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ASPIRE: DETERIMINING THE IMPACT OF CRISABOROLE (Eucrisa) AND TACROLIMUS 0.03% ON PATIENT-REPORTED OUTCOMES AND CAREGIVER BURDEN IN CHILDREN WITH ATOPIC DERMATITIS

Principal Investigator: [redacted]

Co-Investigator: [redacted]

Study Coordinators: [redacted]

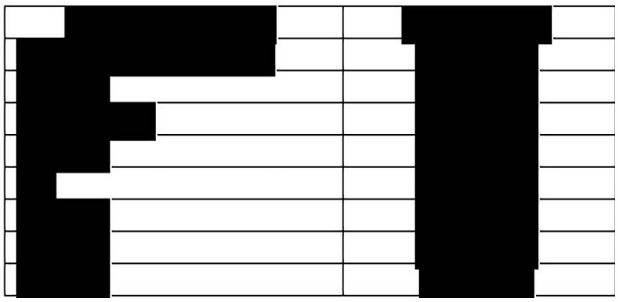

TABLE OF CONTENTS

1. PURPOSE, BACKGROUND, AND OBJECTIVES

1.1 Purpose

Atopic dermatitis (AD) is a common, chronic skin disease affecting 20% of children and 10% of adults worldwide (1-3). Children with AD often develop the disease within the first five years of life, which is a critical time for physical and psychosocial development (4). AD impacts an individual's physical, mental, and social health. Anxiety, itch, sleep disturbance, and depression have been associated with low quality of life scores. Childhood AD also affects the emotional, financial, physical, and social well-being of parents or caregivers (4). Individuals caring for a child with AD report sleep deprivation, poor social support, and stress about parenting (1, 4). Utilizing patient-reported outcomes (PROs) in clinic can provide meaningful data to monitor disease activity and response to different interventions, with the ultimate goal to improve quality of life for the patient and their family members or caregivers. Additionally, PROs can help us better understand the burden of AD. It is still unclear which PROs are most relevant for atopic dermatitis. This study will evaluate the utility of several PROs to monitor response to two different topical ointments, crisaborole (Eucrisa™) and tacrolimus 0.03%, to better understand the impact of these two non-steroidal topical treatments on overall health of children with AD of moderate or less severity and their caregivers.

1.2. Background

AD can have detrimental impacts on overall quality of life for both patients and their families. PROs provide an efficient way to monitor the impact of disease and effect of treatment(s) on patients' physical, mental, and social health. Additionally, PROs can elucidate the impact of the disease on caregivers and families. Topical corticosteroids have been recommended as the first line treatment for AD, but but their chronic use is associated with adverse effects, including dyspigmentation, telangiectasias, acne, and skin atrophy (5). Crisaborole (Eucrisa™) is a recently approved nonsteroidal topical ointment for the treatment of patients (≥ 2 yrs of age) with mild to moderate AD. Crisaborole has a novel mechanism of action by inhibiting the phosphodiesterase-4 enzyme which has been shown to be elevated in AD leukocytes and is thought to be responsible for the tissue inflammation observed in this disease. Like tacrolimus, which has a different mechanism of action (e.g. calcineurin antagonist), it provides a safer alternative to topical steroids, which is especially relevant for children with AD. Unfortunately, it can be difficult to obtain prior authorization for this new medication. In contrast, tacrolimus 0.03% ointment is now available as a generic and is therefore much easier to prescribe because more insurance companies cover it for children (2-15yrs of age) with moderate AD. Many clinicians believe crisaborole to be more effective than tacrolimus; however long-term comparator studies have not been done. Paller *et al* showed that crisaborole was better than vehicle in children and adults with AD; however no baseline secondary measures (e.g., pruritus, signs of AD) were reported (5, 6). Nevertheless, recent post-hoc analysis of Phase 3 crisaborole studies observed a very early reduction in itch that may have a significant effect on patient and caregiver PROs (7) providing a potential advantage for crisaborole. This study will use a series of PROs to monitor the treatment effects of crisaborole and tacrolimus 0.03% over a 12 week period of time. The treatment for a chronic inflammatory disease characterized by flares and remissions must be longer than 30 days (i.e., 1 month) (5). We anticipate that crisaborole will

significantly decrease various PROs and that this effect will be superior to what is seen with tacrolimus 0.03%. We anticipate that the reductions we observe in the PROs will correlate with objective measures of disease severity (e.g. EASI).

1.3 Preliminary Studies

Our preliminary studies suggest the relevance of three PROMIS® domains (Pain Interference, Anxiety, Depression) to AD and treatment responses. In 101 adult AD patients, mean PROMIS® Depression and PROMIS® Anxiety scores were significantly higher for AD patients than all other dermatology patients (Depression = 49.9±10.4 vs. 47.6±9.8, p=0.030; Anxiety = 52.1±9.8 vs. 49.8±10.4, p=0.017). The percentage of AD patients with clinically significant (i.e., notable) scores (i.e., >55) was 36% in Anxiety, 33% in Mood, and 34% in Pain Interference. "Notable" Pain Interference scores associated with severe disease (p=0.020), higher %BSA of disease (p=0.002), uncontrolled disease (p=0.004), and/or unsuccessful treatment (p=0.001). Furthermore, Pain Interference decreased by a clinically important amount, 7.0 ± 11 points, in patients who initiated systemic medication (e.g. dupilumab, cyclosporine, methotrexate, and/or mycophenolate mofetil) to treat their disease (53.9 to 46.9, p=0.029). Depression also decreased by 3.8 ± 8.4 points (51.6 to 47.8, p=0.050). Further evaluation of the impact of other domains, such as itch and sleep, are necessary to fully understand how PROs can be used to monitor disease and treatment responses. Additionally, it is particularly important to understand the impact the disease (and treatments for the disease) have on caregivers. This study will elucidate the impact crisaborole has on children and caregiver PROs compared to tacrolimus 0.03%.

1.4 Objectives

Primary Objective: To investigate the effect of crisaborole (Eucrisa™) treatment on patient-reported itch and pain in patients with mild to moderate atopic dermatitis compared to tacrolimus 0.03%.

- *Hypothesis:* We hypothesize that crisaborole (Eucrisa™) treatment will significantly decrease (i.e., score change ≥ 5) the severity of itch and pain over time and these changes will correlate with improvements Eczema Area and Severity Index (EASI) in atopic dermatitis. We further hypothesize that the improvement in these PROs will be greater in the crisaborole treated subjects compared to those receiving tacrolimus.
- *Primary Outcome Measures:* Change in PROMIS® Itch and PROMIS® Pain Interference measures after 12 weeks of treatment.

Secondary Objective: To investigate the effect of crisaborole (Eucrisa™) treatment on patient-reported quality of life, sleep, anxiety, and depression in patients with mild to moderate atopic dermatitis compared to tacrolimus 0.03%.

- *Hypothesis:* We hypothesize that crisaborole (Eucrisa™) treatment will improve quality of life and decrease (i.e., score change ≥ 5) the severity of one or more of the PROs (sleep, anxiety, or depression). These changes will correlate with improvements in atopic dermatitis (EASI). We also hypothesize that the improvement in these PROs will be greater in the crisaborole treated subjects compared to those receiving tacrolimus.
- *Secondary Outcome Measures:* Change in Children's Dermatology Life Quality Index (CDLQI), PROMIS® Anxiety, PROMIS® Depression, and Children's Sleep Habits Questionnaire (CSHQ) after 12 weeks of treatment.

Tertiary Objective: To elucidate the impact of crisaborole (Eucrisa™) treatment or tacrolimus 0.03% on caregiver burden.

