Quantification Of Improvement In Scratch Behavior And Sleep In Patients With Atopic Dermatitis On Crisaborole Ointment, 2%

NCT05200403

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Statistical Analysis Plan pages 22-24

LIST OF ABBREVIATIONS

Abbreviation	Abbreviation definition
AD	Atopic Dermatitis
AE	Adverse Event
BID	Bis in die (twice daily)
BISQ	Brief Infant Sleep Questionnaire
BSA	Body Surface Area
BU/BUMC	Boston University/Boston University Medical Center
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CSHQ	Children's Sleep Health Questionnaire
CSV	Comma Separated Values
DCQ	Device Comfort Questionnaire
DFIQ	Dermatitis Family Impact Questionnaire
DHT	Digital Health Technologies
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EDC	Electronic Data Capture
FLACC	Faces, Legs, Activity, Cry, Consolability Scale
GCP	Good Clinical Practice
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonization
IDQOL	Infants Dermatitis Quality of Life Index
ISGA	Investigator's Static Global Assessment
LS	Least-squares
MDPQ	Mobile Device Proficiency Questionnaire
MOS	Medical Outcomes Study
ObsRO	Observer Reported Outcome
ODCQ	Observer Device Comfort Questionnaire
OGIC	Observer Global Impression of Change
OGIS	Observer Global Impression of Severity
ORIA	Observer Reported Itch Assessment
PDE-4	Phosphodiesterase-4
POEM	Observer-reported Patient Oriented Eczema Measure
PPNRS	Peak Pruritis Numerical Rating Scale
PRO(s)	Patient Reported Outcome(s)
QoL	Quality of Life
R, L	Right, Left
RRI	Research Related Injury
TCI	Target Controlled Infusion
V01, V02, V03, V04, V05	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5
WASO	Wake After Sleep Onset
WRAT-4	Wide Range Achievement Test 4

Background

Atopic Dermatitis (AD) is one of the most common, chronic, relapsing childhood dermatoses, impacting up to 36% of children worldwide and many have disease that persists into adulthood (Abuabara et al., 2018). It is a condition that not only leads to red inflamed skin, but also is characterized by extensive pruritus/itch, scratching and sleep disturbances. It is stated by patients that the most problematic symptom of AD is pruritus.[1]

While approximately 10-41% of children [3,4] and 7-48% of adults [5,6] experience sleep disturbances, these numbers climb substantially in people with AD (47-80% in children and 33-87.1% in adults).[7] The physical action of scratching can disrupt sleep itself, but also triggers cognitive and behavioral changes that trigger and reinforce insomnia and sleep disruptions.[8] These sleep disturbances impact the QoL of not only the person with the condition but also caregivers and family members. Sleep disturbances can also result in impaired performances on neurobehavioral tasks, hyperactivity/inattention, stunted growth (children), missed workdays, poorer overall health and behavioral and emotional disturbances (including increasing scratching).[8] Measurements of itch, though of significant value, are currently accomplished through subjective methods such as questionnaires and intensity scales (Erickson & Kim, 2019; Hjermstad et al., 2011). This poses several limitations in infants and children where the parents answer the questionnaires on behalf of their children, and recall of itch and scratch during the night can be limited (Erickson & Kim, 2019). Thus, there is a great need to objectively understand and characterize itch and scratch. Objective measurements of sleep disturbances and nocturnal scratch have been employed using wearable sensors such as accelerometers (Mahadevan et al., 2021). Previous studies have used actigraphy and accelerometry to assess sleep and scratch in infants (Pitchford et al., 2017; Wootton et al., 2012).

Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor and was developed as a topical treatment for patients with mild-to-moderate AD. It is currently approved for treatment of mild to moderate AD in patients 3 months of age and older in US, Canada, Argentina, Lebanon, Taiwan, Oman and UAE (and above 2 years in other countries.) While crisaborole is a topical treatment specifically designed to address mild to moderate AD symptoms, it is hypothesized that the reduction in symptomatology in this condition may afford lessening of sleep disturbances as a result of symptom reduction. In clinical trials comparing crisaborole and the vehicle, a strong "vehicle effect" has been observed. For instance, in a phase III AD study (AD-301: NCT02118766), 40.6% of the patients in the vehicle group achieved an ISGA score of clear (0) or almost clear (1) in comparison to the 51.7% of those with crisaborole (Paller et al., 2016). It has been noted, that emollients (such as the vehicle) have protective benefits by improving the skin barrier (Arkwright et al., 2013). In addition, children and adolescent in two-arm clinical trials have reported improvement in their QoL; Of the Vehicle-treated patients, 64.9% reported that their AD had "small effect" to "no effect" on their QoL in comparison to 75.5% of crisaborole-treated patients (Simpson et al., 2018).

Rationale

This study will specifically evaluate the rapid onset of itch and night-time scratch relief, improvement in sleep (both in the participant and their primary caregiver) and improvement in AD-inflammatory markers following crisaborole therapy twice daily (2% BID). To evaluate this experimental paradigm, we propose using wearable Digital Health Technologies (DHT), traditional patient-reported outcome (PRO)/observer-reported outcome (ObsRO) measures, tape stripping biomarker assessment, and physician assessments of AD in a well-controlled study in-laboratory and home measures within the study.

Primary Objective:

1. Evaluate the effects of Crisaborole on itch and night-time scratch (as measured by accelerometry/actigraphy and Observer Reported Itch Assessment (3 months - ≤ 11 years old) in children with mild to moderate AD between the ages of 3 months to ≤ 11 years old.

Secondary Objectives:

1. Evaluate the effects of Crisaborole on sleep in children ages 3 months to ≤ 11 years with mild to moderate AD.
2. Evaluate sleep in primary caregivers.
3. Evaluate the QoL measures in response to Crisaborole treatment (children 3 months to ≤ 11 years).
4. Evaluate QoL measures in response to the child's treatment, to the parents/caregivers/families.
5. Evaluate the effect of crisaborole treatment on AD signs, symptoms and severity in children ages 3 months to ≤ 11 years with mild to moderate AD.

Exploratory Objectives:

1. Evaluate changes in skin biomarkers in response to Crisaborole treatment in children ages 3 months to ≤ 11 years with mild to moderate AD.
2. Evaluate changes in Digital Health Technologies to assess movement and agitation in children (aged 3 months to ≤ 11 years) in response to crisaborole treatment.
3. Evaluate the participant burden and compliance of use of the devices.
4. Evaluate the agreement between ORIA and Patient Reported Itch Severity Scale in children between the ages of 6 to ≤ 11 years old

Endpoints:

Final experimental report and a copy of all data, including these endpoints will be provided at the completion of the study:

Primary Endpoint:

- Daily night-time scratch (Number of scratching episodes, Duration of scratching) as measured by the accelerometry/actigraphy (devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment) and the Observer Reported Itch Assessment (ORIA; 3 months - ≤ 11 years old) for the AD infant and child population.

Secondary Endpoints:

- Sleep:
    - Nighttime Sleep Quantity (as measured by accelerometry/actigraphy; Children ages 3 months to ≤ 11 years and Caregivers ages 18-75 years; devices will be optional for children participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment)
        - Total Sleep Opportunity
        - Total sleep time
        - Percent time asleep
        - Wake after sleep onset (WASO)
        - Sleep onset latency
        - Arousals from sleep
    - Modified Medical Outcomes Study Sleep Scale (MOS-Sleep; Caregivers- ages 18-75)
    - Children's Sleep Health Questionnaire (CSHQ); ages ≥4-≤ 11 years) OR Brief Infant Sleep Questionnaire (BISQ; ages 3 months-<4 years)

- PRO/ ObsRO
  - Disease Severity:
    - Observer Global Impression of Severity (OGIS)
    - Observer Global Impression of Change (OGIC)
    - Observer-reported Patient Oriented Eczema Measure (POEM)

- HRQoL
  - Dermatitis Family Impact Questionnaire (DFI; Caregivers of participants ages 3 months -≤ 11 years)
  - Children's Dermatology Life Quality Index (CDLQI; participants ages ≥4-≤ 11 years) OR Infants Dermatitis Quality Of Life Index (IDQOL; caregivers of participants ages 3 months-<4 years)

Exploratory Endpoints:

- Device Comfort
  - Device Comfort Questionnaire (Caregivers ages 18-75)
  - Observer Device Comfort Questionnaire (ages 3 months - ≤ 11 years)
- Mobile Device Proficiency Questionnaire (MDPQ; Caregivers ages 18-75)
- Faces, Legs, Activity, Cry, and Consolability Scale (FLACC) (ages 3 months - 5 years)
- Peak Pruritis NRS (Caregivers)
- Patient Reported Itch Severity Scale (6 years – ≤ 11 years old)
- Skin biomarkers (as measured by Tape Stripping)
- Digital Health Technologies -assessed movement and agitation in children as measured by Accelerometry/Actigraphy (ages 3 months- ≤ 11 years)
  - Movement (Accelerometry/actigraphy)
  - Temperature

Study Design

The main objective of this single blind study is to evaluate wearable devices and Observer Reported Itch Assessment in children to assess reduction of itch and night-time scratch in response to Crisaborole treatment vs. vehicle treatment (active control comparator without crisaborole[*]) in children with AD. Participants, age 3 months to ≤ 11 years with symptomatic mild to moderate AD, along with their primary caregivers will be recruited and assessed by observed scratch behavior captured from accelerometry/actigraphy.

Approximately 270 children, age 3 months to ≤ 11 years, and their primary caregiver as participants, for a total of 540 participants (270 pairs), will be randomized in 1:1 ratio to either Crisaborole (2% BID) or vehicle treatment and will be followed for 2 weeks, with an objective of approximately 50% of recruited child participants being ages 5 years old or younger. For this study, we will employ a simple randomization procedure. Participants will be randomly assigned (1:1) using computerized random numbers to receive either crisaborole or the vehicle. The participants will be asked to apply a thin even-

[*]An active control comparator in clinical trials "refers to the group of participants in a clinical trial who receive a treatment that is considered effective and most often currently used in clinical care" (U.S. Department of Health and Human Services, (n.d.)). This is further supported by, "the significant efficacy of crisaborole versus vehicle was noted, despite a strong "vehicle effect" observed in these studies, which is a common phenomenon in AD clinical studies that compare active therapeutics with their emollient bases" (Paller et al., 2016).

layer of Crisaborole (2% BID) or vehicle twice daily (excluding mouth, eyes, and vagina, per label), to all locations with active lesions and record location and time of application on the daily dosing form (as identified on the Dosing Record Sheet, breastfeeding women will be instructed to use the provided gloves when applying crisabrole/vehicle). The study will be comprised of an initial screening/baseline visit for children participants who have an existing diagnosis of symptomatic AD, screened and enrolled in the study along with their primary caregivers after signing an informed consent (or parents/guardians and assent when appropriate). Upon enrollment child participants and caregiver participants will complete a one week acclimation and training phase, where the children will not be on medication, for wearing accelerometry/actigraphy and performing observer-reported outcome assessments (caregivers for participants) and self-reported outcome assessments (caregivers). After the one week acclimation and training phase, the child participants will be on a Crisaborole or vehicle treatment for two consecutive weeks. During those 2 weeks, the children, 3 months up to <2 years will wear one actigraphy or one accelerometry device on each wrist and one actigraphy or one accelerometry device on each ankle (optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment). Children 2 years to ≤ 11 years will wear one actigraphy or one accelerometry on each wrist (optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment). The primary caregiver (parents/guardians) will also wear one accelerometer device on each wrist and complete daily assessments related to scratching, sleeping habits, pain, AD severity, quality of life, and device comfort questionnaires (parent/guardian will complete as appropriate). The participants will be asked to return to the laboratory on days 1, 2, 8, and 15 for assessments and biomarker assessment. At the completion of the study, Day 15 (±3 day) participants (and primary caregiver) will return the devices, and will complete additional questionnaires. Participants may come in for an unscheduled visit as needed (i.e., to replace compound, etc.). During the performance of the study, participants will be monitored by the study dermatologist, and assess participant continuation throughout the study.

The goal of this study is to more fully evaluate the rapid onset of night-time itch and scratch relief following treatment with Crisaborole in comparison to vehicle treatment in children with AD. Moreover, this study will assess the QoL and sleep within the associated caregivers.

Significance

Itch, night-time scratch and sleep are key symptoms experienced by patients with AD and impact not only the patient but the families of the patients with AD, particularly for young age children. Therefore, more fully understanding the cessation of the feeling of itch, action of scratch and improvements in sleep following treatment of Crisaborole (2% BID) would provide additional insight to the treatment profile. This study will specifically evaluate the rapid onset of itch and night-time scratch relief, improvement in sleep (both in the participant and their primary caregiver) and improvement in AD-inflammatory markers following crisaborole therapy twice daily (2% BID) in children 3 months to ≤ 11 years old.

This study will also provide critical understanding of the ability of the accelerometry/actigraphy devices to measure drug-induced changes in scratching, movement and sleep quantity in children with symptomatic AD and quality of life in caregivers. It will also provide a physiological comparator for PRO/ObsRO assessments and ultimately enhance understanding of AD.

