Steroid-reducing Effects of Crisaborole
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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Atopic dermatitis (AD) is a chronic skin disease and a common affliction among children. Crisaborole is the newest topical prescription agent approved for treatment of AD in patients aged 2 and older. Crisaborole is a phosphodiesterase-4 inhibitor, while existing topical options for AD include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). Side effects associated with TCS as well as steroid phobia limits their use by patients and especially their parents. The black box warning associated with TCIs makes these agents less than ideal as a steroid-reducing option. We propose that crisaborole reduces TCS usage in patients with AD. Evidence to support this hypothesis would greatly benefit AD patients, their parents, and their providers who are seeking a new TCS-reducing option in the chronic management of AD.

2. Objectives (include all primary and secondary objectives)

The primary objective is to demonstrate that crisaborole reduces topical steroid use in patients with AD. Control group is expected to have greater use of TCS compared to vehicle and crisaborole groups. Vehicle group is expected to have greater use of TCS compared to crisaborole group.

The secondary objective is to demonstrate that patients with AD who use crisaborole in conjunction with TCS and Aquaphor will have greater improvement in AD and quality of life, compared with vehicle and control groups.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Atopic dermatitis (AD) is a chronic skin disease and a common affliction among children. Twice daily topical corticosteroid (TCS) use over several weeks is recommended for active inflammatory disease. Side effects of TCS range from cutaneous atrophy to hypothalamic-pituitary-adrenal axis suppression (Eichenfield 2014). Steroid phobia and misunderstanding often lead to poor compliance and inadequate disease control (Patel 2017). Topical calcineurin inhibitors (TCIs) are currently recommended as steroid-reducing agents, especially on sensitive areas such as the face and skin folds. However, they are associated with burning reactions and come with black box warnings (Eichenfield 2014).

Crisaborole (Eucrisa, manufactured by Pfizer), the newest topical prescription option for AD, is a phosphodiesterase-4 inhibitor with demonstrated efficacy in patients aged 2 and older with mild to moderate AD (Paller 2016). Given the good tolerability and favorable safety profile, crisaborole makes for an excellent alternative topical option to its predecessors. However, corresponding data are lacking. It would be of great interest to patients, patients' families and providers if crisaborole

can be shown to reduce the amount of TCS necessary for control of AD. We therefore propose a proof-of-concept study to investigate whether crisaborole can serve as an effective steroid-reducing agent.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

We propose a proof-of-concept study featuring a randomized, controlled, double-blind prospective design to be conducted at a single academic center. The study will include 60 children. Patients of pediatric dermatologists at Johns Hopkins will be recruited for this study. Informed consent will be obtained from parents/guardians.

If patients are already using TCIs, they will not be excluded from the study. However, they must discontinue TCI use for a wash out period of 2 weeks prior to start of study and will be instructed to not use TCIs during the study period. If patients experience local complications of AD such as secondary skin infections, they will not be removed from the study but rather be treated for the infection according to standard of care by their pediatric dermatologist.

Day 0 corresponds to day of enrollment. Baseline photographs will be obtained (without showing the face or other identifying features). Baseline SCORAD scores (SCORing Atopic Dermatitis [1993]) and pruritus Numerical Rating Scale scores (NRS [Phan 2012]) will be obtained for all enrolled children in the study on Day 0. Evaluation will be performed by a blinded clinician. Quality of life will also be evaluated using Children's Dermatology Life Quality Index (CDLQI [Lewis-Jones 1995]) or Dermatology Life Quality Index (DLQI [Finlay 1994]), depending on patient age, and DFI (Dermatitis Family Impact Questionnaire [Lawson 1998]) at baseline. Patients' guardians will also be provided with a diary, with which they will keep track of how often they apply each topical agent.

Children will be randomly assigned to crisaborole group (crisaborole [blinded] and TCS plus Aquaphor), vehicle group (vehicle [blinded] and TCS plus Aquaphor), or control group (Aquaphor [blinded] and TCS plus Aquaphor). Parents and children will be blinded with regard to their assignments.

In the crisaborole group, the parents will be provided with crisaborole (with unidentifiable packaging) with refills as needed. As for TCS, triamcinolone acetonide 0.1% ointment and hydrocortisone 2.5% ointment will be provided, with refills as needed. Aquaphor is to be applied for maintenance. Crisaborole will be used as the first-line agent for AD lesions. TCS will be used as the second-line agent for AD lesions. See Table 1.

In the vehicle group, parents will be provided vehicle (non-medicated ointment) with unidentifiable packaging, with refills as needed. They will also have triamcinolone acetonide 0.1% ointment and hydrocortisone 2.5% ointment provided, with refills as needed. They will be provided identical instructions to the crisaborole group with regard to usage of the vehicle and TCS. See Table 1.