- *Hypothesis:* We hypothesize that improvements in caregiver burden will correlate with improvements in atopic dermatitis (EASI), as well as deceased severity in PROs.
- *Tertiary Outcome Measures:* Change in Caregiver Burden Inventory and Family Dermatology Life Quality Index (FDLQI) after 12 weeks of treatment.

2. STUDY DESIGN

2.1. Overview

This is an open-label, randomized, cross-sectional study to monitor the effects of crisaborole and tacrolimus 0.03% on patient-reported outcomes and caregiver burden in children (ages 2 to 15 years, inclusive) with ≤ moderate atopic dermatitis over a 12 week period of time. The goal of this study is to detect changes in PROs and caregiver burden during treatment for atopic dermatitis of moderate or less severity. The study design will allow us to correlate PROs and caregiver burden with treatment response and disease improvement in children. Additionally, we will be able to determine if crisaborole is a better overall treatment for children with atopic dermatitis compared to tacrolimus 0.03%.

3. CHARACTERISTICS OF RESEARCH POPULATION

3.1. Number of Subjects

This study will enroll 40 patient and caregiver pairs (i.e., 20 patients and caregivers per topical treatment; 80 subjects total). Adjusting for potential 20% withdrawal or dropout rate, we will accrue up to 48 patient and caregiver pairs. Patients must be between the ages of 2 to 15 years with mild to moderate atopic dermatitis. Caregivers must be the adult parent or guardian (18 years or older) of the eligible patient. Further discussion of sample size and power of sample can be found §11.1 on page 23.

3.2. Gender of Subjects

There are no restrictions based on gender in this study. A recent study involving parent participation reported 84% of participating caregivers were female (8).

3.3. Age of Subjects

This study enrolls children between the ages of 2 to 15 years with mild to moderate atopic dermatitis. This study also enrolls caregivers, who must be the adult (18 years or older) parent or guardian of the eligible patient.

3.4. Racial and Ethnic Origin

There are no restrictions based on race or ethnicity in this study. Based upon an ethnic minority population of 16% in the six county area of Rochester, we expect Rochester accruals to be at least 12% minority. Atopic dermatitis is prevalent in African Americans.

3.5. Inclusion Criteria:

Pediatric Subjects:

a) Male and female subjects of inclusive ages of 2 to 15 years at screening visit.

b) Diagnosis of ≤moderate atopic dermatitis or eczema (ISGA 2 or 3 and ≥3% BSA, excluding scalp).
c) If subject is taking or prescribed antihistamines, subject must be on stable dose of antihistamines.
d) If subject is taking topical steroids, subject must be on stable dose of topical steroid.
e) Subjects currently taking tacroliumus (i.e., Protopic), crisaborole (i.e., Eucrisa), or other topical steroid-sparring medications are eligible for this study if he/she agrees to a two week "washout period" prior to starting study procedures (See "washout period" described below on page 9).
f) If subject is taking systemic anti-inflammatory therapy (i.e., cyclosporine, etc), subject must be on a stable dose of the systemic anti-inflammatory medication for at least six week prior to enrollment and it must be anticipated that this dose would not change during their participation in this study, unless deemed medically necessary. Any changes in medication dose due to flaring of atopic dermatitis or side effects will be documented on the *AD Flare Medication Form* and *AE Source Doc* (see page 19).
g) Caregiver (i.e., adult parent or guardian) must agree to participate in the study with the patient.
h) Subject must be able to read and speak English.
i) Subject, ages ≥8 years, is able to give assent.

Caregiver Subjects:

a) Subject must be at least 18 years old and the parent or guardian of the eligible pediatric subject.
b) Subject must be able to read and speak English.
c) Subject must be able to give informed consent.

3.6. Exclusion Criteria

a) Pediatric subjects <2 years old or >15 years old *are not* eligible for participation in this study.
b) Pediatric subjects with a diagnosis with another skin disease (i.e., not atopic dermatitis or eczema) are excluded to prevent confounding of results.
c) Caregiver subject <18 years old are excluded.
d) Pediatric subject participation without caregiver participation is not allowed.

3.7. Women & Children

This study will enroll both women (18 year or older) and children (ages 2 to 15 years, inclusive).

3.8. Targeted Enrollment

Estimated enrollment for gender, race, and ethnicity for the study is shown below:

Pediatric Subject (2 to 15 years):

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	7	4	0	0	11
White	19	14	1	0	34
More Than One Race	1	0	0	0	1
Total	28	19	1	0	48

Caregiver Subjects (≥18 years):

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	8	3	0	0	11
White	27	5	1	0	33
More Than One Race	1	0	0	0	1
Total	39	8	1	0	48

4. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

4.1. Subject Identification & Recruitment

The Dermatology Clinical Trials Unit (CTU) will identify eligible subjects through electronic medical record for patients between the ages of 2 to 15 years with diagnosis of atopic dermatitis and/or eczema in [redacted]. The treating Dermatologist (i.e., [redacted]), or the CTU MD fellow will determine if patient has mild to moderate atopic dermatitis (ISGA 2 or 3) and 3% BSA can be enrolled in the study.

4.2. Informed Consent Process

Study personnel and/or dermatologist will identify eligible subjects. Eligible subjects will first be asked if they wish to hear about a potential clinical trial for atopic dermatitis. If the subject expresses interest in the study, the study personnel will approach the subject to discuss the study and obtain informed consent/assent from the patient and caregiver.

All study materials are in English, therefore all subjects must be able to read, speak, and understand English. Current FDA, ICH, NCI, state, federal, and institutional regulations concerning informed consent will be followed. Verbal assent will be obtained from pediatric subjects using the study Verbal Assent Script. Study personnel will read the verbal assent script to the pediatric subject and parent, answer all questions, and complete the form if the subject wishes to participate. All pediatric subjects (ages 8 to 12 years) must provide assent using Assent Form 1 and have their parent (i.e., adult caregiver) provide consent for participation in this study. All pediatric subjects (ages 13 to 15 years) must provide assent using Assent Form 2 and have their parent (i.e., adult caregiver) provide consent for participation in this study. Assent is not required for pediatric subjects less than 8 years old; however parent consent and permissions is required. Study personnel will discuss the informed consent form with the adult caregiver subjects (i.e., parent or guardian). The informed consent for will be a dual consent form on which the adult subject consents to participation as a caregiver in the study and also consents to their child's participation in the study. Additionally, during the consent process both subjects will be asked to complete a W9 form for reimbursement purposes. The adult subject will provide their name, mailing address, and signature on the Study Reimbursement Form to ensure that reimbursement can be mailed to him/her after study participation has completed.

The consent and assent process will be free of coercion and undue influence. Study personnel will then explain the project to the potential subjects and answer all questions. The subject will be provided sufficient information and time make a thoughtful and rational decision on participation. The subject will be given the opportunity to take the consent form home for review and discussion with family members before finalizing his/her decision. After the assent form and informed consent forms are signed, subjects will be given a copy of the document, along with the phone numbers of the study personnel to call if they have further questions. The completed assent and consent forms will be kept in the subject's study folder and stored in a locked office in a locked cabinet.

5. METHODS AND PROCEDURES

5.1. Study Procedures

- Study personnel will complete the electronic **Screening Log** to monitor all subjects approached for participation in this study, the outcome of the assent/consent process (declined or enrolled), and reason for declining participation.

- Study Personnel will complete the **Eligibility Checklist** for each pair of subjects who provide assent and consent for participation in this study.