SCHEDULE OF ACTIVITIES

Period/Visit	Screening	V01 (Baseline)	V02	V03	V04	V05
Day	**-28 to -7**	**-7**	**1**	**2**	**8**	**15**
Window(days)	**NA**	**+/- 3**	**+/- 3**	**+ 0.5**	**+/- 3**	**+/- 3**
ENROLLMENT PROCEDURES						
Informed consent / assent	X	X				
Demographics, medical history including AD history/treatment	X	X				
Inclusion and exclusion criteria Review (both child and caregiver)	X					
Inclusion and exclusion criteria ‡ (both child and caregiver)		X				
Pregnancy test for female caregivers of child-bearing potential		X				
Wide Range Achievement Test 4 (WRAT-4; caregivers only)		X				
MEDICAL PROCEDURES						
Vital signs		X				
Height and weight		X				
ASSESSMENTS						
Investigator's Static Global Assessment (ISGA) (both child and caregiver at V01, only child thereafter)		X	X		X	X
Eczema Area and Severity Index (EASI)		X	X		X	X
% Body Surface Area (BSA)		X	X		X	X
Childhood Asthma Control Test (ages 4 to ≤ 11 years)		X				
Tape Stripping (Biomarker Assessment)**		X		X		X
PATIENT REPORTED/OBSERVER-REPORTED OUTCOMES (PROs/ObsROs)						
Observer Reported Itch Assessment (ORIA; 3 months - ≤ 11 years old)		X	------DAILY (Day 1-15 AH)----			X
Patient Reported Itch Severity Scale (6 years - ≤ 11 years old)		X	------DAILY (Day 1-15 AH)----			X
Observer Global Impression of Severity (OGIS)		X	------DAILY (Day 1-15 AH)----			X
PPNRS Caregivers		X	------DAILY (Day 1-15 AH)----			X
Sleep:CSHQ (Age ≥4 - ≤ 11 years)/BISQ(Age 3 months - <4 years)/MOS-Sleep (Caregivers)		X	X		X	X
Observer Global Impression of Change (OGIC)					X	X
Device Comfort Questionnaire (DCQ)/Observer Device Comfort Questionnaire (ODCQ)						X
Mobile Device Proficiency Questionnaire (MDPQ)		X				
Faces, Legs, Activity, Cry, and Consolability Scale (FLACC)		X	X		X	X
Dermatitis Family Impact Questionnaire (DFI)		X	X		X	X
Children's Dermatology Life Quality Index (CDLQI) (Age ≥4 to ≤ 11 years) OR Infants Dermatitis Quality of Life Index (IDQOL) (Age 3 months to <4 years)		X	X		X	X
Patient-Oriented Eczema Scale (POEM) (observer-reported for participants age 3 months-11 years)		X	X		X	X
SAFETY						
Serious and non-serious AE monitoring	X	X ---------- X				
STUDY INTERVENTION						
In-laboratory dose application training			X		X	
At home dosing and dosing record sheet (twice daily)			---------- DAILY ----------			
Drug dispensing			X			
DIGITAL HEALTH TECHNOLOGIES °						
Issue/Train/Retrieve Accelerometry Device; (Children: Ages 2 years to ≤ 11 years; On R & L wrists); (Caregivers: Ages 18 to 75 years; On R & L wrists)****		X Issue			X Retrieve, Re-Issue	X Retrieve
Accelerometry Wear (Children: Ages 2 years to ≤ 11 years; On R & L wrists); Caregivers: Ages 18 to 75 years; On R & L wrists) ****		X ---------- X				
Issue/Train/Retrieve actigraphy or accelerometry (Ages 3 months up to <2 years; On R & L wrists and R & L ankles); (Ages 2 years to ≤ 11 years; On R & L wrists) ****		X Issue				X Retrieve
Actigraphy or accelerometry Wear/Measures Collected (Ages 3 months up to <2 years; On R & L wrists and R & L ankles); (Ages 2 years to ≤ 11 years; On R & L wrists) ****		X ---------- X				

Period/Visit	Screening	V01 (Baseline)	V02	V03	V04	V05
Day	-28 to -7	-7	1	2	8	15
Window(days)	NA	+/- 3	+/- 3	+ 0.5	+/- 3	+/- 3

*per AD = atopic dermatitis; AE= adverse event; BISQ= Brief Infant Sleep Questionnaire; CSHQ= Children's Sleep Health Questionnaire; L= Left; MOS= Medical Outcomes Study; R= Right; V=Visit number; AH = At Home
‡ Participants are randomly assigned to one of the two arms of the study
** Nonlesional tape strips will be collected from an area of skin that is unaffected by atopic dermatitis at the baseline visit (V01). Lesional tape strips will be collected from skin adjacent to an atopic dermatitis lesion at the baseline visit (V01) and on Day 2 (V03) and Day 15 (V05).
° See Appendix for figure
***Participants may come in for an unscheduled visit as needed (i.e., to replace compound or vehicle, etc.)
****Devices will be optional for children participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment

1. INTRODUCTION OF RATIONALE

Atopic Dermatitis (AD) is one of the most common, chronic, relapsing childhood dermatoses, impacting up to 36% of children worldwide and many have disease that persists into adulthood (Abuabara et al., 2018). It is a condition that not only leads to red inflamed skin, but also is characterized by extensive pruritus/itch, scratching and sleep disturbances. It is stated by patients that the most problematic symptom of AD is pruritus.[1]

While approximately 10-41% of children [3,4] and 7-48% of adults [5,6] experience sleep disturbances, these numbers climb substantially in people with AD (47-80% in children and 33-87.1% in adults).[7] The physical action of scratching can disrupt sleep itself, but also triggers cognitive and behavioral changes that trigger and reinforce insomnia and sleep disruptions.[8] These sleep disturbances impact the QoL of not only the person with the condition but also caregivers and family members. Sleep disturbances can also result in impaired performances on neurobehavioral tasks, hyperactivity/inattention, stunted growth (children), missed workdays, poorer overall health and behavioral and emotional disturbances (including increasing scratching).[8] Measurements of itch, though of significant value, are currently accomplished through subjective methods such as questionnaires and intensity scales (Erickson & Kim, 2019; Hjermstad et al., 2011). This poses several limitations in infants and children where the parents answer the questionnaires on behalf of their children, and recall of itch and scratch during the night can be limited (Erickson & Kim, 2019). Thus, there is a great need to objectively understand and characterize itch and scratch.Objective measurements of sleep disturbances and nocturnal scratch have been employed using wearable sensors such as accelerometers (Mahadevan et al., 2021). Previous studies have used actigraphy and accelerometry to assess sleep and scratch in infants (Pitchford et al., 2017; Wootton et al., 2012).

Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor and was developed as a topical treatment for patients with mild-to-moderate AD. It is currently approved for use in patients 3 months of age and older in US, Canada, Argentina, Lebanon, Taiwan, Oman and UAE (and above 2 years in other countries). In clinical trials comparing crisaborole and the vehicle, a strong "vehicle effect" has been observed. For instance, in a phase III AD study (AD-301: NCT02118766), 40.6% of the patients in the vehicle group achieved an ISGA score of clear (0) or almost clear (1) in comparison to the 51.7% of those with crisaborole (Paller et al., 2016). It has been noted, that emollients (such as the vehicle) have protective benefits by improving the skin barrier (Arkwright et al., 2013). In addition, children and adolescent in two-arm clinical trials have reported improvement in their QoL; Of the Vehicle-treated patients, 64.9% reported that their AD had "small effect" to "no effect" on their QoL in comparison to 75.5% of crisaborole-treated patients (Simpson et al., 2018).

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:

1. Evaluate the effects of Crisaborole on itch and night-time scratch (as measured by accelerometry/actigraphy and Observer Reported Itch Assessment (3 months - ≤ 11 years old) in children with mild to moderate AD between the ages of 3 months to ≤ 11 years old.

Secondary Objectives:

1. Evaluate the effects of Crisaborole on sleep in children ages 3 months to ≤ 11 years with mild to moderate AD.
2. Evaluate sleep in primary caregivers.
3. Evaluate the QoL measures in response to Crisaborole treatment (children 3 months to ≤ 11 years).
4. Evaluate QoL measures in response to the child's treatment, to the parents/caregivers/families.
5. Evaluate the effect of crisaborole treatment on AD signs, symptoms and severity in children ages 3 months to ≤ 11 years with mild to moderate AD.

Exploratory Objectives:

1. Evaluate changes in skin biomarkers in response to Crisaborole treatment in children ages 3 months to ≤ 11 years with mild to moderate AD.
2. Evaluate changes in Digital Health Technologies -assessed movement and agitation in children (aged 3 months to ≤ 11 years) in response to crisaborole treatment.
3. Evaluate the participant burden and compliance of use of the devices.
4. Evaluate the agreement between ORIA and Patient Reported Itch Severity Scale in children between the ages of 6 to ≤ 11 years old

ENDPOINTS

Endpoints:

Final experimental report and a copy of all data, including these endpoints:

Primary Endpoint:

- Daily night-time scratch (Number of scratching episodes, Duration of scratching) as measured by the accelerometry/actigraphy (optional for children participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment) and the Observer Reported Itch Assessment (ORIA; 3 months - ≤ 11 years old) for the AD infant and child population.

Secondary Endpoints:

- Sleep:
    - Nighttime Sleep Quantity (as measured by accelerometry/actigraphy; Children ages 3 months to ≤ 11 years and Caregivers ages 18-75 years; devices will be optional for children participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment)
        - Total Sleep Opportunity
        - Total sleep time
        - Percent time asleep
        - Wake after sleep onset (WASO)
        - Sleep onset latency
        - Arousals from sleep

    - Modified Medical Outcomes Study Sleep Scale (MOS-Sleep; Caregivers- ages 18-75)
    - Children's Sleep Health Questionnaire (CSHQ); ages ≥4-≤ 11 years) OR Brief Infant Sleep Questionnaire (BISQ; ages 3 months-<4 years)

- PRO/ ObsRO
    - Disease Severity:
        - Observer Global Impression of Severity (OGIS)
        - Observer Global Impression of Change (OGIC)
        - Observer-reported Patient Oriented Eczema Measure (POEM)
- HRQoL
    - Dermatitis Family Impact Questionnaire (DFI; Caregivers of participants ages 3 months -≤ 11 years)
    - Children's Dermatology Life Quality Index (CDLQI; participants ages ≥4-≤ 11 years) OR Infants Dermatitis Quality Of Life Index (IDQOL; caregivers of participants ages 3 months-<4 years)

Exploratory Endpoints:

- Device Comfort
    - Device Comfort Questionnaire (Caregivers ages 18-75)
    - Observer Device Comfort Questionnaire (ages 3 months - ≤ 11 years)
- Mobile Device Proficiency Questionnaire (MDPQ; Caregivers ages 18-75)
- Faces, Legs, Activity, Cry, and Consolability Scale (FLACC) (ages 3 months - 5 years)
- Peak Pruritis NRS (Caregivers)
- Patient Reported Itch Severity Scale (6 years – ≤ 11 years old)
- Skin biomarkers (as measured by Tape Stripping)
- Digital Health Technologies -assessed movement and agitation in children as measured by Actigraphy/accelerometry (ages 3 months- ≤ 11 years)
    - Movement (Accelerometry/actigraphy)
    - Temperature

DEVICE ENDPOINTS

GENEActiv Wrist Accelerometry Device (50 Hz sampling rate)

- Accelerometry Raw Data in x, y, and z
- Units of g and collected at 50Hz
- Ambient light level (lux)
- Out of Bed time (hh:mm)
- Wake duration (mins)
- Non wear time (mins)
- Sedentary activity time (mins)
- Light activity time (mins)
- Moderate activity time (mins)
- Vigorous activity time (mins)
- Sedentary activity (%)
- Light activity (%)
- Moderate activity (%)
- Vigorous activity (%)
- Sedentary activity estimated MET.mins

- Light activity estimated MET.mins
- Moderate activity estimated MET.mins
- Vigorous activity estimated MET.mins
- Number of Vigorous periods (> 10 mins)
- Going to bed time (hh:mm)
- Bed duration (mins)
- Total sleep time (mins)
- Sleep efficiency (% total sleep time divided by total time in bed)
- Number of Active periods
- Median activity period (mins)
- Temperature

- Actigraphy Digital Health Technology (ages 3 months - ≤ 11 years)
  - Actigraphy at 25 Hz (X,Y,Z movement)

3. STUDY DESIGN

The main objective of this single blind study is to evaluate wearable devices and Observer Reported Itch Assessment in children to assess reduction of itch and night-time scratch in response to Crisaborole treatment vs. vehicle treatment in children with AD. Participants, age 3 months to ≤ 11 years with symptomatic mild to moderate AD, along with their primary caregivers will be recruited and assessed by observed scratch behavior captured from accelerometry/actigraphy.