In the control group, parent(s) will be provided control (Aquaphor) in unidentifiable packaging, with refills as needed. They will also be provided triamcinolone acetonide 0.1% ointment and hydrocortisone 2.5% ointment, with refills as needed. They will be given identical instructions to the crisaborole and vehicle groups with regard to usage of TCS.

Severity of affected area	**Instruction for patient and parents**
Clear (no scratching, no redness, no raised skin)	Apply Aquaphor twice daily.
Mild (occasional scratching, mild redness, slightly	Apply crisaborole* twice daily as needed until

raised skin)	improved from mild to clear.
Moderate (frequent scratching, significant redness, significantly raised skin)	Apply TCS** twice daily as needed until improved from moderate to mild.

Table 1. *Crisaborole is replaced by vehicle in the vehicle group and by Aquaphor in the control group. **Low-potency TCS, hydrocortisone 2.5% ointment, is to be used for moderate AD lesions on sensitive areas such as face, axillae, groin. Mid-potency TCS, triamcinolone acetonide 0.1% ointment, is to be used for moderate AD lesions elsewhere on the body.

1 week after the initial visit and study enrollment, parent(s)/guardian(s) of the patient will receive a phone call confirming that they understand the instructions for usage of topicals.

For patients using TCI at baseline, day 0 will be after patients have undergone a 2 week wash out period from TCI.

30 days counted from Day 0 (D30 +up to 10 days depending on patient and family's scheduling convenience), a blinded clinician will repeat the assessments of AD severity, pruritus, and quality of life using EASI, pruritus NRS, CDLQI or DLQI, and DFI. Parents will be instructed to bring all vehicle, crisaborole, and TCS tubes that they have used during the study period. The remaining amount will be weighed and the grams of product will be recorded. Their diaries will also be collected. The number of refills requested for TCS and crisaborole/vehicle will be recorded. Photographs will be obtained.

The same protocol as the D30 visit will be conducted at 90 days (+up to 10 days) counted from Day 0.

Routine care for AD consists of regular moisturizer use (such as Aquaphor) and TCS application for mild to moderately affected areas. Use of crisaborole for mild to moderate AD lesions is also routine AD care.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

b. Study duration and number of study visits required of research participants.

Study duration will be 90 days from day of enrollment (+2 weeks if wash out period from TCI is required). 3 study visits (Day 0, day 30, day 90) will be required of research participants.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants, their parents, and clinicians performing assessments will be blinded during this study. The participant's assignment to control versus vehicle versus crisaborole group will be the subject of blinding. Participants will be provided with unlabeled tubes of a topical agent which may be Aquaphor, vehicle, versus crisaborole.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Regular use of a bland moisturizer such as Aquaphor and TCS / TCI use for inflamed areas of AD are standard of care for AD management. However, patients who are currently using TCI such as tacrolimus or pimecrolimus will have to discontinue use of these agents in a 2 week wash-out period. This is because in assessing whether crisaborole reduces TCS use, participants should not be applying an additional non-steroid topical medication such as TCIs.

e. Justification for inclusion of a placebo or non-treatment group.

We will have a control group where participants will be using TCS, Aquaphor, and a blinded control (Aquaphor) to manage their AD. We will also have a vehicle group where participants will be using TCS, Aquaphor, and vehicle (for crisaborole) to manage their AD. While these groups are considered placebo / non-treatment groups since crisaborole is not used, the treatment regimen still falls within standard of care for AD which consists of regular moisturizer use (such as Aquaphor) and TCS use for affected areas.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed if they are unable to follow up for return visits as required in the study or if they are unable to follow the instructions provided at the start of the study. If a participant becomes pregnant they will be removed from the study.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

When the study ends or if a participant is prematurely removed from the study, the participant should continue to follow up with their regular dermatologist and manage their AD as instructed by their dermatologist.

5. Inclusion/Exclusion Criteria

Inclusion criteria:
1. Children aged 2 or older (<18).
2. Diagnosed with atopic dermatitis.
3. At baseline, AD is mild to moderate (score of 2 [mild] to 3 [moderate]) on the Investigator's Global Assessment scale (IGA; scores range 0-4, higher indicates greater severity).

Exclusion criteria:
1. Known allergy to a constituent of the studied products (crisaborole, vehicle, Aquaphor, topical steroids [hydrocortisone 2.5% ointment and triamcinolone acetonide 0.1% ointment]).
2. At baseline, AD is severe (score of 4 [severe] on the IGA scale).
3. Medical problems which interfere with completion of protocols in this study.
4. Pregnant or lactating females. (Females who have experienced menarche will be required to take a urine pregnancy test.)
5. Participant is enrolled in another research study.
6. Participant or their guardian(s) are unable to follow instructions as required in this study.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Crisaborole is chosen because it is the newest non-steroid FDA-approved prescription topical medication for treatment of mild to moderate AD in children 2 years of age and older. The FDA-approved dosage is application of a thin layer twice daily to affected areas.