- **Washout Period:** Patients who are already taking tacrolimus (i.e., Protopic), crisaborole (i.e., Eucrisa), or any steroid- sparring medication for atopic dermatitis are eligible for the study if he/she agrees to discontinuation of the medication for two weeks (i.e., 14 days) prior to starting study procedures. If the patient agrees to the two week "washout period", assent and informed consent can be obtained during that clinic visit. A study visit will be scheduled for the patient and caregiver at a convenient time at least two weeks (i.e., 14

days) from the day of assent/consent. After the two week "washout period", the subject will return to clinic for the baseline study visit and be randomized to tacrolimus 0.03% or crisaborole. The subject will either be given a tube of tacrolimus 0.03% or crisaborole. All study procedures will continue as described below starting with the ASPIRE On-study Form.

- Assent and informed consent are obtained from each subject, without coercion, prior start of any study procedures. Assent Form 1 will be used for subjects ages 8 to 12 years and Assent Form 2 will be used for subjects ages 13 to 15 years. Informed consent will be completed by the parent/adult caregiver. The caregiver subject will provide their name, mailing address, and signature on the **Study Reimbursement Form**. Each subject (child and adult) will complete a W9 form for study reimbursement.

- Study personnel will notify the caregiver that they will be contacted by phone for reminders about upcoming study appointments and screening for any adverse reactions. Study personnel will ask if leaving a voicemail message is okay in case a call is missed. This information will be kept in a password-protected excel file **Call Log** located in the study folder on the Dermatology CTU's University sharedrive. Study personnel will only have access to this study folder and the excel file.

- Study personnel will add appropriate subject information and study progress to the **Comprehensive Study Log**, as required by RSRB. This log is a password-protected excel file located in the study folder on the Dermatology CTU's University sharedrive. Study personnel will only have access to this study folder and excel file.

- Subjects will be on study for at least 12 weeks. Subjects will be assessed at three different time points (Baseline, 6 Weeks, and 12 Weeks). Each assessment will be performed in the dermatology clinic and take approximately 30 minutes or less

- Pediatric subjects will be randomized 1:1 to one of two topical treatments: crisaborole or tacrolimus 0.03%. Both of these topical treatments are standard care for mild to moderate atopic dermatitis. Study personnel will obtain randomization in REDCap. After randomization, the treating dermatologist (i.e., [redacted]) will prescribe crisaborole or tacrolimus 0.03% to the pediatric subject for treatment of atopic dermatitis. Study personnel will dispense a tube of tacrolimus 0.03% or crisaborole to the subject based on randomization. The topical treatments will be applied to all affected areas twice daily for at least 12 weeks on this study. Additional tubes of tacrolimus 0.03% or crisaborole will be dispensed to the subject if needed to complete the 12 week treatment and assessment period. At the completion of the study, the treating dermatologist may continue or change the prescribed treatment for atopic dermatitis.

- Study personnel will complete the **ASPIRE On-Study Form** in REDCap. This form collects demographic information on both the pediatric subject and caregiver subject. Additionally, the form collects treatment information related to atopic dermatitis, all current medications, and medical history for the pediatric subject. This form will be completed after assent and consent are obtained.

- **Baseline Assessment:**
    - *Study personnel:* Trained study personnel (MD/NP) will perform Eczema Area & Severity Index (EASI), Investigator Static Global Assessment (ISGA), and Percentage Body Surface Area (%BSA) for the severity of atopic dermatitis. Study personnel Study personnel will also weigh the tube of crisaborole and tacrolimus 0.03% prior to distribution to the subject. Study personnel will have an average weight for tube of tacrolimus prescribed. Study personnel will enter EASI, ISGA, and tube weight into the electronic **Assessment Form (Baseline)** in REDCap.

    - *Pediatric Subjects:* Pediatric subjects (≥5 years) will complete five self-report outcome measures **(PROMIS® Itch, PROMIS® Pain Interference, Children's Dermatology Life Quality Index (CDLQI), PROMIS® Anxiety, PROMIS® Depression**) on an iPad. All self-report measures can be completed with the assistance of their parent or guardian. All five self-report outcome measures can be completed in 20 minutes or less. Pediatric subjects <5 years will not complete any self-report measures on the iPad.

    - *Caregiver Subjects:* All caregivers will complete one self-report questionnaire about their child's sleep habits **(Children's Sleep Habits Questionnaire (CSHQ)**) and two self-report measures for caregiver burden (**Caregiver Burden Inventory (CBI**)) and quality of life (**Family Dermatology Life Quality Index (FDLQI)** on an iPad. All self-report measures can be completed in 5 minutes.

- Pediatric subjects will complete a Pediatric Subject Reimbursement Form at the end of the Baseline Assessment. The pediatric subject will print their name, address, sign and date the form. The adult caregiver may help the child complete the form if he/she has difficulty writing. Pediatric subject ≥5 years must sign the form. Study personnel will give the pediatric subject a $10 gift card after for the completion of this form for completion of the Baseline Assessment. For pediatric subjects <5 years, the adult caregiver will complete and sign the form. Study personnel will give the adult caregiver subject a $10 gift card after for the completion of this form for completion of the Baseline Assessment.

- Study personnel will call the caregiver by phone during the Week 3 of treatment for adverse event monitoring of their child who is participating and on topical treatment. Study personnel will ask: 1) Has your child been able to use the topical treatment without any problems?; 2) Has your child experienced any burning from the topical treatment?; and 3) Has your child experienced any side effects or adverse reactions while using the topical treatment?. Study personnel will document the phone call in the Call Log. Adverse events will be documented on AE source doc.

- Study personnel will call the caregiver by phone at least 48 hours prior to the 6 Week Assessment to remind he/she of their upcoming appointment and to bring their tube of topical treatment with them to the appointment. Study personnel will also monitor for

adverse events by asking: 1) Has your child been able to use the topical treatment without any problems?; 2) Has your child experienced any burning from the topical treatment?; and 3) Has your child experienced any side effects or adverse reactions while using the topical treatment?. Study personnel will document the phone call in the Call Log. Adverse events will be documented on AE source doc.

- **6 Week Assessment:**
    - This assessment should occur 6 weeks (±7 days) after the start of topical treatment (i.e., after Baseline Assessment). This study visit may be performed by telemedicine (i.e., zoom visit) if deemed appropriate and preferred by physician and subject. All currently scheduled and enrolled subjects will be given the option to have a study visit performed by telemedicine or in clinic. Study personnel will contact the enrolled subjects with scheduled 6 week and 12 week study visits by phone to ask if the subject would preferred to keep their in clinic study visit or have the study visit by telemedicine (zoom visit). All visits will be scheduled at a convenient time for the subject.

    - *Study personnel:* Trained study personnel (MD/NP) will perform EASI and ISGA for the severity of atopic dermatitis. Study personnel Study personnel will also weigh the tube of crisaborole and tacrolimus 0.03% prior to distribution to the subject. Study personnel will enter the EASI, ISGA, and tube weight into the electronic **Assessment Form (6 Week)** in REDCap.

    - *Pediatric Subjects:* Pediatric subjects ≥5 years will complete five self-report outcome measures **(PROMIS® Itch, PROMIS® Pain Interference, Children's Dermatology Life Quality Index (CDLQI), PROMIS® Anxiety, PROMIS® Depression**) on an iPad. All self-report measures can be completed with the assistance of their parent or guardian. All five self-report outcome measures can be completed in 20 minutes or less. Pediatric subjects <5 years will not complete any self-report measures on the iPad.

    - *Caregiver Subjects:* All caregivers will complete one self-report questionnaire about their child's sleep habits **(Children's Sleep Habits Questionnaire (CSHQ))** and two self-report measures for caregiver burden (**Caregiver Burden Inventory (CBI**)) and quality of life (**Family Dermatology Life Quality Index (FDLQI)** on an iPad. All self-report measures can be completed in 5 minutes.

- Pediatric subjects will complete a Pediatric Subject Reimbursement Form at the end of the 6 Week Assessment. The pediatric subject will print their name, address, sign and date the form. The adult caregiver may help the child complete the form if he/she has difficulty writing. Pediatric subject ≥5 years must sign the form. Study personnel will give the pediatric subject a $10 gift card after for the completion of this form for completion of the 6 Week Assessment. For pediatric subjects <5 years, the adult caregiver will complete and sign the form. Study personnel will give the adult caregiver subject a $10 gift card after for the completion of this form for completion of the Baseline Assessment.

- Study personnel will call the caregiver by phone during the Week 9 of treatment for adverse event monitoring of their child who is participating and on topical treatment. Study personnel will ask: 1) Has you child been able to use the topical treatment without any problems?; and 2) Has your child experienced any side effects or adverse reactions while using the topical treatment?. Study personnel will document the phone call in the Call Log. Adverse events will be documented on AE source doc.

- Study personnel will call the caregiver by phone at least 48 hours prior to the 6 Week Assessment to remind he/she of their upcoming appointment and to bring their tube of topical treatment with them to the appointment. Study personnel will also monitor for adverse events by asking: 1) Has you child been able to use the topical treatment without any problems?; and 2) Has your child experienced any side effects or adverse reactions while using the topical treatment?. Study personnel will document the phone call in the Call Log. Adverse events will be documented on AE source doc.

- **12 Week Assessment:**
    - This assessment should occur 6 weeks (±7 days) after the 6 Week Assessment (i.e., 12 weeks after Baseline Assessment). This study visit may be performed by telemedicine (i.e., zoom visit) if deemed appropriate and preferred by physician and subject. All currently scheduled and enrolled subjects will be given the option to have a study visit performed by telemedicine or in clinic. Study personnel will contact the enrolled subjects with scheduled 6 week and 12 week study visits by phone to ask if the subject would preferred to keep their in clinic study visit or have the study visit by telemedicine (zoom visit). All visits will be scheduled at a convenient time for the subject.

    - *Study personnel:* Trained study personnel (MD/NP) will perform EASI and ISGA for the severity of atopic dermatitis. Study personnel Study personnel will also weigh the tube of crisaborole and tacrolimus 0.03% prior to distribution to the subject. Study personnel will enter the EASI, ISGA, and tube weight into the electronic **Assessment Form (12 Week)** in REDCap.

    - *Pediatric Subjects:* Pediatric subjects ≥5 years will complete five self-report outcome measures **(PROMIS® Itch, PROMIS® Pain Interference, Children's Dermatology Life Quality Index (CDLQI), PROMIS® Anxiety, PROMIS® Depression**) on an iPad. All self-report measures can be completed with the assistance of their parent or guardian. All five self-report outcome measures can be completed in 20 minutes or less. Pediatric subjects <5 years will not complete any self-report measures on the iPad.

    - *Caregiver Subjects:* All caregivers will complete one self-report questionnaire about their child's sleep habits **(Children's Sleep Habits Questionnaire (CSHQ)**) and two self-report measures for caregiver burden (**Caregiver Burden Inventory (CBI**)) and quality of life (**Family Dermatology Life Quality Index (FDLQI)** on an iPad. All self-report measures can be completed in 5 minutes.

- Pediatric subjects will complete a Pediatric Subject Reimbursement Form at the end of the 12 Week Assessment. The pediatric subject will print their name, address, sign and date the form. The adult caregiver may help the child complete the form if he/she has difficulty writing. Pediatric subject ≥5 years must sign the form. Study personnel will give the pediatric subject a $10 gift card after for the completion of this form for completion of the 12 Week Assessment. For pediatric subjects <5 years, the adult caregiver will complete and sign the form. Study personnel will give the adult caregiver subject a $10 gift card after for the completion of this form for completion of the Baseline Assessment.

- After completion of study procedures, the adult caregiver will be reimbursed for their study participation. Subjects completing all study procedures will be reimbursed $100. Reimbursement will be pro-rated to reimburse subjects for any and all of their study participation (i.e., $20 for completion of Baseline Assessment; $40 for completion of 6 Week Assessment; and $40 for completion of 12 Week Assessment. A check will be mailed by University of Rochester to the adult caregiver at the address provided on the Study Reimbursement Form for their participation in this study.

- After study procedures are completed, the child's treatment of atopic dermatitis will continue as deemed appropriate by the treating dermatologist.

5.2. Topical Agent Distribution and Application

This is an open-label study using two topical treatments (crisaborole and tacrolimus 0.03%), which are both standard care topical treatments for ≤moderate atopic dermatitis:

- *Crisaborole:* Crisaborole is approved for atopic dermatitis in ages 2 years and older. Crisaborole will be provided to subject (provide by Pfizer) by study personnel in the clinic. Pfizer provided tubes of crisaborole for this study to avoid issues with non-coverage by medical insurances. The provided tubes of crisaborole will be stored at room temperature a locked cabinet in the CTU in University of Rochester Dermatology. A **Drug Accountability Record** will be kept with the crisaborole and completed each time a tube is dispensed to a subject. The Drug Accountability Record will record inventory and dispensing information. Inventory information will include: date received, number of tube, lot number, expiration date, staff initials, and balance. The Dispensing information will include: Subject ID, Date dispensed, number of tubes dispensed, lot number, balance forwarded, and staff initials. Study personnel will distribute the assigned tube of crisaborole to the subject at the Baseline Assessment. Study personnel will instruct the subject to apply the topical ointment to all affected areas twice daily throughout the study. Study personnel will instruct the subject to bring their tube of topical treatment with them to the 6 Week Assessment and the 12 Week Assessment for weighing.

  Expired or Unused Crisaborole: The PI will monitor the expiration status of all crisaborole supplies and ensure that study subjects only receive crisaborole that is within its expiration date. The PI will provide Pfizer with sufficient notice (as defined by the mutual agreement of both parties before study initiation) if resupply is needed because of

pending expiration of existing supplies. Unless otherwise instructed by Pfizer in writing, Rochester will destroy any crisaborole supplies that expire during the study, as well as unused product at the termination of the study and agreement. Rochester will destroy these materials in accordance with applicable law and institutional policies.

- *Tacrolimus 0.03%:* Tacrolimus 0.03% is approved for atopic dermatitis in ages 2 to 15 years. Tacrolimus 0.03% will be provided to subject by study personnel in the clinic. Tacrolimus 0.03% will be purchased through the Investigational Drug Pharmacy at URMC as part of this study in order to provide the medication to subjects. Since this is an open-label study, the topical treatments will not be in matching tubes. Study personnel will instruct the subject to apply the topical ointment to all affected areas twice daily throughout the study. Study personnel will instruct the subject to bring their tube of topical treatment with them to the 6 Week Assessment and the 12 Week Assessment for weighing.

  Expired or Unused Tacrolimus: The PI will monitor the expiration status of all Tacrolimus supplies and ensure that study subjects only receive tacrolimus 0.03% that is within its expiration date. The PI will provide the Investigation Drug Pharmacy with sufficient notice (as defined by the mutual agreement of both parties) if resupply is needed because of pending expiration of existing supplies. Unless otherwise instructed by the Investigational Drug Pharmacy, study personnel will destroy any tacrolimus supplies that expire during the study. The PI will return any non-expired, unused product to the Investigational Drug Pharmacy at the termination of the study and agreement. Rochester will destroy these materials in accordance with applicable law and institutional policies.

5.3. Outcome Measures and Study Forms

Eczema Area & Severity Index (EASI): The EASI is a tool used to measure the extent (area) and severity of AD. It does not include a grade for dryness or scaling and includes only inflamed areas (9). Area score is recorded for four regions of the body (head and neck, trunk including genital area, upper limbs, and lower limbs including buttocks). For head and neck region, the face occupies 33% (17% each side), the neck 33% (17% front and back), and the scalp occupies 33%. For the trunk region, the front occupies 55% and back 45%. For the upper limbs region, each arm occupies 50%, with the front or back of one arm equal to 25%. For the lower limbs region, each leg occupies 45%, with the front or back of one leg equal to 22.5% and the buttocks occupies 10%. The area score is the percentage of skin affected by AD for each body region. The **area score** is a 7-point scale representing the percentage of skin affected by AD for each body region (e.g., 0 = None; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; and 6 = 90-100%. The **severity score** is recorded for each of the four regions of the body and is the sum of the intensity scores for four signs. The four signs include redness, thickness, scratching, and lichenification. The intensity scores are performed using a 4-pont scale (e.g., 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe). A severity score is the sum of the intensity scores for the four signs. For each body region, the severity score is multiplied by the area score and by a multiplier:

- Head and neck: severity score x area score x 0.1 (in children 0–7 years, x 0.2)
- Trunk: severity score x area score x 0.3
- Upper limbs: severity score x area score x 0.2

- Lower limbs: severity score x area score x 0.4 (in children 0–7 years, x 0.3)

The final EASI score is the sum of the total scores for each region. Add up the total scores for each region to determine the final EASI score. The minimum EASI score is 0 and the maximum EASI score is 72.

Investigator Static Global Assessment (ISGA): The ISGA, a five-point global static assessment of AD severity, will be used to characterize subjects' overall disease severity across all treatable AD lesions (Table 1) (10). Training on how to assess the ISGA will be provided by Dr. Beck. Each ISGA assessment during the study must be done by trained study personnel.

Tabel 1: Investigator's Static Global Assessment

Score	Grade	Definition
0	Clear	Minor residual discoloration; 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

Percentage Body Surface Area (%BSA): The %BSA will be calculated by trained study personnel using the "rule of 9's" (11). This method assigns percentages for body areas. In children the percentages are: Head & Neck = 9% (4.5% front or back); Chest = 18%; Back = 18%; Right arm = 9% (4.5% front or back); Hands = 2% (1% front or back); genitals = 1%; Right leg (including foot) = 18% (9% front or back); Left leg (including foot) = 18% (9% front or back).

PROMIS® Itch (Pediatric): PROMIS® is the patient reported outcome measurement information system developed and validated by NIH and consists of domain-specific, but not disease-specific, measures within physical, mental and social health. PROMIS® Itch is a newly validated 8-item short-form spanning four domains (general, activity, mood/sleep, and scratching behavior). Each item is scored on a scale of 1 to 5. This PRO will be completed on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center. This measure was created by Dr. Amy Paller at Northwestern University. We have a DUA in place with Dr. Paller to use the Pediatric PROMIS Itch Short-form in this study. We will share de-identified data collected during this study with Dr. Paller to assist in further validation of the Pediatric PROMIS® Itch Short-Form. Unlike, the other PROMIS measures used in this protocol, the PROMIS Itch measure will not be automatically scored due to its novelty. It will be scored during data analyses using the appropriate conversion tables provided by Dr. Paller.

PROMIS®Pain Interference (Pediatric): PROMIS® Pain Interference is a computer adaptive test (CAT) consisting of 4-12 questions related to how pain interferes with daily activities. The number of questions a patient answers depends on how he or she answers each question. A domain score of 50 is the average score for the general population. A score above 55 is considered "clinically significant" for each domain (12, 13). A score change of 5 or more is considered a clinically important change in domain severity (12, 13). This measure will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

PROMIS® Anxiety and Depression (Pediatric): These PROs will be completed electronically on an iPad. These domains are secondary outcome measures and are CAT domain consisting of 4-12 questions on feelings related to anxiety or depression. The number of questions a patient answers depends on how he or she answers each question. A domain score of 50 is the average score for the general population. A score above 55 is considered "clinically significant" for each domain (12, 13). A score change of 5 or more is considered a clinically important change in domain severity (12, 13). These two measures will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

Children's Dermatology Life Quality Index: This PRO will be completed using an iPad. The 10-item questionnaire designed for use in parents of children (i.e., ages 4-17) to obtain information on children's quality of life (14, 15). It is self-explanatory and can be simply handed to the patient who is asked to fill it in with the help of the child's parent or guardian. Each question relates to a component of quality of life: Symptoms/Feelings (items 1-2); Leisure (items 4-6); School (item 7); Relationships (items 3-8); Sleep (item 9), and Treatment (item 10). Children answer each question using a 4-point scale: Not at all = 0, A Little = 1, Quite A Lot = 2, Very Much = 3. The scores from each item are summed to create a severity burden score (i.e., maximum score = 30). The scores represent degree of severity burden on quality of life: No effect = 0-1; Small effect = 2-6; Moderate effect = 7-12; Very large effect = 13-18; and Extremely large effect = 19-30. This measure will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

Children's Sleep Habits Questionnaire (CSHQ): This PRO will be completed using an iPad. This is a validated and abbreviated form of the original CSHQ containing 22 items instead of 45 items (16, 17). This abbreviated CSHQ questionnaire consists of 4 subscales: Bedtime, Sleep Behavior, Waking During the Night, and Morning Wake Up. The patient/parent will answer each item choosing from: "Always" if something occurs every night; "Usually" if it occurs 5 or 6 times a week; "Sometimes" if it occurs 2 to 4 times a week; "Rarely" if it occurs once a week; and "Never" if it occurs less than once a week. Each question is scored on a 3-point scale as 1 = Usually and Always (5-7 times/week); 2 = Sometimes" (2–4 times/week); or 3 = Rarely and Never (0-1 time/week). The scores are combined from each subscale to generate a Total Sleep Disturbance Score, which can range from 22 to 66. A Total Sleep Disturbances score over 28 represent clinically significant sleep disturbance. This measure will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

Caregiver Burden Inventory (CBI): The CBI is a 24-item, five-subscale Caregiver Burden Inventory (CBI) and demonstrates its use as a diagnostic tool for caregiver burden (18-20). The five subscales include: Time Dependency, Development, Physical Health, Emotional Health, and Social Relationships. Each subscale contains 4-5 items which are statements of feelings. Caregivers use a 5-point scale, anchored by "0" = "Never" and "4" = "Nearly Always", to show how often the statement describes his/her feelings. Overall scores can range from 0 to 96, where a score near or above 36 indicates significant burden. All subscales have a maximum score of 20, except Physical Health which has a maximum score of 16. Subscale scores and item scores help identify the underlying cause of caregiver burden. This measure will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

Family Dermatology Life Quality Index (FDLQI): The FDLQI is a 10-item questionnaire designed for adult family members of a patient with a skin disease (21, 22). It measures the impact of the patient's skin disease on the family member's quality of life. The caregiver will answer each question using a 4-point scale: Not at all = 0, A Little = 1, Quite A Lot = 2, Very Much = 3. The scores from each item are summed to create a severity burden score (i.e., maximum score = 30). The scores represent degree of severity burden on quality of life: No effect = 0-1; Small effect = 2-6; Moderate effect = 7-12; Very large effect = 13-18; and Extremely large effect = 19-30. This measure will be completed electronically on an iPad and data will be submitted directly to the secure RedCap database at the University of Rochester Medical Center.

Screening Log: This electronic form (REDCap) will be used to document the eligibility of subjects, if the subject consented or declined participation, and reason for declining participation. The Screening Log will help create a CONSORT diagram at the completion of the study. This form will electronically capture screening information for the study and submit the information directly to the secure RedCap database at the University of Rochester Medical Center. Study personnel will access the form electronically through a specific URL link.

Eligibility Checklist: This form contains the inclusion and exclusion criteria for participation in this study. This form is completed to ensure eligibility for the trial. Study personnel obtaining assent/consent will complete this form.

Study Reimbursement Form: This form is required along with a signed W9 for reimbursement of the adult caregiver in this study. The address on this form must match the signed W9 completed by the subject at the start of the study. After the assent/consent process is completed, the adult subject (i.e., Caregiver) will print their name, mailing address, sign, and date this form, as well as complete a W9 form.At the end of the subjects' participation, the study coordinator or PI will circle the appropriate number of visits completed, indicate the number of visits completed, and indicate the amount to be reimbursed. A total of $100 will be reimbursed for completion of all study procedures.

Pedaitric Subject Reimbursement Form: This form is required at the end of each study visit to reimburse the pediatric subject with a $10 gift card for completion of each visit (i.e., a total of

$30 in gift cards). The address on this form must match the signed W9 completed by the subject at the start of the study. After completion of each study visit, the pediatric subject will print their name, mailing address, sign, and date this form. The adult caregiver may assist the pediatric subject with completion of this form; however the pediatric subject must sign the form. A $10 gift card will be given to the pediatric subject after completion of this form.

Call Log: This is a password-protected excel spreadsheet that will contain contact information for the adult subjects. The spreadsheet contains Subject Pair ID, Caregiver Subject Name, Caregiver Subject Phone Number, and if voicemail can be left. The form will also capture each phone call made to the subject by study personnel. Study personnel will call the adult subject four different times during the study (i.e., Week 3, Week 6, Week 9, and Week 12) to screen for adverse reactions and reminders for study visits. Additional contact may occur to prevent loss to follow-up if subjects do not show up to an assessment or cancels their assessment appointments.

Comprehensive Study Log: This is a password-protected excel spreadsheet that contains a log for all subjects in the study. The information kept in this file include: Subject Pair ID, Caregiver Name, AD Patient Name, AD Patient MRN, Screened & Eligible, Assent Completed, Consent Completed, Screen Fail, Baseline Complete, 6 Week Complete, 12 Week Complete, Completed Study, Withdrawal, Loss to Follow-up, and Topical Treatment. Study personnel will complete the required subject information and check the appropriate boxes as the study progresses to monitor subject participation in the study.

ASPIRE On-Study Form: This form captures demographic information on both the caregiver and patient subjects, as well as relevant clinical information for the patient subjects. This form will be completed electronically and submit information directly to the secure REDCap database at the University of Rochester Medical Center. This form will collect the following:

- Subject Pair ID
- On Study Date
- Washout Period Required (yes/no)
- Caregiver Initials
- Relation of Caregiver
- Caregiver Gender
- Caregiver Age
- Caregiver Race
- Caregiver Ethnicity
- AD Patient Initials
- AD Patient Gender
- AD Patient Race
- AD Patient Ethnicity
- AD Patient Medical History
- AD Patient Current/Previous Treatments for AD
- AD Patient All Current Medications

Assessment Forms: These forms capture the EASI score, ISGA score, %BSA score, and topical treatment tube weight at each assessment (Baseline, 6 Week Assessment, and 12 Week Assessment). These forms will be completed electronically in REDCap during each specified assessment.

Withdrawal Form: This electronic form (REDCap) will be used to document the time and reasons for withdrawals during the study. This form will electronically capture withdrawal information for the study and submit the information directly to a secure REDCap database at the University of Rochester Medical Center.

AD Flare Medication Form: This electronic form (REDCap) will be used to document any extra medication prescribed to control an atopic dermatitis flare in a study subject. Study personnel will record the name of medication, dosage, date started, date ended, and continued for remainder of study (yes/no) for the extra medication. Subjects will remain on study unless he/she has is prescribed systemic anti-inflammatory therapy for atopic dermatitis. The treating dermatologist will manage and monitor the flare at their discretion.

AE Source Doc: This REDCap form will be completed by study personnel electronically (or on paper) to document any adverse reaction reported during the study. The form will record a description of the adverse event, date of onset, Serious (Yes/No), Intensity (Mild/Moderate/Severe), Relation to Study Drug (Definite/Probable/Possible/Unlikely/Unrelated), Action with Study Drug (No Action/Interrupted/Stopped Entirely).

Drug Accountability Record: This is a paper form that will be kept with the stock of tubes of crisaborole and tacrolimus 0.03% in a locked cabinet in the CTU in [redacted]. This form will record: the number of tubes in stock, the dispense date of the tube, Subject Pair ID for the tube, initials of study personnel, number of tubes dispensed, and adjusted number of tubes in stock. This form will be completed each time a tube of crisaborole or tacrolimus 0.03% is dispensed to a study subject.

5.4. Randomization

Randomization will assign a pediatric subject to one of two topical treatments (crisaborole or tacrolimus 0.03%) at a ratio of 1:1. Randomization will use a computerized pseudorandom number generator and will employ a random block size of 4 or 6. Study personnel will obtain randomization assignment in REDCap.

5.5. Blinding Methods

This is an open-label study and is not blinded.

5.6. Subject Compliance

Subject compliance will be assessed using tube weight of the assigned topical treatment. A tube of crisaborole and a tube of tacrolimus 0.03% will be weighed at the start of the study by study personnel to serve as the baseline weight for all subjects in the study. Study personnel will weigh the tube at 6 Weeks and 12 Weeks to ensure that the subject is using the topical treatment for atopic dermatitis.

5.7. Costs to Subject

There is no cost to subjects for participation in this study. All study medications and study materials will be provided to the subject without cost.

5.8. Reimbursement for Participation

All pediatric subjects will receive a $10 gift card at the end of each study visit for their participation in this study (i.e., total $30 in gift cards). All adult caregiver subjects will be reimbursed $100 for completion of all study procedures. Payment will be prorated based on number of assessments completed in the study. Subjects will be paid $20 for completion of Baseline Assessment, $40 for completion of 6 Week Assessment, and $40 for completion of 12 Week Assessment. A check will be issued to the adult caregiver (i.e., caregiver) after completion of 12 Week Assessment or whenever their participation in the study has ended.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Systemic anti-inflammatory therapies for atopic dermatitis are allowed if the subject is taking a stable dose of the systemic anti-inflammatory medication for at least six week prior to enrollment. It must be anticipated that this stable dose would not change during their participation in this study, unless deemed medically necessary. Any changes in systemic medication dose due to flaring of atopic dermatitis or side effects will be documented on the *AD Flare Medication Form* and *AE Source Doc* (see page 19). These therapies are not usually used in children with atopic dermatitis of moderate or less severity. If a subject is newly prescribed systemic anti-inflammatory therapy during the course of the study due to worsening atopic dermatitis, the subject will be withdrawn from the study.

7. SUBJECT WITHDRAWALS

Subjects will be advised during the consent/assent process that they have the right to withdraw from the study at any time without prejudice or reason. Criteria for investigator-initiated subject withdrawal include: inability to make study visits, subject lost to follow-up, non-compliance to study procedures, or death. The reason for discontinuation will be recorded in the subject's medical records. The date of occurrence and reasons for any subject withdrawal will be recorded and documented on the **Withdrawal Form**. Subjects that withdraw from the study will be replaced with another subject.

8. STOPPING PROCEDURES

- Subjects will remain on study during an atopic dermatitis flare. Any extra medication prescribed to control the flare will be documented on the electronic AD Flare Medication Form. Subjects will continue all study procedures as described in the protocol. Subjects will continue to use their assigned study topical medication.
- Subject will be withdrawn from the study if systemic anti-inflammatory therapy is newly prescribed and required for control of their atopic dermatitis.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Monitoring

This study does not involve interventional or clinical endpoints for individual patients. The treatment prescribed to patients in the study is part of standard care for mild to moderate atopic dermatitis in children and adolescents. Although the patients will receive one of two topical treatments for atopic dermatitis, the primary outcome of the study is not clinical response to treatment. Crisaborole and tacrolimus 0.03% ointments are both FDA-approved for atopic dermatitis and applied twice daily to affected areas of skin. Although this is an open-label, cross-sectional study, safety information may be identified during the course of data collection. Adverse event monitoring will be performed by phone at four different times during the study (i.e., Week 3, Week 6, Week 9, and Week 12). Any AEs will be documented on the AE Source Doc. Any safety information for an individual patient that is volunteered by a study subject during the course of this research must be reported as described below:

All adverse event, whether observed by the Investigator, elicited from, or volunteered by the subject, should be documented. Each adverse event will be recorded on the electronic AE Source Doc. This form will record the will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any actions taken. This description will be in the summary not during a subject's regularly scheduled clinic appointment.

Adverse event (AE): is any untoward medical occurrence in a subject administered study drug (active drug or placebo), and which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. The relationship of each adverse event to the study drug (active drug or placebo) must be recorded as one of the choices on the scale described below.

Attribution: An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
Life Threatening Adverse Event: Any AE that places the subject at immediate risk of death from the AE as it occurred.
Serious Adverse Event (SAE): Any adverse event occurring at any dose that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2. Recording Adverse Events

Study personnel will assess adverse events by recording all voluntary complaints of the subject. Any side effects and adverse reactions will be noted on the AE Source Doc. Study personnel will check with the nurse and/or treating physician regarding any reported adverse reactions. All adverse events, whether observed by the Investigator, the treating physician, or volunteered by the subject, will be documented. Adverse events will be reported per the RSRB and CTO reporting requirements. Each adverse event will include a brief description of the experience, the date of onset, the severity of the event, the relationship to investigational intervention, and any action taken with respect to the study and intervention. Adverse event monitoring will occur at the start of topical treatment until completion of the study.

The relationship to the study drug and the severity of each adverse event (i.e., attribution) as judged by the investigator must also be recorded. An adverse event is any untoward medical occurrence in a patient administered study drug (active drug or placebo), and which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. The relationship of each adverse event to the study drug (active drug or placebo) must be recorded as one of the choices on the scale below:

DEFINITE: Causal relationship is certain (e.g., the temporal relationship between drug exposure and the adverse event onset/course is reasonable; there is a clinically compatible response to de-challenge; other causes have been eliminated; and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure, if necessary).

PROBABLE: High degree of certainty for causal relationship (e.g., the temporal relationship between drug exposure and the adverse event onset/course is reasonable; there is a clinically compatible response to de-challenge [re-challenge is not required]; and other causes have been eliminated or are unlikely).

POSSIBLE: Causal relationship is uncertain (e.g., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown; de-challenge/re-challenge information is either unknown or equivocal; and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable).

UNLIKELY: Not reasonably related, although a causal relationship cannot be ruled out (e.g., while the temporal relationship between drug exposure and the adverse event onset/course

does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug).

UNRELATED: No possible relationship (e.g., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to the drug is not plausible).

9.3. Reporting Serious Adverse Events

Serious adverse events (SAEs), while a subject is enrolled in the study until the subject completes the study, will be reported in writing to the University RSRB as per their requirements. A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study, will not be considered serious adverse events.The onset date, resolution date, treatment, and outcome of each adverse event will be reported to the Research Subjects Review Board (RSRB) and to the Safety Coordinator using the MedWatch Form FDA 3500A-Mandatory Reporting. Unanticipated problems that involve risks to subjects or others (UPIRTSO) will be reported to RSRB.

Pfizer: Serious adverse events must be reported to Pfizer using the Pfizer-provided SAE form. The Pfizer SAE form will be faxed to [redacted] along with the MedWatch Form FDA 3500A-Mandatory Reporting and Pfizer Reportable Event Cover Sheet. SAEs should be reported to Pfizer immediately upon awareness, if the SAE is fatal or life-threatening (i.e., causes an immediate risk of death) —regardless of the extent of available information. Alternatively, SAEs should be reported within 24 hours of first awareness of the SAE, if the SAE is not fatal or life threatening. Non-serious adverse events observed in the trial *are not* reported to Pfizer.

IRB: As described above, on-study adverse reactions are reported to the University of Rochester Research Subjects Review Board (RSRB). Modifications to the protocol will be reviewed by RSRB before implementation. The RSRB also provides initial and continuing review of study conduct and consent.

Research staff (i.e., PI, Co-investigators, or study coordinator): Will also conduct continuous review of data and subject safety. The review will include for each treatment arm/dose level: the number of subjects, adverse reactions, and responses observed. The Investigator will submit summaries of this data to the Data Safety Monitoring Committee for review as required in the study's protocol review committee approval letter.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

The proposed study is a low risk clinical trial. Subjects (patients & caregivers) will be completing self-report questionnaires at three different regularly schedule clinic visits. The two topical treatments in the study are FDA-approved and standard care for ≤moderate atopic dermatitis. Crisaborole is approved for use in ages 2 years and older. Known side effects to crisaborole include pain at the site of application. Tacrolimus 0.03% is approved for use in ages 2 to 15 years. Know side effects to tacrolimus 0.03% include burning sensation, stinging, soreness, or pruritus at the site of application. These localized symptoms may occur during the first few days of use and subside as atopic dermatitis lesions improve. Subjects using tacrolimus should limit sun exposure and should not use ultraviolet light therapy, sun lamps, or tanning beds. Tacrolimus-treated skin should not be covered with bandages, dressings, or wraps. Contact of tacrolimus with eyes or mouth should be avoided. Unexpected side effects, such as allergic reactions, may occur and are unpredictable. This reaction may be mild, such as a skin rash, or you may have more severe symptoms like swelling of the throat, low blood pressure, and shortness of breath. If any of these unexpected side effects occur, subjects will be advised to stop use of their intervention immediately. Subjects will be informed about any additional potential risks if they are discovered. Furthermore, while we make every effort to keep all data and study information private, this cannot be guaranteed. All data will be de-identified and stored in a locked file in a locked office. All appropriate procedures will be taken to maintain subject privacy and data collected during this study.

10.2. Protection Against Risks

Study forms and patient-report forms are either electronic forms through REDCap or paper forms. All data from paper forms will be entered electronically into REDCap database as it is received from the subjects. All electronically captured data will be securely stored in the secure REDCap database at the University of Rochester Medical Center. To protect the confidentiality of subjects, questionnaires and data collected on each subject will be coded, the form collected will contain a numerical Subject ID and Subject Initials. The forms *WILL NOT* contain any personal identifiers. The key list with all Subject IDs will be kept in a locked file. All forms will also be kept in a locked file that is separate from the key list that links the subject name and the code number. When data analyses are completed, the key list and paper forms will be destroyed. The required informed consent will be the only record kept of those subjects who have participated in the research. The interventions that will be studied in this project are not associated with any risks.

Any safety information for an individual patient that is volunteered by a study participant during the course of this research must be reported. All adverse event, whether observed by the Investigator, elicited from, or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any actions taken. This description will be in the summary not during a subject's regularly scheduled clinic appointment.

10.3. Potential Benefit to the Subjects

It is not possible to predict whether subjects will feel any personal benefit from participation in this research study. Subjects may have relief of atopic dermatitis and improved quality of life. The study will provide insight into impact of topical treatments on caregiver burden. Subjects will received their assigned topical medication free of charge for the duration of

the study. Subjects will receive reimbursement for their participation in this study (See §5.8 on page 18).

10.4. Alternatives to Participation

Subjects will receive routine standard care with or without participation in this study. Study participation is voluntary. Subjects can are free not to take part or withdraw from the study at any time, for whatever reason.

11. DATA ANALYSES AND MONITORING

11.1. Sample Size Determination

We will accrue 48 patient and caregiver pairs, accounting for 20% withdrawal or dropout rate, to ensure evaluation of 40 patient and caregiver pairs (i.e., 20 per AD patient/caregiver pairs per topical treatment). All statistical tests will be performed at the two-tailed 0.05 level of significance. For an effect size of 5.0 in a population with standard deviation of 10.0, a sample size of 16 will provide 80% power to detect a score change of 4 in the two primary outcome measures. An electronic medical record search for the last year counted 900 patients with the diagnosis of atopic dermatitis between the ages of 1 and 17 years. However, it is unclear how many of these patients have mild or moderate AD. We will enroll a total of 40 evaluable patients and caregivers (i.e., 20 per AD treatment; 80 total participants). Our sample size will all us to detect a change of at least 4 (i.e., clinically significant change) in the itch and pain PROs between baseline and 12 weeks of treatment. Subjects that complete at least the 6 week assessment will be considered evaluable. In this study, the superiority of crisaborole is not dependent on the clinical change (EASI); superiority is dependent on significant changes in PROs and their potential correlation with EASI. Therefore, crisaborole would be superior to tacrolimus if crisaborole improves PROs (and/or caregiver burden), but its clinical effectiveness (EASI) is not statistically significantly different than tacrolimus.

11.2. Planned Statistical Analyses

All statistical analyses will be performed at a two-tailed 0.05 level of significance. Descriptive statistics will be performed using the demographic information (i.e., gender, age, race, ethnicity, disease severity) to characterize the patient and caregiver population at baseline. Descriptive statistics will also be utilized to identify PROs most affected by AD and the extent of caregiver burden related to AD. Primary analyses will use ANCOVA, correlative analyses, and regression analyses to identify significant changes in itch or pain interference from baseline to 12 weeks (Baseline Assessment to Treatment Assessment #2). Longitudinal analyses will be performed to examine changes in itch and pain interference over time. Additionally, we will determine the association between itch and pain interference at baseline and over time. Furthermore, we will correlate change in severity of itch and pain interference with change in %BSA of treatable AD. Two-tailed t-tests will compare changes in itch and pain interference between crisaborole and tacrolimus. Secondary and tertiary analyses will employ similar statistical methodology as the primary analyses but to anxiety, depression, sleep, quality of life, and caregiver burden.

11.3. Data Safety Monitoring Plan

[redacted]. Approval of protocol, informed consent procedures, and recruitment will be obtained from the IRB. Because this study's procedures pose relatively low risk to subjects, monthly data and procedural reviews by the Clinical Monitor and Investigator in consultation with study personnel will be sufficient to identify and ameliorate any potential safety issues. Any safety concerns about the clinical protocol will be brought to the immediate attention of the Principal Investigator and Co-Principal Investigator. Study personnel will follow aforementioned reporting procedures for adverse event reporting, including any serious adverse events. Protocol deviations and quality issues will be recorded and reported to the IRB per local policies. Remedial and/or corrective action to prevent reoccurrence of protocol deviations or quality issues will be instituted as necessary.

12. DATA HANDLING, CONFIDENTIALITY, AND STORAGE

All research data are specifically used for only research purposes and will not contain any personal identifiers. All written materials will be kept confidential, locked in the private office of the research coordinator and identified only by Subject Pair IDs (i.e., numbers) and initials. All data will be stored in a locked office in a locked cabinet and/or on a password-protected computer in a locked office. Results of the research may be presented at meetings or published for scientific purposes, but subject identification information will not be used. All of the forms listed below will be used in this study:

- Screening Log
- Study Reimbursement Form
- Pediatric Reimbursement Form
- W9 Form
- Withdrawal Form
- Call Log
- Comprehensive Study Log
- ASPIRE On-Study Form
- Assessment Form
- Patient PROs (PROMIS Itch, Pain Interference, Anxiety, Depression, CDLQI, CSHQ)
- Caregiver PROs (FDLQI, CBI)
- AD Flare Medication Form
- AE Source Doc
- Pfizer SAE Form & Cover Sheet
- Drug Accountability Record

Majority of forms will be completed electronically. The Call Log and Comprehensive Study Log are password-protected excel files only accessible by study personnel and will be stored in the study folder on the secure Dermatology CTU's sharedrive (i.e., smd drive). All other study forms will be electronic forms completed using REDCap. The patient and caregiver PROs will be completed via iPad and electronically stored in REDCap. All forms will be available in pdf format for completion on paper in case there are any issues with the electronic forms. Forms completed on paper will be kept confidential, locked in the private office of the research coordinator or the study PI.

Data Storage: All measures completed on the iPad will be electronically stored in REDCap database at the [redacted] and assigned study personnel using their University-specific login and password. All completed paper questionnaires will be stored in study folders in a locked cabinet in [redacted] All paper questionnaire data will be electronically entered into the RedCap database using a electronic data collection form. All forms will be coded by Subject Pair ID and Initials. The coding key will be stored electronically on the password-protected, encrypted, desktop computer connected to the University's secure server in [redacted]. The coding key will be stored for the length of the study and then permanently deleted at the completion of the study.

Data Monitoring: The REDCap database will be audited monthly to ensure accurate data collection and entry. No subject identifying data will be used. All of the written material will be kept confidential, locked in the private office of the principal investigator and identified only by Subject Pair ID. At completion of the whole study (including final analyses), all paper forms will be destroyed.

Data Storage and Confidentiality: All data for this study is electronic and will be stored in the secure, study-specific, password-protected REDCap database or on the secure [redacted] All paper documents will be stored in a locked file cabinet in [redacted]. Study personnel will have access to the study data. Statistical analyses will be performed on de-identified dataset containing Subject Pair IDs.

13. SCHEDULE OF EVENTS AND DATA COLLECTION

Study Procedures	Screening	Baseline Assessment	3 Week	6 Week Assessment	9 Week	12 Week Assessment
Eligibility Checklist[1]	X	X				
Assent and Informed Consent[2]	X	X				

Randomization[3]	X	X				
Screening Log	X					
Comprehensive Study Log	Completed as needed throughout the study.					
Reimbursement Form/W9[3]	X	X				
ASPIRE On-Study Log[3]	X	X				
Drug Accountability Record		X				
Assessment Form:						
ISGA		X		X		X
EASI		X		X		X
%BSA		X		X		X
AD Patient PROs:						
PROMIS Itch		X		X		X
PROMIS Pain Interference		X		X		X
PROMIS Anxiety		X		X		X
PROMIS Depression		X		X		X
CDLQI		X		X		X
CSHQ		X		X		X
Caregiver PROs:						
CBI		X		X		X
FDLQI		X		X		X
AD Flare Medication Form		Completed as necessary during study.				
AE Monitoring			X	X	X	X
Call Log			X	X	X	X
AE Source Doc		Completed as necessary during study.				
Pfizer SAE Form/Cover Sheet		Completed as necessary during study.				
Withdrawal Form		Completed as necessary during study.				
Pediatric Subject Reimbursement Form/$10 Gift Card		X[4]		X[4]		X[4]
Request For Payment (RFP) for Caregiver Reimbursement		Completed at completion of study procedures and/or subject participation				

[1]Eligibility checklist can be completed before or at the Baseline Assessment.
[2]Assent and consent can be obtained prior to Baseline Assessment.
[3]Completed after assent and consent are obtained and can be same visit as assent and consent.
[4]Pediatric subject reimbursed with gift card at completion of study visit. Subjects must complete and sign the Pediatric Reimbursement Form at each visit to receive the $10 gift card

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