Approximately 270 children, age 3 months to ≤ 11 years, and their primary caregiver as participants, for a total of 540 participants (270 pairs), will be randomized in 1:1 ratio to either Crisaborole (2% BID) or vehicle treatment and will be followed for 2 weeks, with an objective of approximately 50% of recruited child participants being ages 5 years old or younger. For this study, we will employ a simple randomization procedure. Participants will be randomly assigned (1:1) using computerized random numbers to receive either crisaborole or the vehicle.The participants will be asked to apply a thin even-layer of Crisaborole 2% or vehicle twice daily (excluding mouth, eyes, and vagina, per label), to all locations with active lesions and record location and time of application on the daily dosing form (as identified on the Dosing Record Sheet, breastfeeding women will be instructed to use the provided gloves when applying crisabrole/vehicle). The study will be comprised of an initial screening/baseline visit for children participants who have an existing diagnosis of symptomatic AD, screened and enrolled in the study along with their primary caregivers after signing an informed consent (or parents/guardians and assent when appropriate). Upon enrollment child participants and caregiver participants will complete a one week acclimation and training phase, where the children will not be on medication, for wearing accelerometry/actigraphy and performing observer-reported outcome assessments (caregivers for participants) and self-reported outcome assessments (caregivers). After the one week acclimation and training phase, the child participants will be on a Crisaborole or vehicle treatment for two consecutive weeks. During those 2 weeks, the children, 3 months up to <2 years will wear one actigraphy or one accelerometry device on each wrist and one actigraphy or one accelerometry device on each ankle (optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment). Children 2 years to ≤ 11 years will wear one actigraphy or one accelerometry device on each wrist (optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment). The primary caregiver (parents/guardians) will also wear one accelerometer device on each wrist and complete daily assessments related to scratching, sleeping habits, pain, AD severity, quality of life, and device comfort questionnaires (parent/guardian will complete as appropriate). The participants will be asked to return to the laboratory

on days 1, 2, 8, and 15 for assessments and biomarker assessment. At the completion of the study, Day 15 (±3 day) participants (and primary caregiver) will return the devices, and will complete additional questionnaires. Participants may come in for an unscheduled visit as needed (i.e., to replace compound, etc.)

The goal of this study is to more fully evaluate the rapid onset of night-time itch and scratch relief following treatment with Crisaborole in comparison to vehicle treatment in children with AD. Moreover, this study will assess the QoL and sleep within the associated caregivers.

4. PARTICIPANT SELECTION

This protocol can fulfill its objectives only if appropriate participants are enrolled. Prior to undergoing any study procedures, a participant must meet this protocol's Inclusion/Exclusion criteria.

4.1. Inclusion Criteria

Both child and caregiver participants must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Children (3 months to ≤ 11 years)

1. Male or female paticipants aged between ≥3 months of age and ≤11 years of age at Day -7.
2. Written informed consent from participant/parent(s)/guardian(s).
3. Native English or demonstrated fluency in English (as age appropriate).
4. Participants and parent(s)/guardian(s) are willing and able to comply with study instructions, study visits, procedures, and device placement (devices will be optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment).
5. Have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka.
6. Have AD involvement ≥ 5% Treatable % Body Surface Area (BSA) excluding the scalp and less than 40% BSA.
7. Have an ISGA score of Mild (2) or Moderate (3) at the baseline visit.
8. Have an EASI total score of ≥3 at Day -7.
9. Have a minimum Observer Reported Itch Assessment score of 2 at Day -7 (ages 3 months - ≤ 5 years only) or a minimum Patient Reported Itch Severity Scale score of 2 (ages 6 years - ≤ 11 years old) at Day -7.
10. Participant/parent(s)/guardian(s) agrees to refrain from applying diaper rash creams, lotions, ointments, powders, etc. where AD lesions are present, unless AD lesions are present where crisaborole cannot be applied (face within 1 or 2 fingers away from the mouth and hands/fingers).
11. Participants must agree to refrain from applying crisaborole/vehicle to AD lesions on the fingers or hands or within 1 or 2 fingers away from the the mouth to prevent inadvertent ingestion of ointment.

Adult Caregiver

1. Primary caregiver of the child participant, between ≥18 years of age and ≤75 years of age.
2. Able to understand and cooperate with study procedures and give informed consent.
3. Native English or demonstrated fluency in English.
4. Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.
5. ISGA score of 0 or 1 of AD at the baseline visit, and no reported diagnosis of Atopic Dermatitis.
6. WRAT-4 Word Reading Subtest equivalent to 8th grade reading level or greater.

4.2. Exclusion Criteria

Participants (either child or caregiver) presenting with any of the following will not be included in the study:

Children (3 months to ≤ 11 years)

1. Has any clinically significant medical disorder, condition, disease (including active or potentially recurrent non-AD dermatological conditions and known genetic dermatological conditions that overlap with AD, such as Netherton syndrome) or clinically significant finding at baseline that precludes participant's participation in study activities.
2. Participants who are on systemic corticosteroids or immunosuppressive agents within 28 days of Day -7 (V01).
3. Participants who are on topical AD treatment such as low-to-high-potency corticosteroids, TCIs, antihistamines, antibiotics, sodium hypochlorite-based products, antibacterial soaps, bleach baths, diaper rash creams, lotions, ointments, powders, light therapy, and use of bland emollients on or overlapping with treatable AD-involved areas within 7 days of Day -7 (V01), unless AD lesions are present where crisaborole cannot be applied (face within 1 or 2 fingers away from the of mouth and hands/fingers).
4. Participants who are or have been on crisaborole treatment regimen in the past.
5. Allergy to polyurethane resin (strap/wristband component), skin nickel allergy, silicone, and/or adhesives.
6. Has documented non-AD related insomnia, sleep apnea or other sleep-related disorders (e.g., narcolepsy, restless legs syndrome, circadian rhythm disorder).
7. Participant has a known lack of efficacy to any component of crisaborole.
8. Participant scores <20 on the Childhood Asthma Control Test (ages 4-≤ 11) indicating poorly controlled asthma.
9. If participant has a history of angioedema or anaphylaxis.
10. Has a significant active systemic or localized infection, including actively infected AD.
11. Has any planned surgical or medical procedure that would overlap with study participation.
12. Participants with cardiac pacemakers, electronic pumps or any other implanted medical devices.
13. Participants who are unable to wear at least one wrist device (one accelerometry device on at least one wrist).

Adult Caregiver

1. Has any clinically significant medical disorder, condition, disease or clinically significant finding at baseline that precludes Caregivers participation in study activities (e.g., sleep apnea, narcolepsy, etc.)
2. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) wine, 12 ounces (360 mL) of beer, or 1.5 ounces (45 mL) of hard liquor) within 6 months of baseline as disclosed by participant during evaluation. *
3. Current shift worker or travel across more than two time zones in the past 2 weeks, and/or during the study period.
4. Has any planned surgical or medical procedure that would overlap with study participation.
5. Participants who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are BU/BMC employees directly involved in the conduct of the study.
6. Allergy to polyurethane resin (strap/wristband component), skin nickel allergy, silicone, and/or adhesives.
7. A female who is pregnant.†
8. The primary caregiver or share the same domicile of another child who has previously been or is currently enrolled in the study.

[*] One of our secondary objectives is to evaluate sleep in primary caregivers. It is noted in the literature that alcohol use and abuse has significant effect on sleep as it can cause insomnia, excessive daytime sleepiness, and changes in sleep homeostasis/architecture (Colrain, Turlington, & Baker, 2009; Hu, et al., 2020). Thus to ensure that we can effectively capture sleep in primary caregivers of children with AD (who experience sleep disturbances), we will be excluding caregivers who have sleep disorders, are shiftworkers or have traveled more than two time zones in the past 2 weeks and/or during the study period, as well as those who have a history of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males.

[†]There is currently no data available regarding associated risks of pregnant women applying crisaborole to their child. Thus, pregnant women are excluded from the study as a precautionary measure. Furthermore, per the crisaborole FDA label, for the use of crisaborole on pregnant women "There is no available data with EUCRISA in pregnant women to inform the drug-associated risk for major birth defects and miscarriage." Since this data is not available, the risks of including a pregnant woman do not outweigh the benefits of the study. Women of child-bearing potential will be pregnancy tested using a standard drug-store urine test at the Laboratory for Human Neurobiology. If the participant suspects that they are pregnant, or test results indicate that they may be pregnant, they will be asked to follow up with their doctor and they will not be included in the study.

5. STUDY PROCEDURES

The study will consist of a screening/baseline (in- laboratory) visit on Day -7 (V01), an in- laboratory visit Day 1 (V02), an in- laboratory visit on Day 2 (V03) for tape-striping, and Day 8 (V04) for an assessment of the severity of the AD and a final in- laboratory visit on Day 15 (V05) for an assessment of the AD, tape-stripping, completion of ObsROs and return devices. Throughout the study, the participants and caregivers will wear accelerometry/actigraphy devices continuously (optional for those who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment; devices may be removed for short periods of time for such things as the purposes of bathing, etc.). Enrolled participants will be randomly assigned to each arm of the study. Participants may come in for an unscheduled visit as needed (i.e., to replace compound, etc.). All in-person study activities, including informed consent and pregnancy testing, will be completed at the Laboratory for Human Neurobiology, 650 Albany St X140, Boston, MA, 02118. All activities performed in the laboratory are accomplished in private rooms. Primary caregivers will be provided with ample time and a privacy curtain to change into a gown during assessment for exclusion of Atopic Dermatitis, and primary caregivers will accompany children during all activities to ensure participant privacy. All at-home study activities will be completed in the participants' home.

Phone Screening - Day-28 to -7 (~15 minutes):

- Verbal consent (including assent where applicable)
- Assign Participant ID (a sequentially assigned numerical ID used to identify participant on all study documents and in the electronic data capture [EDC] system)
- Screening demographics, medical history including AD history/treatment (includes, race, ethnicity, and gender)
- Eligibility screening (review of inclusion and exclusion criteria)

Baseline Visit 1 (V01)/Day -7 (+/- 3) – In Laboratory (~2 hours):

- Written Informed consent (including assent when applicable)
- Participants are randomly assigned to one of the two arms of the study
- Screening demographics (includes race, ethnicity, gender, and significant medical

history/treatment)
- Pregnancy test for female caregivers of child-bearing potential
- Wide Range Achievement Test 4 (WRAT-4)
- Eligibility Screening (Inclusion/Exclusion criteria)
- Vital signs
- Height and weight
- Investigator's Static Global Assessment (ISGA) (scored by a dermatologist or a medically qualified individual who has been trained in the assessment; rater to be consistent throughout study)
- EASI assessment (scored by a dermatologist or a medically qualified individual who has been trained in the assessment; rater to be consistent throughout study)
- Calculate % body surface area (BSA) affected with AD
- Childhood Asthma Control Test
- Tape Stripping (Biomarker Assessment)
- Observer Reported Itch Assessment (ORIA; ages 3 months - ≤ 11 years)
- Patient Reported Itch Severity Scale (ages 6 years to ≤ 11 years old)
- Observer Global Impression of Severity (OGIS; ages 3 months - ≤ 11 years)
- Peak Pruritis NRS (Caregivers)
- Children's Sleep Health Questionnaire (CSHQ; ages ≥4-≤ 11) OR Brief Infant Sleep Questionnaire(BISQ; ages 3 months-<4 years)
- Medical Outcome Sleep Scale (MOS; caregivers only)
- Mobile Device Proficiency Questionnaire (MDPQ; caregivers only)
- Faces, Legs, Activity, Cry, and Consolability Scale (FLACCS)
- Dermatitis Family Impact Questionnaire (DFI; parent/guardian(s); ages 3 months- ≤ 11 years)
- Children's Dermatology Life Quality Index (CDLQI; ages ≥4-≤ 11 years) OR Infants Dermatitis Quality Of Life Index (IDQOL; ages 3 months-<4 years)
- Observer-reported Patient-Oriented Eczema Measure (POEM); ages 3 months – ≤ 11 years)
- The participant will be asked to don the accelerometry/actigraphy devices (coordinator will log dispensing) as follows: The participant will be provided the accelerometry/actigraphy devices immediately after completion of informed consent and will be trained. Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.
    - Accelerometry
        - Children: Ages 2 years to ≤ 11 years; On R & L wrists
        - Caregivers: Ages 18 to 75 years; On R & L wrists
    - Actigraphy or accelerometry:
        - (Ages 3 months up to ≤ 11 years; On R & L wrists and R & L ankles for 3 months - <2 years; R & L wrists only for 2 – ≤ 11 years)

<u>Out-of-Laboratory (At-Home) Assessments (Days -7–Day 1; Between Visits 1 & 2)</u>:
The purpose of the out-of-laboratory assessment is to evaluate wearable devices in a home/routine setting (defined as the participant's routine environment/activities). Participants will be provided a fully-charged set of accelerometery devices for use at home. Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.

1. Continuously wear Accelerometry devices as much as possible

2. Continuously wear Actigraphy devices as much as possible

Visit 2 (V02)/ Day 1 (+/- 3 days)- In Laboratory (~1 hour):

1. ISGA
2. EASI
3. % affected BSA calculation
4. Children's Sleep Health Questionnaire (CSHQ; ages ≥4 to ≤ 11 years) OR BISQ (Brief Infant Sleep Questionnaire; ages 3 months - <4 years)
5. Medical Outcome Sleep Scale (MOS-Sleep; caregivers only)
6. Faces, Legs, Activity, Cry, and Consolability Scale (FLACC)
7. Dermatitis Family Impact Questionnaire (DFI; parent/guardian(s); ages 3 months - ≤ 11 years
8. Children's Dermatology Life Quality Index (CDLQI; ages ≥4 - ≤ 11) OR Infants Dermatitis Quality Of Life Index (IDQOL; ages 3 months - <4 years)
9. Observer-Reported Patient-Oriented Eczema Measure (POEM; ages 3 months – ≤ 11 years)
10. In laboratory dose application training, including weight of the compound or vehicle tube
11. Drug Dispensing
12. Continuous accelerometry wear (Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.)
13. Continuous actigraphy wear (Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.)

Out-of-Laboratory (At-Home) Assessments (Days 1-15) (~15 minutes per day):

The purpose of the out-of-laboratory assessment is to evaluate wearable devices and ORIA/Patient Reported Itch Severity Scale in a home/routine setting (defined as the participant's routine environment/activities) while the child participant is receiving either crisabole or vehicle. Participants will be provided a fully-charged set of accelerometery devices for use at home.

1. Caregiver to complete ObsRO/PRO measurements as instructed:
    - Observer Reported Itch Assessment (ORIA; ages 3 months-≤ 11 years)
    - Observer Global Impression of Severity (OGIS; ages 3 months-≤ 11 years)
    - Peak Pruritis NRS (Caregivers)
    - Patient Reported Itch Severity Scale (Children 6-≤ 11 years old)
2. At-home dosing (crisaborole or vehicle) in all affected areas except mouth, eyes, and vagina, per label
3. Continuous Accelerometry wear (Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.)
4. Continuous Actigraphy wear (Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.)

Visit 3 (V03)/ Day 2 (+/- 12 hours) – In Laboratory (~30 minutes):

1. Collect Tape Stripping
2. Weigh tube of compound or vehicle

Visit 4 (V04) / Day 8 (+/- 3 day) In Laboratory (~1 hour):

1. ISGA
2. EASI
3. % affected BSA calculation
4. Children's Sleep Health Questionnaire (CSHQ; ages ≥4 to ≤ 11 years) OR BISQ (Brief Infant Sleep Questionnaire; ages 3 months - <4 years)
5. Medical Outcome Sleep Scale (MOS-Sleep; caregivers only)
6. Observer Global Impression of Change (OGIC)
7. Faces, Legs, Activity, Cry, and Consolability Scale (FLACC)
8. Dermatitis Family Impact Questionnaire (DFI; parent/guardian(s); ages 3 months – ≤ 11 years
9. Children's Dermatology Life Quality Index (CDLQI; ages ≥4 – ≤ 11) OR Infants Dermatitis Quality Of Life Index (IDQOL; ages 3 months- <4 years)
10. Observer-Reported Patient-Oriented Eczema Measure (POEM; ages 3 months – ≤ 11 years)
11. In laboratory dose application training, including weight of the compound or vehicle tube
12. Retrieve and re-issue Accelerometry devices (Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.)

Visit 5 (V05) / Day 15 (+/- 3 day) or Early Termination (ET)– In laboratory (~2 hours):

The primary purpose of this visit is to retrieve devices and complete end-of-study assessments. In addition, the following procedures will occur.

1. ISGA
2. EASI
3. % affected BSA calculation
4. Tape Stripping
5. Observer Reported Itch assessment (ORIA; ages 3 months - ≤ 11 years)
6. Patient Reported Itch Severity Scale (ages 6 years to ≤ 11 years old)
7. Observer Global Impression of Severity (OGIS; ages 3 months - ≤ 11 years)
8. Peak Pruritis NRS (Caregivers)
9. Children's Sleep Health Questionnaire (CSHQ; ages ≥4 to ≤ 11 years) OR BISQ (Brief Infant Sleep Questionnaire; ages 3 months - <4 years)
10. Medical Outcome Sleep Scale (MOS-Sleep; caregivers only)
11. Observer Global Impression of Change (OGIC)
12. Device Comfort Questionnaire (DCQ) / Observer Device Comfort Questionnaire (ODCQ)
13. Faces, Legs, Activity, Cry, and Consolability Scale (FLACC)
14. Dermatitis Family Impact Questionnaire (DFI; parent/guardian(s); ages 3 months-≤ 11 years
15. Children's Dermatology Life Quality Index (CDLQI; ages ≥4- ≤ 11) OR Infants Dermatitis Quality Of Life Index (IDQOL; ages 3 months-<4 years)
16. Observer-Reported Patient-Oriented Eczema Measure (POEM; ages 3 months – ≤ 11 years)
17. Coordinator to retrieve and track return of devices.
18. Weigh and return compound or vehicle tube
19. Record participant disposition (completed study, left study early and reasons)

Participant Withdrawal/Stopping Rules
Participant comfort with the proposed procedures will be regularly assessed and no procedure will continue if the participant expresses discomfort or a desire to stop for any reason. If one Unanticipated Problem (UP) occurs, the study will be suspended until the investigators determine, with the BUMC/BMC IRB's input, that sufficient corrective measures can be put into place to allow it to proceed.

7. ASSESSMENTS
Below are the descriptions of the tasks chosen for this study; these brief summaries provide an overview of the range of task's objectives.

Tape Stripping:
Tape strips will be collected from participants from nonlesional and lesional skin at the time points outlined in the SoA. The area(s) to be used for tape stripping will be selected predose at V01 (Day -7) and documented. Index lesion selected as noted at V01, and documented on the Lesion/Non-Lesion Tape Stripping Site Identification Form, must be skin that is affected by atopic dermatitis and the lesional tape strip at V01 should be taken from skin that is adjacent to an affected skin lesion and must be part of the designated treatment area. Tape strips at subsequent visits should be taken from the same site as the initial index lesion, even if the lesion severity changes during the course of treatment.

Details on the processes for selection of lesional and non-lesional skin and collection and shipment of these samples can be found in the appendix.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study and may be used for possible additional exploratory analysis only for this study, with all remaining samples being destroyed. Biomarkers may include, but are not limited to target expression, nucleic acid analyses, and protein analyses. Samples may be analyzed for assessments related to inflammatory skin disease, the mechanism of action of crisaborole and/or responder/non-responder analyses.

All other assessments are included within the appendix section of this protocol.

8. SAFETY
8.1. Adverse Events
Any Adverse Events or Serious Adverse Events (defined below) encountered in the study will be monitored and reported to the BUMC IRB as per established procedures.

Adverse Event: Any untoward or unfavorable physical or psychological occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

Serious Adverse Event: Any adverse event that:
1) Results in death
2) Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
3) Results in inpatient hospitalization or prolongation of existing hospitalization
4) Results in a persistent or significant disability/incapacity
5) Based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event.

8.2 Safety Review

Safety review for this study will be accomplished throughout the study and monitor all study activities identified in the schedule of activities. Risks to be monitored include: hypersensitivity, application site pain, application site discomfort, skin irritation, pyrexia, upper respiratory tract infection, diarrhea, cough, and any unknown risks or unanticipated problem identified in the performance of the study. This will be accomplished by study staff personnel as part of each visit activity, spontaneously reported by the caregivers, and monitored for all participants enrolled throughout the study. Specifically during each study visit, study staff will assess the level of skin irritation and participant reported discomfort (or AD flare up) from both the wearing of devices and/or subsequent topical application of crisaborole/vehicle. The Principal Investigator will be notified of any AEs immediately. All other reporting plans are outlined in section 8.3.

Signs of AD (based on % BSA) will be measured and evaluated throughout the study period on laboratory visits 3, 4, and 5 (days 2, 8, 15) by the study dermatologist. Participants whose BSA exceeds 40% at visits 3 and 4, will be instructed to terminate the use of vehicle/crisaborole and will be withdrawn from the study. We will monitor collected BSA percentages at each time point and their change from baseline. Participants will also be provided with a 24/7 phone number should they need to contact the laboratory after hours.

Appropriate documentation of any and all identified unanticipated or adverse events will be properly reported to the IRB including appropriate mitigation and reports for recommended changes, with unanticipated problems within 7 days. A document listing any identified safety related events will be maintained and monitoring of this list will be ongoing throughout the study as a means to track and review these events (accomplished by comparative analysis of each event in comparison to all other events throughout the study) to determine expectedness, relatedness, or suggestion of new risks that may have been identified. Other events will be documented, assessed and monitored by staff and investigators and reported at the time of continuing review. Monthly reviews of blinded adverse events will be

conducted to assess frequency of events, severity, seriousness, and relatedness to determine any potential trending study related items that may indicated a potential safety concern.

The data for adverse events (observed by study staff or spontaneously reported by caregivers) will be aggregated using descriptive statistics. Overlap of adverse events will be recorded.
Caregiver reported treatment-related adverse events will be recorded using MedDRA Version 24.1. Severity of adverse events will be categorized as follows: Mild-Symptom(s) barely noticeable with no reported participant discomfort; Moderate- Symptom(s) reported as uncomfortable; Severe- Symptom(s) causing severe discomfort resulting in participant withdrawl. Relatedness of reported events will be categorized as follows: Unrelated- The event deemed to be clearly not study related; Possibly related- The event is temporally aligned with study activies but possibly may be due to another circumstance; Related- The event is temporally aligned to study activities with no alternative causes present.

8.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus will be reported to the IRB within 7 days of the investigator learning of the event.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places participants or others at a greater risk of harm than was previously known.
- Monthly reviews of blinded unanticipated problems and adverse events will be reviewed with Pfizer to assess frequency of events, severity, seriousness, and relatedness to determine any potential trending study related items that may indicated a potential safety concern.

8.4 Research Related Injury
Possible social risks**:** These are extremely low in this study and pertain to the unintentional release of personal information.
Mitigation of social risks**:** To safeguard confidentiality and the privacy of protected information, each study participant will be assigned a unique code number. A separate file linking the participants' name with study number and identifiers will be kept in a password-protected data file, accessible only by the PI and the study coordinator. All study forms will be kept in secure locked file cabinets. The study investigators will assume full responsibility to maintain the confidentiality of all data. All study results will be presented only as statistical aggregates that will neither identify, nor permit identification of, individual participants.

Possible risk associated with digital health devices: The risks associated with these devices include physical discomfort if the participant is not used to wearing wrist accelerometers and/or ankle devices, and possible skin irritation or reaction, such as an AD flare-up in children with the skin condition. If the participant experiences skin irritation or notice signs of an AD flare-up in the area that the child wears the device(s), they will be instructed to remove the device(s) and notify the study team immediately.

Mitigation of risks associated with digital health devices: If the participant is unable to wear the device due to discomfort (or AD flare up) the participant will notify study staff and the Principal Investigator may allow the participant to continue the study without wearing the discomforting device or withdraw the

participant from the study. Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.

Possible risk associated with tape stripping: Tape stripping is routinely performed and is considered a minimally invasive approach for identifying biomarkers for Atopic Dermatitis and is an acceptable alternative to traditional biopsies. The only minimal risk associated with tape stripping is mild discomfort and potentially superficial surface reddening of the skin at the location of the tape. This is typically reported after 50-60 tape strippings. In this study we will only be doing ~20 tape strippings per sample. Tape stripping sensation is similar to removal of a band-aid.
Mitigation of risk associated with tape stripping: Tape strippings will only be conducted three times with a minimum of 3 days between each tape stripping. If the participant experiences discomfort, adjacent sites to previous stripping area will be used.

Possible risk associated with crisaborole: Possible risks associated with crisaborole include application site pain or burning/stinging sensation (lasting one to two days) and/or hypersensitivity reaction and/or development of a skin allergy and/or severe pruritis and/or swelling and/or erythema. Less common risks (<1%) include contact urticaria (hives - a skin reaction that results in red, itchy welts). AD by nature is a disease that has recurrent flares on active treatment or without active treatment. Therefore, participants on crisaborole or vehicle could experience worsening of their natural course of disease.
Mitigation of risk associated with crisaborole: If the participant develops a hypersensitivity reaction, severe pruritis, swelling, or erythema, (and/or development of skin allergy (e.g. hives)), dosing will be discontinued and the site will be contacted, and the participant should seek medical attention as needed. If minor application site pain or burning/stinging sensation is reported, and participant is uncomfortable with continuation, the principal investigator may allow the participant to continue in the study with dosing discontinued, or participant will be withdrawn. If signs and symptoms of hypersensitivity occur, discontinue EUCRISA immediately and initiate appropriate therapy. Hypersensitivity Reactions Advise patients to discontinue EUCRISA and seek medical attention immediately if signs or symptoms of hypersensitivity occur *[see Warnings and Precautions (5.1) from label]*. Administration Instructions Advise patients or caregivers that EUCRISA is for external use only and is not for ophthalmic, oral, or intravaginal use. All participants may withdraw from the study at any time, including if they experience worsening of symptoms.

Possible Risk Associated with vehicle treatment: Possible risks associated with vehicle include application site pain or burning/stinging sensation, severe pruritis (itching), swelling, redness and/or hypersensitivity reaction (an exaggerated immune response which may cause skin discomfort) and/or development of a skin allergy. Possible risks associated with vehicle treatment where vehicle contains the excipients of crisaborole ointment, and the base of crisaborole ointment has no difference in appearance, texture, color, or odor to crisaborole ointment, 2% and as such no specific risks identified other than hypersensitivity reaction and/or development of skin allergy. No additional risks are known with respect to vehicle treatment as it provides white petrolatum as the main excipient and base of crisaborole ointment, 2%, which was selected for its emollient properties and favorable tolerability profile, where the importance of an emollient effect is highlighted by the use of emollients in basic skin care for patients with AD, to aid in restoration of barrier function
Mitigation of Risk Associated with vehicle treatment: If the participant develops a hypersensitivity reaction, severe pruritis (itching), swelling, redness (and/or development of skin allergy (e.g. hives)), dosing will be discontinued and the site will be contacted, and the participant should seek medical attention as needed. If minor application site pain or burning/stinging sensation is reported, and participant is uncomfortable with continuation, the principal investigator may allow the participant to continue in the study with dosing discontinued, or participant will be withdrawn. AD by nature is a

disease that has recurrent flares on active treatment or without active treatment. Therefore, participants on vehicle could experience worsening of their natural course of disease.

Participants may become bored/fatigued over the course of a testing session. The same considerations apply to the study visits.

9. DATA ANALYSIS

Study Hypotheses: The primary objective of this study is to evaluate the reduction of itch and nighttime scratch (as measured by accelerometry/actigraphy and Observer Reported Itch Assessment (ages 3 months to ≤ 11 years old) with application of crisaborole. A clinically significant change in scratching as measured by accelerometry/actigraphy has not yet been determined. The relationship between accelerometry/actigraphy scratching parameters and PRO scratching assessments is being studied currently. This study adds to the knowledge base by studying the association between changes in PRO scratching assessments and changes in accelerometry/actigraphy scratching parameters when treatment is initiated or changed. Estimates of their variability from this study can also fill the literature gap and be used to help design future studies.

As this study is a research collaborative agreement, both the Laboratory for Human Neurobiology and the collaborator/sponsor will perform statistical analyses. Only deidentified data is shared with the collaborator.

Sample Size: The sample size calculation of this study is therefore based on the primary endpoint for itch assessment. An open-label internal Pfizer study with a similar scale to the Observer Reported Itch Assessment in 3-months to 5-year olds, the reduction of itch/scratch was evaluated from baseline to 14 days. Based on the results of that study, a 2.6 points common standard deviation in the observer reported pruritus score change from baseline for 2 weeks in children ages 3 months to 5 years with mild to moderate AD was assumed. There is no data available for 6-≤ 11 year olds. Therefore, the assumption is made that children ages 6 to ≤ 11 will have the same standard deviation. We will employ a simple randomized procedure using a computerized random numbers to assign participants to the two groups. A total of 244 randomized participants (in 1:1 ratio) will provide approximately 85% power to detect a 1.0 points of the observer reported pruritus score reduction difference in crisaborole treatment group compared to vehicle group, with a two-sided 5% significance.

With an expected dropout rate of ~10%, approximately 540 (270 children and 270 primary adult caregivers) are expected to be recruited for this study.

Statistical Methods and Analysis:

The primary and secondary endpoints will be tested at the significance level of 0.05 (2-sided). There is no multiplicity adjustment. Number, percent and 95% confidence interval (CI) will be presented for binary endpoints. Descriptive summary statistics (n, Mean, Std. Dev, Median, Min., Max.) will be presented for continuous endpoints. In addition, graphics may be used to present the data.

The primary objective is to evaluate the effects of Crisaborole on itch and night-time scratch. The primary endpoints include number of scratching episodes (children aged 2 – ≤ 11 years), duration of scratching (children aged 2 – ≤ 11 years), and ORIA (ages 3 months to ≤ 11 years). For these endpoints, change from baseline will be analyzed using a mixed-effects model with repeated measures (MMRM) including data from Day 1 (for acceleometry measured scratch episodes and duration)/Day 2 (for ORIA) to Day 15 with baseline score as a covariate and an unstructed covariance matrix. The least-squares (LS) means and

the corresponding 95% CIs, the LS mean difference between treatment groups, and the corresponding 95% CI will be presented for change from baseline for all postbaseline timepoints. As a sensitivity analysis, instead of daily data, average of every 3 days data will be used to account for day-to-day variation.

The binary endpoints will be descriptively summarized using sample size, number, percentage and 95% confidence interval (CI) of percentage at each time point. Binary data will be analyzed by comparing response rates between treatment groups. Normal approximation to the difference in response rates will be used to obtain p-values and 95% CI. For binary endpoints analyzed at each scheduled visit separately, participants who drop out for any reason or require a prohibited medication for the treatment of their atopic dermatitis will be defined as "non-responsive" at all subsequent visits. This method of handling missing response is known as missing response as non-response (MR-NR).

Mixed model repeated measures (MMRM) will be used to analyze longitudinal continuous data. Treatment, visit, treatment-by-visit interaction are fixed effects in the model, baseline value as a covariate. Within-participant variability will be accounted for using a random effect with the unstructured covariance matrix. If this is a convergence issue, other type of covariance matrix will be used. The following structures will be executed in the order specified (essentially in decreasing order of complexity) until convergence is achieved: heterogeneous Toeplitz, heterogeneous first order autoregressive, autoregressive, heterogeneous compound symmetry, compound symmetry, and variance components. The first structure yielding convergence will be used as the primary analysis. The Kenward and Roger method for calculating the denominator degrees of freedom for tests of fixed effects will be used. Least square (LS) estimates of mean values and the LS mean differences between crisaborole 2% BID and vehicle groups at each visit will be derived from the model. The corresponding p-value, standard error (SE) and 95% CI will also be derived from the model.

ANCOVA model will be used to analyze nonlongitudinal continuous endpoints with treatment as a factor baseline value as a covariate. Least square (LS) estimates of mean values and the LS mean differences between crisaborole 2% BID and vehicle groups at each visit will be derived from the model. The corresponding p-value, standard error (SE) and 95% CI will also be derived from the model.

For any accelerometry/actigraphy continuous variables that exhibit right skewed distribution (i.e. skewed to positive values), log transformation may be used as appropriate. Specifically, for number of scratching, length of time scratching, arousals from sleep, WASO, and sleep onset latency, log(x+1) transformation will be employed (to include possible zero values). For time duration between scratching, log(x) will be employed.

For efficacy continuous endpoint not measured longitudinally, the post-baseline missing values will not be imputed, ie, the values are assumed to be missing completely at random. For efficacy continuous endpoints measured longitudinally, missing values post-baseline will be handled in a linear mixed-effect model with repeated measures for this continuous variable, where the values are assumed to be missing at random. For the continuous ObsROs variables, rules suggested by the developers of these instruments will be followed in calculating the missing values. If these rules are not enough for imputing a value, then the missing values will be handled in the same way as efficacy variables.

Specific analyses to be conducted:

- Evaluate drug-induced changes of itch ORIA, scratching and sleep quantity, and additional PRO/ObsRO and biomakers; comparing start of the study to measures obtained while on treatment
- Summary of AEs and RRIs

- Comparison of PRO/ObsRO assessments to scratching and sleep values obtained from device measurements.
- Comparison of digital measures of scratching and sleep with QoL PRO assessments.

10. DATA HANDLING, RECORD KEEPING, QUALITY CONTROL AND QUALITY ASSURANCE

Data handling, record keeping, quality control and quality assurance is discussed in the approved Boston University Institutional Review Board (IRB) application.

10.1 Confidentiality

In order to minimize the accidental release of sensitive test information, study data will be labeled with only the participant's randomly generated study ID. To protect the confidentiality of each participant, the only place where the participant ID and their identifiable information will exist together will be on a separate master spreadsheet, which will be password protected and to which the PI and the study coordinator will have access to. In order to further ensure the confidentiality of the participants, the password for this master spreadsheet will be different than the password for documents containing the de-identified data. We will use a coded ID number on all results and data acquired and stored.

Only the consent form, screening forms, BuildClinical recruitment database, and the master identifier spreadsheet will contain identifiable information. Consent and screening forms will be locked in a cabinet at the Spivack Center. All electronic data will be stored in password-protected computers located in a secure lab space in the Spivack Center. Data being stored electronically will be stored according to BU policy for the secure storage of such data.

No identifiable data will go anywhere outside of BU. All data transferred will be coded with no direct identifiers with a unique study ID.

The master identifier spreadsheet will be kept past the end of the study for a minimum of 7 years after which point it will be securely deleted (electronic) or shredded (paper forms). Only the Principal Investigator and study coordinator will have access to this data. Publications will not contain the participants' names or any identifying characteristics

The study monitor or other authorized representatives of the sponsor may inspect all deidentified documents and records required to be maintained by the investigator, including but not limited to pharmacy records, for the participants in this study. The clinical study site will permit access to such records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify participants. The website may be updated to include a summary of the results.

10.2 Data handling, data collection and extract transform and load (etl) processes

Electronic Data Capture: Both a web-based electronic data capture (EDC) system and computing applications (apps) on a mobile device will be utilized for this study, in addition to sensor data.

Source Documents: Study visit data (e.g., screening, demographics, medical history, ISGA, EASI, BSA, vitals, concomitant medications, and inclusion exclusion criteria) will be collected for all screened and enrolled participants and entered into Excel CSV files for transfer via CONFORM to Pfizer.

Sensor-acquired data (Actigraphy/accelerometry devices) will include no identifiable information and will be exported from each sensor device via each device's proprietary companion software application. Data obtained from the watches will be transferred to Pfizer for processing via a cloud-based data repository, CONFORM, and the results will then be subsequently shared back with BU via CONFORM.

Data dictionary will be aligned to CDISC and Pfizer Standards. Device type, manufacturer, serial number, firmware and software versioning will also be collected as well as all the pertinent metadata associated with the generated files.

Data generated by the methods described in the protocol will be recorded in the participants' study records and/or study progress notes. Data may be transcribed legibly on study records for each participant or directly inputted into an electronic system or any combination thereof.

BuildClinical Recruitment Database: The BuildClinical online database for participant recruitment will be maintained until the end of the study.

10.3 Participant Study Records and Report Forms

The participant study records and report forms will be the primary data collection instrument for the study. All data requested on the participant records will be recorded. All missing data will be explained. If a space on the participant records is left blank because the procedure was not done or the question was not asked, "NaN" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. There will be no erasures or white-out on participant records. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

10.4 Study Records Retention

Data from the intake of eligible participants will be retained in a locked file cabinet. The investigators will maintain a password-protected list containing the names and contact information of those individuals who are ineligible. All files will be destroyed 7 years after study completion. Only approved researchers will have access to these files. Answers to screening questions will be destroyed for both persons who are eligible and persons who are not eligible. The only information that will be retained from persons who were screened will be contact information and general reason for screening out (for those who are not eligible). The BuildClinical database for participant recruitment will be maintained until the end of the study. All potential participants who respond to BuildClinical recruitment materials will be contacted by study staff to verify eligibility via the Phone Screening Questionnaire. The only information that will be retained from persons who were screened will be contact information and general reason for screening out (for those who are not eligible).

The BMC/BU Medical Campus IRB requires that documentation of informed consent of participants be retained for at least seven years after the study is closed. Such records will be preserved in hardcopy and/or electronic or other media form and must be accessible for inspection and copying by authorized individuals.

11. COMPLIANCE WITH GOOD CLINICAL PRACTICE

11.1. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants, adopted by the General Assembly of the World Medical Association (2008).

In addition, the study will be conducted in accordance with the protocol, the principles of the International Conference on Harmonization (ICH) guideline on Good Clinical Practice (GCP) and applicable local regulatory requirements and laws.

11.2. Institutional Review Board (IRB)/Ethics Committee (EC)

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

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the investigator must notify the IRB/EC in writing within 5 working days after the implementation.

11.3. Participant Information and Consent

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a participant, using the IRB-approved consent form, must be obtained before that participant is submitted to any study procedure. Consent will be documented as required by the IRB.

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

When study data is compiled for transfer to other authorized parties, participant names, addresses, and other identifiable data will be replaced by a numerical code in order to anonymize study participants. The study site will maintain a confidential list of participants who participated in the study linking their numerical code to the participant's actual identity. In case of data transfer, all parties will maintain high standards of confidentiality and protection of participant personal data consistent with applicable privacy laws.

The informed consent and assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. The investigator will ensure that each study participant and his or her parent(s)/legal guardian are fully informed about the nature and objectives of the study and possible risks associated with participation. The informed consent and assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection. The investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant's legal guardian before any study-specific activity is performed, unless a waiver of

informed consent has been granted by an IRB/EC. The investigator will retain the original of each participant's guardian(s) signed consent document.

The informed consent document used during the informed consent process will convey that only anonymized information (including protected health information related to age, and sex) from each participant may be conveyed to Pfizer and its third parties/affiliates.

11.4 Participant Recruitment and Participation

Recruitment: Advertisements, including via patient advocacy groups and pediatric dermatology clinics, approved by ethics committees and investigator databases may be used as recruitment procedures. Participants will be recruited via electronic announcements, the BUMC Corporate Communications weekly email, and posted flyers. Moreover, participants will be recruited through physician referral at the dermatology clinics. BuildClinical, a recruitment platform, will also be used to identify potential study participants, in accordance with BUMC policy. Individuals who respond to recruitment materials will be provided with a brief description of the study, including the methodologies used, and asked a series of questions to determine eligibility and informed that snacks and liquids will be available during onsite study visits. The investigators will maintain a list containing the names and contact information (but absolutely no protected health information) of those individuals who are ineligible.

Location where study will be performed: Boston University

Participant payment:

Participants who partially complete study activities will be compensated based on activities completed, outlined below. Participants whose total amount of compensation for activities completed is less than $400 will be paid through Cash Cards. Participants whose total amount of compensation for activities completed is greater than $400 will be paid via checks after study withdrawal or completion. Participant Compensation (inclusive of child and caregiver; all study activities): $1,350

- V01 [Day -7] (Intake): $25
- V01 [Day -7] (Baseline: completion of PROs, training, tape stripping, assessments): $150
- V02 [Day 1] (Completion of PROs / assessments): $100
- V03 [Day 2]: (Tape stripping): $200
- V04 [Day 8]: Completion of PROs / assessments): $100
- In-Home Activities [Day -7 to Day 15]: $525
- V05 [Day 15]: (In-lab assessments, turn-in wearable devices): $250

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Appendix A- Instruments attached below are the assessments to be performed. In all cases only participant ID will be recorded in locations where name is identified. In no case will identifiable data be recorded.

Appendix A: INCLUSION CRITERIA

Per Inclusion Criterion, a participant is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka (1980).

Table 1: Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Major Criteria: Must have three or more basic features described below:
Pruritus
Typical morphology and distribution:
Flexural lichenification in adults
Facial and extensor eruptions in infants and children
Chronic or chronically-relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Minor Criteria: Must have three or more following minor features:
Xerosis
Ichthyosis/palmar hyperlinearity, keratosis pilaris
Immediate (type 1) skin test reaction
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (esp. staph. aureus and herpes simplex), impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor, facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Periofollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors

White demographism, delayed blanch

Suggested Universal Criteria for Atopic Dermatitis (AD) by American Academy of Dermatology

A. Essential features; must be present and, if complete, are sufficient for diagnosis:

1. Pruritus
2. Eczematous changes that are acute, subacute, or chronic:

a. Typical and age-specific patterns

(i) Facial, neck, and extensor involvement in infants and children

(ii) Current or prior flexural lesions in adults/any age

(iii) Sparing of groin and axillary regions

b. Chronic or relapsing course

B. Important features that are seen in most cases, adding support to the diagnosis:

1. Early age at onset
2. Atopy (IgE reactivity)
3. Xerosis

C. Associated features: Clinical associations; help in suggesting the diagnosis of AD but are too nonspecific to be used for defining or detecting AD for research and epidemiologic studies

1. Keratosis pilaris/Ichthyosis/Palmar hyperlinearity
2. Atypical vascular responses
3. Perifollicular accentuation/Lichenification/Prurigo
4. Ocular/periorbital changes
5. Perioral/periauricular lesions

D. Exclusions: Firm diagnosis of AD depends on excluding conditions such as scabies, allergic contact dermatitis, seborrheic dermatitis, cutaneous lymphoma, ichthyoses, psoriasis, and other primary disease entities.

Subject ID: _____ Date: _____ Technician Initials: _____

Investigator's Static Global Assessment

The ISGA is a 5-point scale (0-4), reflecting a global assessment of AD severity based on erythema, induration/papulation, and oozing/crusting. ISGA will be assessed to characterize participants' overall disease severity across all treatable AD lesions (excluding the scalp). The assessment will be a static evaluation without regard to the score at a previous visit.

OVERALL ISGA SCORE:

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

*The ISGA will exclude scalp from the assessment/scoring

Location of AD:

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

*The ISGA will exclude scalp from the assessment/scoring

Location of AD:

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

*The ISGA will exclude scalp from the assessment/scoring

Location of AD:

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

*The ISGA will exclude scalp from the assessment/scoring

Eczema Area and Severity Index (EASI)

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

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

Table 1.Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

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

The extent (%) to which each of the 4 body regions is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria.

Table 3. Eczema Area and Severity Index (EASI) Area Score Criteria

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

Table 4. Eczema Area and Severity Index (EASI) Body Region Weighting

Body Region	**Body Region Weighting for ≥8 years old participants**	**Body Region Weighting for ≤7 years old participants**
Head and Neck	0.1	0.2
Upper Limbs	0.2	0.2
Trunk (including axillae)	0.3	0.3
Lower Limbs (including buttocks)	0.4	0.3

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

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

Equation 2 (participants aged ≤7 years old): EASI =0.2Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+Exu+Lu) + 0.3At(Et+It+Ext+Lt) + 0.3Al(El+Il+Exl+Ll)

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

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

Eczema Area and Severity Index (EASI)

Important Notes for Accessors:

% BSA within a Region	Corresponding Area Score
0 %	0
> 0 - <10%	1
10 - < 30%	2
30 - < 50%	3
50 - < 70%	4
70 - < 90%	5
90 - 100%	6

Erythema, Induration/Palpation, Excoriation, Lichenification are scored as follows:
0 – Absent
1 – Mild
2 – Moderate
3 – Severe

Head and Neck:

Exam	Score
1. BSA - Area Score	
2. Erythema	
3. Induration/Palpation	
4. Excoriation	
5. Lichenification	

Trunk:

Exam	Score
11. BSA - Area Score	
12. Erythema	
13. Induration/Palpation	
14. Excoriation	
15. Lichenification	

Upper Limbs:

Exam	Score
6. BSA - Area Score	
7. Erythema	
8. Induration/Palpation	
9. Excoriation	
10. Lichenification	

Lower Limbs (Including Buttocks):

Exam	Score
16. BSA - Area Score	
17. Erythema	
18. Induration/Palpation	
19. Excoriation	
20. Lichenification	

Equation if ≥8:

EASI SCORE = $0.1(\underset{1.}{\_\_\_})(\underset{2}{\_\_\_} + \underset{3}{\_\_\_} + \underset{4.}{\_\_\_} + \underset{5}{\_\_\_}) + 0.2(\underset{6}{\_\_\_})(\underset{7.}{\_\_\_} + \underset{8}{\_\_\_} + \underset{9}{\_\_\_} + \underset{10}{\_\_\_}) +$

$0.3(\underset{11.}{\_\_\_})(\underset{12}{\_\_\_} + \underset{13}{\_\_\_} + \underset{14.}{\_\_\_} + \underset{15}{\_\_\_}) + 0.4(\underset{16.}{\_\_\_})(\underset{17.}{\_\_\_} + \underset{18.}{\_\_\_} + \underset{19.}{\_\_\_} + \underset{20}{\_\_\_}) =$ _____

Equation if 2-7:

EASI SCORE = $0.2(\underset{1.}{\_\_\_})(\underset{2}{\_\_\_} + \underset{3}{\_\_\_} + \underset{4.}{\_\_\_} + \underset{5}{\_\_\_}) + 0.2(\underset{6}{\_\_\_})(\underset{7.}{\_\_\_} + \underset{8}{\_\_\_} + \underset{9}{\_\_\_} + \underset{10}{\_\_\_}) +$

$0.3(\underset{11.}{\_\_\_})(\underset{12}{\_\_\_} + \underset{13}{\_\_\_} + \underset{14.}{\_\_\_} + \underset{15}{\_\_\_}) + 0.3(\underset{16.}{\_\_\_})(\underset{17.}{\_\_\_} + \underset{18.}{\_\_\_} + \underset{19.}{\_\_\_} + \underset{20}{\_\_\_}) =$ _____

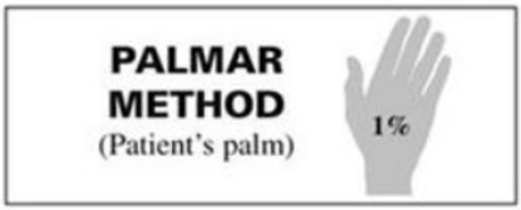
EASI Score = _____

Body Surface Area Assessment (BSA)

Table 1. Handprint Determination of Body Region Surface Area

Body Region	BSA%	BSA%	BSA%	BSA%
	≤ 1 year of age	1- ≤ 4 years of age	5-9 years of age	10-11 years of age
Head and Neck	18%	19%	15%	13%
Upper Limbs	18%	19%	19%	19%
Trunk (including axillae)	36%	32%	32%	32%
Lower Limbs (including buttocks)	28%	30%	34%	36%

The extent (%) to which the individual is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria .
Based on the palmer method, patient's palm = 1%



Estimated BSA for atopic dermatitis = _____

asthma.com

Subject ID: _____ Date: _____
Technician Initials: _____

Childhood Asthma Control Test for children 4 to 11 years

Know your score.

Parent or Guardian: The Childhood Asthma Control Test* is a way to help your child's healthcare provider determine if your child's asthma symptoms are well controlled. Take this test with your child (ages 4 to 11). Share the results with your child's healthcare provider.

Step 1: Have your child answer **the first four questions (1 to 4).** If your child needs help, you may help, but let your child choose the answer.

Step 2: Answer the last **three questions (5 to 7)** on your own. Don't let your child's answers influence yours. There are no right or wrong answers.

Step 3: Write the number of each answer in the score box to the right.

Step 4: Add up each score box for the total.

Step 5: Take the COMPLETED test to your child's healthcare provider to talk about your child's total score.

19 or less

IF YOUR CHILD'S SCORE IS 19 OR LESS, **Your child's asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your child's healthcare provider to talk about your child's results.**

NOTE: If your child's score is 12 or less, his or her asthma may be very poorly controlled. Please contact your child's healthcare provider right away.

Have your child complete these questions.

1. How is your asthma today?

0	1	2	3	SCORE
Very bad	Bad	Good	Very good	

2. How much of a problem is your asthma when you run, exercise or play sports?

0	1	2	3	
It's a big problem, I can't do what I want to do.	It's a problem and I don't like it.	It's a little problem but it's okay.	It's not a problem.	

3. Do you cough because of your asthma?

0	1	2	3	
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.	

4. Do you wake up during the night because of your asthma?

0	1	2	3	
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.	

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

7. During the last 4 weeks, how many days did your child wake up during the night because of the asthma?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

TOTAL

*The Childhood Asthma Control Test was developed by GSK.

This material was developed by GSK.

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<u>Appendix B:</u> PATIENT REPORTED OUTCOME (PRO) / OBSERVER REPORTED OUTCOME(ObsRO) ASSESSMENTS

Observer Reported Itch Assessment

The Observer Reported Itch Assessment assesses the severity of itch (pruritus) in the child due to AD. The participants primary caregiver will be asked to assess their child's worst itch (I.e., scratching, rubbing) due to AD over the past 24 hours in an eDiary every day during the study. Observer Reported Itch Assessment for 3 months - ≤ 11 years of age is an 11-point scale and must be completed by an observer (caregiver). Instruments to be provided to participants as age appropriate below:

Subject ID: _____ Date: _____

Observer Reported Itch Assessment for ages ≥3 months to <2 years of age:

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your observation of your child's itch (i.e., scratching, rubbing) at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

☐ Cannot answer. I am unable to observe signs of itch-related

Subject ID: _____ Date: _____

Observer Reported Itch Assessment for ages ≥2 years to ≤11 of age:

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your observation of your child's itch (i.e., scratching, rubbing) at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

Subject ID: _____ Date: _____ Technician Initials: _____

PAD Patient Reported Itch Severity Scale for 6-11 years of age:

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

Not Itchy **Very Itchy**

Subject ID: _____ Date: _____

Observer Reported Global Impression Severity (OGIS)

The scale will be completed by an observer every day, preferably at the same time as the Observer Reported scratch assessment. The Observer Reported Global Impression Severity (OGIS) is a one-item 7-point rating scale and completed by observers/caregivers of subjects to assess a subject's illness severity at a given point in time. The OGIS will be used as an anchor for defining a "clinical important difference" on the scratch assessments and can also be used to create severity categorization to enhance interpretation. The observer/caregiver of a child is asked to rate the severity of an illness of the child right now as follows:

Please rate the severity of the child's atopic dermatitis right now (select only ONE response):

- Not present ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Moderately Severe ☐
- Severe ☐
- Extremely Severe ☐

Subject ID: _____ Date: _____ Tech Initials: _____

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(Country (Language) **MOS 12-Item Sleep Scale Acute–Revised**)

Your Sleep

For each of the following questions, please select the one response that best describes your answer.

How long did it usually take for you to fall asleep during the past week?

0-15 minutes
16-30 minutes
31-45 minutes
46-60 minutes
More than 60 minutes

On the average, how many hours did you sleep each night during the past week?

How often during the past week did you…

Feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

How often during the past week did you…

Get enough sleep to feel rested upon waking in the morning?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

Subject ID: _____ Date: _____ Tech Initials: _____

How often during the past week did you… Awaken short of breath or with a headache? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Feel drowsy or sleepy during the day? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Have trouble falling asleep? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Awaken during your sleep time and have trouble falling asleep again? All of the time Most of the time Some of the time A little of the time None of the time

Subject ID: _____ Date: _____ Tech Initials: _____

How often during the past week did you… Have trouble staying awake during the day? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Snore during your sleep? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Take naps (5 minutes or longer) during the day? All of the time Most of the time Some of the time A little of the time None of the time
How often during the past week did you… Get the amount of sleep you needed? All of the time Most of the time Some of the time A little of the time None of the time

Subject ID: _____ Date: _____ Technician Initials: _____

Device Comfort Questionnaire

- Please rate the overall comfort of the wrist device sensors where 0 means that they were only tolerable enough to participate in the study and 5 means that you did not notice them once the study began. (Circle one)

  0 1 2 3 4 5

- Were the sensors' locations that were used (e.g., wrist) particularly comfortable? (Circle one)

  Yes No

- How likely are you to be willing to wear the wrist device continuously, at home, for multiple days? (Circle one) Very unlikely Unlikely Likely Very Likely

Observer Device Comfort Questionnaire

- Please rate the overall comfort of the wrist device sensors for your child, where 0 means that they were only tolerable enough to participate in the study and 5 means that they did not notice them once the study began. (Circle one)

  0 1 2 3 4 5

- Were the sensors' locations that were used (e.g., wrist) particularly comfortable for your child? (Circle one)

  Yes No

- How likely is your child to be willing to wear the wrist device continuously, at home, for multiple days? (Circle one)

  Very unlikely Unlikely Likely Very Likely

Subject ID: _____ Date: _____ Technician Initials: _____

PAD Brief Infant Sleep Questionnaire (BISQ)
Please mark only one (most appropriate) choice, when you respond to items with a few options.

Name of Responder: _____**KEEP BLANK**_____ Date: _____

Role of Responder: _ Father _ Mother _ Grandparent _ Other, Specify: _____
Name of the child: ___**KEEP BLANK**____ Date of Birth: Month _**1**_ Day: _**1**_ Year: _____

Sex: _ Male _ Female Birth order of the child: _ Oldest _ Middle _ Youngest

Sleeping arrangement:
_ Infant crib in a separate room _ Infant crib in parents' room
_ In parents' bed _ Infant crib in room with sibling
_ Other, Specify: _____

In what position does your child sleep most of the time?
_ On his/her belly _ On his/her side _ On his/her back

How much time does your child spend in sleep during the NIGHT (between 7 in the evening and 7 in the
morning)? Hours: _____ Minutes: _____

How much time does your child spend in sleep during the DAY (between 7 in the morning and 7 in the
evening)? Hours: _____ Minutes: _____

Average number of night wakings per night: _____
How much time during the night does your child spend in wakefulness (from 10 in the evening to 6 in the
morning)? Hours: _____ Minutes: _____

How long does it take to put your baby to sleep in the evening?
Hours: _____ Minutes: _____

How does your baby fall asleep?
_ While feeding _ Being rocked _ Being held
_ In bed alone _ In bed near parent

When does your baby usually fall asleep for the night:
Hours: _____ Minutes: _____

Do you consider your child's sleep as a problem?
_ A very serious problem _ A small problem _ Not a problem at all

Subject ID: _____ Date: _____
Technician Initials: _____

Child's Sleep Habits
(Preschool and School-Aged)
(Abbreviated Version)

_____
Coding

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if something occurs **5 or more times** in a week; answer SOMETIMES if it occurs **2-4 times** in a week; answer RARELY if something occurs **never or 1 time** during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A)".

Bedtime

Write in child's bedtime: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
1) Child goes to bed at the same time at night (R)	☐	☐	☐	Yes No N/A
2) Child falls asleep within 20 minutes after going to bed (R)	☐	☐	☐	Yes No N/A
3) Child falls asleep alone in own bed (R)	☐	☐	☐	Yes No N/A
4) Child falls asleep in parent's or sibling's bed	☐	☐	☐	Yes No N/A
5) Child needs parent in the room to fall asleep	☐	☐	☐	Yes No N/A
6) Child struggles at bedtime (cries, refuses to stay in bed, etc.)	☐	☐	☐	Yes No N/A
7) Child is afraid of sleeping in the dark	☐	☐	☐	Yes No N/A
8) Child is afraid of sleep alone	☐	☐	☐	Yes No N/A

Sleep Behavior

Child's usual amount of sleep each day: _____ hours and _____ minutes
(combining nighttime sleep and naps)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
9) Child sleeps too little	☐	☐	☐	Yes No N/A
10) Child sleeps the right amount (R)	☐	☐	☐	Yes No N/A
11) Child sleeps about the same amount each day (R)	☐	☐	☐	Yes No N/A
12) Child wets the bed at night	☐	☐	☐	Yes No N/A
13) Child talks during sleep	☐	☐	☐	Yes No N/A
14) Child is restless and moves a lot during sleep	☐	☐	☐	Yes No N/A
15) Child sleepwalks during the night	☐	☐	☐	Yes No N/A
16) Child moves to someone else's bed during the night (parent, brother, sister, etc.)	☐	☐	☐	Yes No N/A
17) Child grinds teeth during sleep (your dentist may have told you this)	☐	☐	☐	Yes No N/A
18) Child snores loudly	☐	☐	☐	Yes No N/A

CSHQ Abbreviated

Subject ID: _____ Date: _____
Technician Initials: _____

Coding

Sleep Behavior (continued)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
19) Child seems to stop breathing during sleep	☐	☐	☐	Yes No N/A
20) Child snorts and/or gasps during sleep	☐	☐	☐	Yes No N/A
21) Child has trouble sleeping away from home (visiting relatives, vacation)	☐	☐	☐	Yes No N/A
22) Child awakens during night screaming, sweating, and inconsolable	☐	☐	☐	Yes No N/A
23) Child awakens alarmed by a frightening dream	☐	☐	☐	Yes No N/A

Waking During the Night

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
24) Child awakes once during the night	☐	☐	☐	Yes No N/A
25) Child awakes more than once during the night	☐	☐	☐	Yes No N/A

Write the number of minutes a night waking usually lasts: _____

Morning Waking/Daytime Sleepiness

Write in the time of day child usually wakes in the morning: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?
26) Child wakes up by him/herself (R)	☐	☐	☐	Yes No N/A
27) Child wakes up in negative mood	☐	☐	☐	Yes No N/A
28) Adults or siblings wake up child	☐	☐	☐	Yes No N/A
29) Child has difficulty getting out of bed in the morning	☐	☐	☐	Yes No N/A
30) Child takes a long time to become alert in the morning	☐	☐	☐	Yes No N/A
31) Child seems tired	☐	☐	☐	Yes No N/A

Child has appeared very sleepy or fallen asleep during the following (check all that apply):

	1 Not Sleepy	2 Very Sleepy	3 Falls Asleep
32) Watching TV	☐	☐	☐
33) Riding in car	☐	☐	☐

Appendix C. QUALITY OF LIFE (QoL) QUESTIONNAIRES

Dermatology-related QoL scores will be collected during the study.

- The Dermatitis Family Impact Questionnaire will be completed by all parents/guardians of participants aged 3 months-≤ 11 years, based on the age at enrollment.
- The CDLQI will be completed by all participants aged ≥4 - ≤ 11 years
- The IDLQI will be completed by all participants aged 3 months - <4 years

The following Quality-of-Life (QoL) questionnaires will be administered to the participant and/or parent/guardian of the participant on a supplied tablet (the paper form is shown below for review). Directions on how to complete the assessments will be provided to the participant and/or parent/guardian. The Schedule of Activities identifies the administration timing for the various assessments.

Subject ID: _____ Date: _____ Technician Initials: _____

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school Very much Quite a lot Only a little Not at all Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

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Subject ID: _____ Date: _____ Technician Initials: _____

"Dermatitis Family Impact Questionnaire"

Child's Name: LEAVE BLANK **Mother/Father/Carer** **Date:** **Score** ☐

The aim of this questionnaire is to measure how much your child's skin problem has affected you and your family OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how much effect has your child having eczema had on **housework**, e.g. washing, cleaning.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how much effect has your child having eczema had on **food preparation** and **feeding**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much effect has your child having eczema had on the **sleep of others in family**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much effect has your child having eczema had on **family leisure activities**, eg swimming.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much effect has your child having eczema had on **time spent on shopping for the family.**	Very much A lot A little Not at all	❒ ❒ ❒ ❒
6.	Over the last week, how much effect has your child having eczema had on your **expenditure**, eg costs related to treatment, clothes, etc.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
7.	Over the last week, how much effect has your child having eczema had on causing **tiredness** or **exhaustion** in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
8.	Over the last week, how much effect has your child having eczema had on causing **emotional distress** such as depression, frustration or guilt in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
9.	Over the last week, how much effect has your child having eczema had on **relationships** between the **main carer and partner** or between the **main carer and other children** in the family.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
10.	Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life.	Very much A lot A little Not at all	❒ ❒ ❒ ❒

Please check you have answered EVERY question. Thank you

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Subject ID: _____ Date: _____ Technician Initials: _____

INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)

Name: LEAVE BLANK **Date:** **IDQOL SCORE** ☐

Address:

The aim of this chart is to record how your child's dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please could you answer every question.

Dermatitis Severity

Over the last week, **how severe** do you think your child's dermatitis has been?; i.e. how red, scaly, inflamed or widespread.

- Extremely severe ☐
- Severe ☐
- Average ☐
- Fairly good ☐
- None ☐

Life Quality Index

1. Over the last week, how much has your child been **itching and scratching**?
   - All the time ☐
   - A lot ☐
   - A little ☐
   - None ☐

2. Over the last week, what has your child's **mood** been?
   - Always crying, extremely difficult ☐
   - Very fretful ☐
   - Slightly fretful ☐
   - Happy ☐

3. Over the last week approximately how much **time** on average has it taken **to get your child off to sleep** each night?
   - More than 2 hrs ☐
   - 1 - 2 hrs ☐
   - 15mins - 1 hr ☐
   - 0-15mins ☐

4. Over the last week, what was the **total time** that your child's **sleep was disturbed** on average each night?
   - 5 hrs or more ☐
   - 3 - 4 hrs ☐
   - 1 - 2 hrs ☐
   - Less than 1 hour ☐

5. Over the last week, has your child's eczema interfered with **playing or swimming**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

6. Over the last week, has your child's eczema interfered with your child **taking part in** or **enjoying other family activities**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - Not at all ☐

7. Over the last week, have there been problems with your child at **mealtimes** because of the eczema?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - None ☐

8. Over the last week, have there been problems with your child caused by the **treatment**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - None ☐

9. Over the last week, has your child's eczema meant that **dressing and undressing** the child has been **uncomfortable**?
   - Very much ☐
   - A lot ☐
   - A little ☐
   - None ☐

10. Over the last week how much has your child having eczema been a problem at **bathtime**?
    - Very much ☐
    - A lot ☐
    - A little ☐
    - None ☐

Please can you check that you have answered every question.

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Subject ID: _____ Date: _____ Technician Initials: _____

OBSERVER REPORTED GLOBAL IMPRESSION OF CHANGE (OGIC)

Place an X in the box you feel most closely describes any change which the child has experienced. Take into account all change, whether or not you believe it is entirely due to drug treatment.

Select only ONE response.

Since the start of the study, the child's atopic dermatitis is:

- Very much improved ☐
- Much improved ☐
- Minimally improved ☐
- No change ☐
- Minimally worse ☐
- Much worse ☐
- Very much worse ☐

Subject ID: _____ Date: _____
Technician Initials: _____

Mobile Device Proficiency Questionnaire (MDPQ-16)

About the MDPQ
This questionnaire asks about your ability to perform a number of tasks with a **mobile device**.

What is a Mobile Device?
A mobile device is a device that allows you to perform many of the same tasks as a standard computer but without the use of a physical keyboard and mouse. Instead, these devices use a touchscreen as their interface between the user and computer programs (called Apps – short for applications).

Mobile devices come in many sizes. Depicted above are two different sized tablets, as well as a smartphone. These are the types of devices we are interested in.

ROQUE, N. & BOOT, W.R. (IN PRESS). A NEW TOOL FOR ASSESSING MOBILE DEVICE PROFICIENCY IN OLDER ADULTS: THE MOBILE DEVICE PROFICIENCY QUESTIONNAIRE (MDPQ). JOURNAL OF APPLIED GERONTOLOGY.

Subject ID: _____ Date: _____
Technician Initials: _____

Please answer each question by placing an X in the box that is most appropriate.

If you have not tried to perform a task with a mobile device or do not know what a task is, please mark "NEVER TRIED", regardless of whether or not you think you may be able to perform the task. **Remember, you are rating your ability to perform each of these tasks specifically using a mobile device (tablet or smartphone).**

---

1. Mobile Device Basics

Using a mobile device I can:	**Never tried (1)**	**Not at all (2)**	**Not very easily (3)**	**Somewhat easily (4)**	**Very easily (5)**
a. Navigate onscreen menus using the touchscreen					
b. Use the onscreen keyboard to type					

2. Communication

Using a mobile device I can:	**Never tried (1)**	**Not at all (2)**	**Not very easily (3)**	**Somewhat easily (4)**	**Very easily (5)**
a. Send emails					
b. Send pictures by email					

Subject ID: _____ Date: _____
Technician Initials: _____

3. Data and File Storage

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Transfer information (files such as music, pictures, documents) on my mobile device *to* my computer					
b. Transfer information (files such as music, pictures, documents) on my computer *to* my mobile device					

4. Internet

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Find information about my hobbies and interests on the Internet					
b. Find health information on the Internet					

Subject ID: _____ Date: _____
Technician Initials: _____

5. Calendar

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Enter events and appointments into a calendar					
b. Check the date and time of upcoming and prior appointments					

6. Entertainment

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Use the device's online "store" to find games and other forms of entertainment (e.g. using Apple App Store or Google Play Store)					
b. Listen to music					

Subject ID: _____ Date: _____
Technician Initials: _____

7. Privacy

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Setup a password to lock/unlock the device					
b. Erase all Internet browsing history and temporary files					

8. Troubleshooting & Software Management

Using a mobile device I can:	Never tried (1)	Not at all (2)	Not very easily (3)	Somewhat easily (4)	Very easily (5)
a. Update games and other applications					
b. Delete games and other applications					

Subject ID: _____ Date: _____ Technician Initials: _____

Table 1. FLACC Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.			

Subject ID: _____ Date: _____

PP-NRS for Caregivers ages 18-75:

Select the number that "On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
No Itch										Worst Itch Imaginable

Subject ID: _____ Date: _____ Technician Initials: _____

POEM

Patient-Oriented Eczema Measure

The University of Nottingham

UNITED KINGDOM • CHINA • MALAYSIA

POEM for proxy completion (e.g by parent)

Patient Details: _____

Leave blank

Date: _____

Please circle one response for each of the seven questions below about your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your child's skin been itchy because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your child's sleep been disturbed because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your child's skin been bleeding because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your child's skin been weeping or oozing clear fluid because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your child's skin been cracked because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your child's skin been flaking off because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your child's skin felt dry or rough because of their eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): .....

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Subject ID: _____ Date: _____ Technician Initials: _____

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

POEM for proxy completion (e.g by parent)

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

• 0 to 2	= Clear or almost clear
• 3 to 7	= Mild eczema
• 8 to 16	= Moderate eczema
• 17 to 24	= Severe eczema
• 25 to 28	= Very severe eczema

Do I need permission to use the scale?

Whilst the POEM scale is protected by copyright, it is freely available for use and can be downloaded from: www.nottingham.ac.uk/dermatology
We do however ask that you register your use of the POEM by e-mailing cebd@nottingham.ac.uk with details of how you would like to use the scale, and which countries the scale will be used in.

References

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140:1513-1519

Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. Dec 2013; 169(6): 1326–1332.

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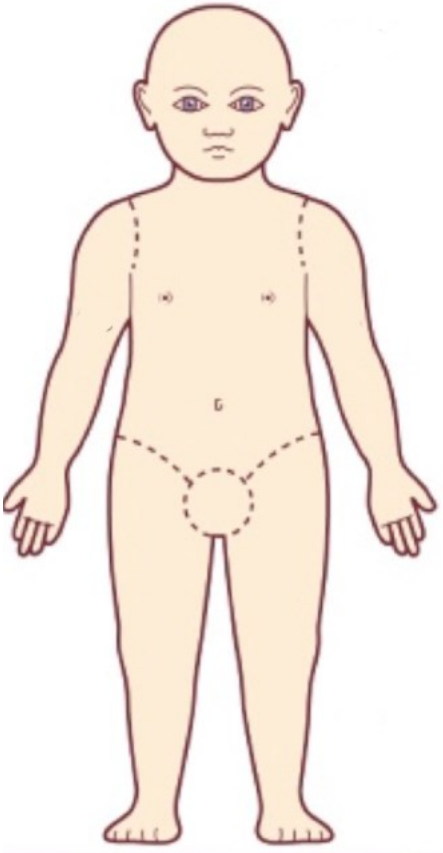
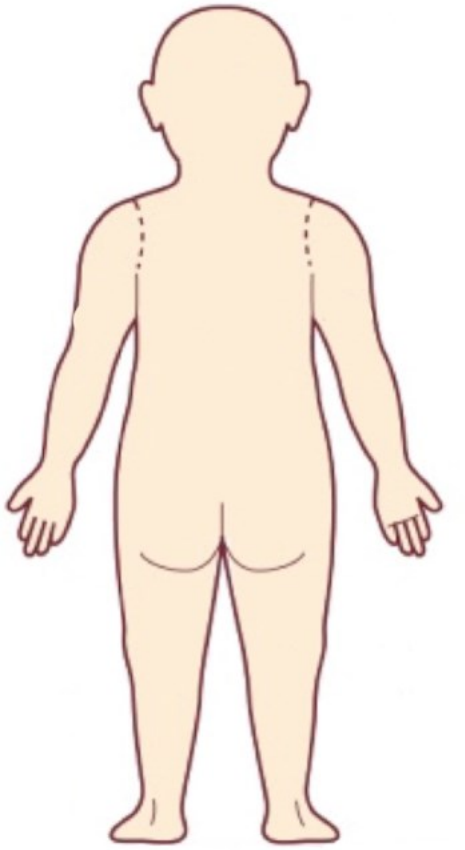
Dosing record sheet Subject ID: _____

Instructions: Everyday, you will be applying the ointment twice a day on all affected areas in thin even layers except on the eyes, mouth, and vagina. Do not apply the study ointment to the face within 1 or 2 fingers away from the of the mouth, or hands/fingers to avoid inadvertent ingestion of the ointment. Wash your hands after everytime you apply the ointment; if you are breastfeeding, use the provided gloves to apply the ointment. Following diaper change, any study ointment inadvertently wiped off soiled skin should not be reapplied until the next scheduled dose. In the case of rash in the diaper area without AD involvement, standard treatments may be applied, and agree to refrain from applying diaper rash creams, lotions, ointments, powders, etc. where AD lesions are present, unless the lesions are on locations where the study ointment may not be applied (face within 1 or 2 fingers away from the of mouth and hands/fingers).

Every time you apply the ointment, please record the date and time on a separate sheet. On each dosing record sheet, please circle on the pictures where you applied the ointment each application time.

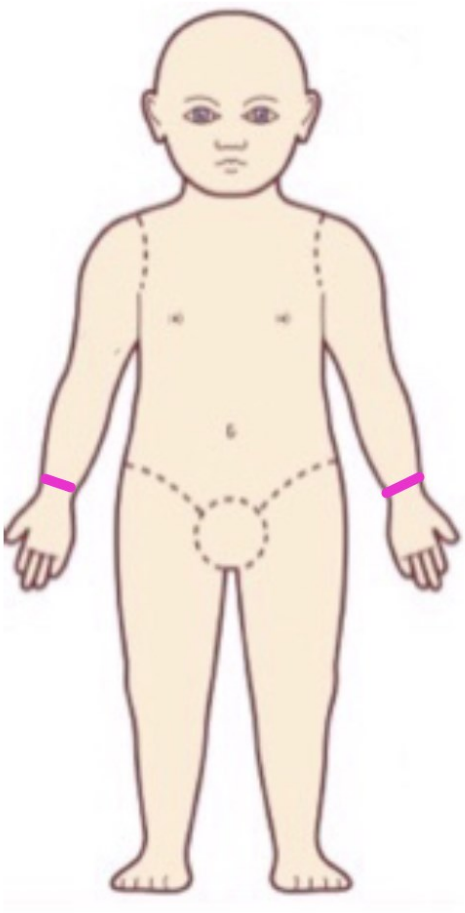
Date: _____ Time: _____





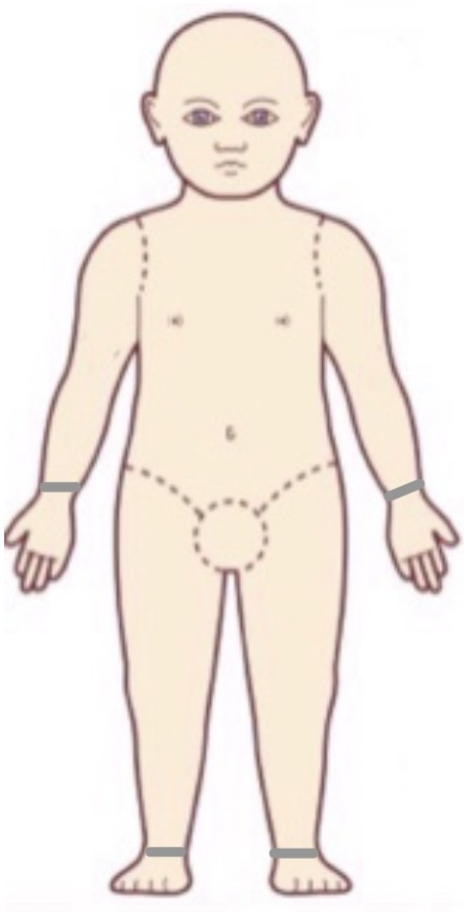
Appendix B- Location of accelerometry and actigraphy devices on the children participants Devices will be optional for child participants who have active AD on location of device placement, with a minimum of at least one wrist device needed for enrollment.

2 – ≤ 11 years old



Accelerometry

3 months - < 2 years old



Actigraphy or Accelerometry

Subject ID: _____ Date: _____ Technician Initials: _____

Lesion/Non-Lesion Tape Stripping Guide and Lesional/Non-Lesional Site Identification Form

Selection of lesional and non-lesional body location is as follows:

Lesional site: Identified at V01 based on BSA assessment (same site used throughout the study):

Lesional site anatomical location: _____
De-identified photo of lesional location captured: Y_____ N _____

Non-lesional site: Identified at V01 based on BSA assessment from skin that is unaffected by atopic dermatitis in a similar region of the body as the lesional site (opposite side of body is acceptable).

Non-lesional site anatomical location: _____
De-identified photo of non-lesional location captured: Y_____ N _____

Lesional tape strips will be collected from skin adjacent to an atopic dermatitis lesion that is part of the planned treatment area at the baseline (V01), Day 2 (V03), and the Day 15 (V05) visits. V03 and V05 lesional collections should be from the location as the V01 lesional collection, even if the severity of the lesion has changed.

Nonlesional tape strips will be collected from skin that is unaffected by atopic dermatitis at the baseline visit (V01) only. If possible, the nonlesional area where tape strips are collected should be in a similar region of the body (opposite side is okay) to where the lesional strips are collected and should be at least 2 cm from the selected lesion.

Mitigation of risk associated with tape stripping: Tape stripping will only be conducted three times during the study, with a minimum of 3 days between each tape stripping. If the participant experiences discomfort, adjacent sites to previous stripping area will be used, and this should be noted on the sample manifest.

Skin Tape Strip Collection Procedure:

1. Wearing gloves, apply a tape strip to the target area. Using a marker pen, make small marks on the skin after placement of the first tape strip to ensure consistent placement of subsequent tape strips at each site. Change to a fresh pair of gloves between non-lesional and lesional collections in order to avoid cross-contamination.
2. Apply pressure with the D-Squame pressure instrument for approximately three to five seconds. The pressure instrument has a plunger mechanism to ensure even/consistent pressure is applied to each tape strip.
3. As soon as the pressure is applied and released, the tape strips should be removed with gloved hands and stuck onto the D-Squame storage cards, as described above.
4. Cards with tape strips should be immediately stored on dry ice (or in a -20°C freezer) in the appropriate labeled specimen bag and then transferred to a -80°C freezer until shipment.

Samples collected and stored at site should be shipped approximately once every two weeks to Pfizer Clinical PGx Lab. Samples should be packaged using dry ice above and below the bags containing the frozen tape strips. Dry ice should be added to a Styrofoam shipping container and placed within a cardboard box. The shipping container should be at least ½ to ¾ filled with dry ice to ensure that the specimens do not thaw during travel.

WORD READING SUBTEST

AGES 7 OR YOUNGER: Administer Part 1: Letter Reading first, followed by Part 2: Word Reading. Discontinue testing if a Participant has responded incorrectly to 10 consecutive items (*10 RULE*).

AGES 8 OR OLDER: Administer Part 2: Word Reading first. Discontinue the Word Reading section if the Participant has answered 10 consecutive items incorrectly (*10 RULE*). If the Participant has correctly answered 5 or more items on the Word Reading section before meeting the discontinue criterion, do not administer the preliminary Letter Reading section. If the Participant did not answer at least 5 items correctly on the Word Reading section, then administer Part 1: Letter Reading (*5 RULE*).

Part 1: Letter Reading Administration Instructions

After handing the Participant the Green Word Reading List, say, **I want you to look at the letters on this line.** (Point to the row of letters at the top of the card) **Read to me the letters one-by-one across the line.** After the Participant has finished, say, **That's all. Now let's do something different.**

A	B	O	S	E	R	T	H	U	P	I	V	Z	J	Q
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)

Part 2: Word Reading Administration Instructions

After handing the Participant the Green Word Reading List, say, **Look at each of these words carefully.** (Point to the words) **Read the words across the page so I can hear you. When you finish the first line, go right on to the second line, and so on down the page until you finish or I tell you to stop. Read slowly and say the words clearly.** Allow 10 seconds for the Participant to respond to each word. If there is no response after 10 seconds, say, **OK, try the next one.** If you did not hear a word clearly, say, **I could not hear you clearly. Please say the word again just as you did the first time.** When the Participant has finished the Word Reading section, say, **That's all. Good job. Thanks. Now we are going to do something else.**

1. **see**
   see
2. **red**
   red
3. **milk**
   milk
4. **was**
   wuz, woz
5. **then**
   then
6. **jar**
   jahr
7. **letter**
   let-ĕr
8. **city**
   sit-ee
9. **between**
   bi-tween
10. **cliff**
    klif
11. **listen**
    lis-ĕn
12. **wrap**
    rap
13. **plot**
    plot
14. **grunt**
    grunt
15. **sour**
    sowr
16. **huge**
    hyooj
17. **privilege**
    priv-ĭ-lij
18. **license**
    li-sĕns
19. **humidity**
    hyoo-**mid**-i-tee
20. **gadget**
    gaj-it
21. **tough**
    tuf
22. **residence**
    rez-i-dĕns
23. **urge**
    urj
24. **clarify**
    klar-i-fī
25. **rancid**
    ran-sid
26. **suspicion**
    sŭ-**spish**-ŏn
27. **conspiracy**
    kