imaging. This area should be  $\geq 3$  cm in each diameter.
3. The **tape-strips lesional target skin site** will preferably be adjacent to the AD lesional target skin site and will have a local ISGA score of 2 or 3. If there are not two adjacent target skin sites for OCT and tape-strips, an alternate location for tape-strips may be located at the site bilateral to the OCT target skin site. The same target skin site will be used for all tape-strip collections throughout the duration of the sub-study. This target skin site will be recorded on a sub-study body map for reference so that the location is used consistently for all subsequent collections. This area should be  $\geq 3$  cm in each diameter without overlapping with the AD lesional target skin site.

### **Treatment of target skin sites**

The OCT AD lesional target skin site and the tape-strips AD lesional target skin site will be included in the main study treatment area and will be treated for 28 days with investigational product even if the AD resolves during the course of treatment.

The non-lesional target skin site at the volar forearm will be free of AD, however this area will be treated with investigational product for the duration of the 28-day treatment period.

Treatment with investigational product on all target skin sites should be withheld on all study visit days until after the study visit procedures. The time since last investigational product treatment of the target skin sites and the time of study visit procedures will be collected.

### **Local ISGA score**

A local target ISGA score will be obtained and recorded for all three target skin sites on Baseline/Day 1, Day 8, Day 15, Day 22, Day 29, and Day 60 in addition to the overall ISGA.

## **EASI assessment**

An EASI assessment will be performed on Day 60 in addition to the Days specified in the main protocol (Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 and Day 43).

## **Photography of target skin sites**

Each sub-study target skin site will be photographed in addition to any photography performed for the main study at Baseline/Day 1, Day 15, and Day 29. Each photograph will be labeled with the corresponding target skin site.

## **OCT measurements, TEWL, and Tape-strips**

Technical detail and set-up of the OCT measurements, TEWL, and the tape-strip procedure will be provided to participating centers in Laboratory Manuals. All sub-study evaluations will be completed after and in addition to main study procedures completed at those clinic visits. Both the operator and the accessor of images will be blinded. OCT measurements will be obtained first, followed by TEWL (if applicable) at OCT AD lesional and non-lesional target skin sites. Tape-strips for biomarkers will be conducted after OCT and TEWL measurements at the tape-strips target skin site.

Both the OCT AD lesional target skin site and the non-lesional target skin site will be imaged by OCT in triplicate on Baseline/Day 1, Day 8, Day 15, Day 22, Day 29, and Day 60. The operator should be consistent across all imaging taken for each individual subject. An Imaging partner will be responsible for standardizing the OCT image acquisition, training the centers on the imaging protocol, ensuring equipment and image quality assurance and quality control. Image analysis will be conducted by a central reader(s) who will be blinded. Detailed procedures for obtaining and processing the OCT image, conducting image quality assurance/quality control and endpoint analyses will be described in study specific documents and provided as appropriate to the study centers.

TEWL will be measured at both the OCT AD lesional target skin site and the non-lesional target skin site (not at the tape-strips lesional target skin site) on Baseline/Day 1, Day 8, Day 15, Day 22, Day 29, and Day 60 at selected sub-study centers. The operator should be consistent across all measurements taken for each individual subject.

Tape-strips for biomarker collection will be completed at the non-lesional target skin site on Baseline/Day 1 only. Tape-strips for biomarker collection will be completed at the tape-strips lesional target skin site on Baseline/Day 1, Day 15, and Day 29. The operator should be consistent across all tape-strip collections for each individual subject. The operator will be blinded. A tape strips biomarker partner will be responsible for standardizing the collection and analysis of biomarkers. Detailed procedures for biomarker collection, processing and analysis will be described in a separate document and provided to the study centers.

## Prior and concomitant treatments

Prior and concomitant topical treatments (per section 5.8) used on sub-study target skin sites will be recorded in the CRF. In addition to restrictions regarding concomitant medications described in section 5.8.4 of protocol, all effort should be made to not apply AD treatments to sub-study defined target skin sites after the treatment phase until the Day 60, End of Study Visit, even if other lesions are necessary to treat with concurrent treatment for AD.

## 7. Data Analysis/Statistical Methods

Approximately 60 subjects (15, 15, 30 in vehicle, crisaborole, hydrocortisone groups respectively) will participate this sub-study from Cohort 1. This sub-study is a pilot and there is no formal hypothesis testing. The sample size is not based on a power calculation and an estimation approach will be used for data analysis and interpretation.

The analysis of change from baseline to Day 8, Day 15, Day 22, Day 29, and Day 60 in epidermal skin thickness, will be analyzed using mixed model repeated measure (MMRM) with treatment, visit, treatment by visit interaction as factors and baseline value as a covariate, separately for OCT AD lesional target skin site and non-lesional target skin site. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix.

The same models as above will be used for percentage change from baseline in TEWL at Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 and Day 60. No baseline value will be included as a covariate in the model.

Intra-subject difference of change from baseline to Day 8, Day 15, Day 22, Day 29, and Day 60 in epidermal skin thickness between OCT AD lesional target skin site and non-lesional target skin site will be analyzed using MMRM model with visit as a factor for each treatment group.

For the tape-strip biomarkers, Log2-scale quantitative reverse transcription polymerase chain reaction expression data will be modeled by a linear mixed effect model with visit, treatment, visit by treatment interaction as fixed effects and a random effect for each subject. Means of each group will be estimated using least squares means and comparisons of interest will be tested using contrast.

This sub-study will be reported independently from the main Clinical Study Report.

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