Crisaborole vehicle is chosen because this contains only the inactive ingredients found in crisaborole, to serve as placebo.

Aquaphor is chosen because this is a skin moisturizer which is routinely used by patients with AD.

Hydrocortisone and triamcinolone are chosen because these are commonly prescribed topical steroids for treatment of mild to moderate AD in children 2 years of age and older. Hydrocortisone is a low-potency topical steroid, and triamcinolone is a mid-potency topical steroid. The FDA-approved dosage for hydrocortisone and triamcinolone is application of a thin layer twice daily to affected areas.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A.

7. Study Statistics

a. Primary outcome variable.

Primary outcome variable is quantity of TCS use. TCS use will be quantified in number of refills requested, amount of medication remaining by weight (D90 compared with D0 and D30), and frequency based on usage diaries completed by participants and or their parents.

b. Secondary outcome variables.

Secondary outcome variables include improvement in AD as measured in severity, pruritus, and quality of life (SCORAD, pruritus NRS, CDLQI/DLQI, DFI), recorded over the duration of the study (D0, D30, D90). A blinded investigator will review photographs obtained at Day 0, 30, 90 to determine whether AD has improved, worsened, or stayed the same during the study.

c. Statistical plan including sample size justification and interim data analysis.

This is a proof-of-concept study and therefore the sample size is small (n=60 total, 20 participants in each group).

d. Early stopping rules.

N/A. This study poses minimal risks to participants.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Crisaborole is associated with application site pain in 4% of patients. Hypersensitivity reactions and urticaria secondary to crisaborole occur in less than 1% of patients (UpToDate, crisaborole).

Adverse reactions to TCS include (frequency not defined for the following): localized burning, acneiform eruption, allergic contact dermatitis, atrophic striae, folliculitis, hypertrichosis, hypopigmentation, maceration of the skin, miliaria, perioral dermatitis, pruritus, secondary skin infection, skin atrophy, xeroderma, HPA-axis suppression, hyperglycemia, hypokalemia, local irritation (UpToDate, triamcinolone).

There is risk of allergic reaction or irritation from vehicle and Aquaphor products used in the study.

In females who have experienced menarche, urine pregnancy testing may be stressful and inconvenient for the participant and guardian. There is risk of participant and their guardian finding out that the participant is pregnant.

Participants may find photographs and skin exams stressful. There is risk of loss of confidentiality with regard to the photographs. No identifiable features will be included in photographs.

Participants and their guardians may experience fatigue or boredom from questionnaires.

b. Steps taken to minimize the risks.

Risks are minimized through our inclusion and exclusion criteria. Only participants with mild to moderate AD will be included, such that limited amounts of topical medication (crisaborole, TCS, vehicle / Aquaphor) will be required for disease management. Hence risk of systemic absorption will be minimal. Participants who experience significant adverse reactions such as allergy to a studied agent will be removed from the study. No identifiable features will be included in photographs. Participants / guardians can leave questionnaires incomplete if they would rather not complete them. Participants / guardians can decline photographs and or skin exams.

c. Plan for reporting unanticipated problems or study deviations.

Any clinical findings determined by the Investigator to be important and/or unusual will be referred to as an adverse event (AE). Study participants' parents are asked to contact research staff immediately if they experience an adverse reaction at any time during the study. These will be documented in a problem events log. The Investigator will use their discretion to remove participants from the study, and all problem events will be reported to IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are minimal risks in terms of confidentiality. All study participant information will be de-identified. Any photographs which are obtained will be such that no identifying features (e.g. face) are captured. Since this is a pilot study, no confidential or protected information would be taken outside of the standard.

e. Financial risks to the participants.

There is very low financial risk to the participants in the rare event that complications occur requiring additional medical care for which the financial reimbursement from participation in the study is insufficient.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants will benefit from free medication and close monitoring of their AD. It would be of great interest to AD patients, patients' families and providers if crisaborole can be shown to reduce the amount of TCS used for AD. TCS has multiple adverse effects, and steroid phobia limits compliance, resulting in inadequate control of AD.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

$18 for parking costs across 3 study visits. $100 for D0 visit. $100 for D30 visit. $100 for D90 visit. $100 bonus for study completion. ($418 total)

Participants will not receive compensation for visits they have not completed. If they do not follow instructions appropriately for a visit (such as neglecting to bring medication or diary entries) the compensation will be reduced by 50% for the visit.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

We will provide participants with Aquaphor, TCS, and crisaborole / vehicle / control (Aquaphor). We will also reimburse participants for their visits. Funding is provided by Pfizer. Pfizer will also provide us with crisaborole and vehicle.

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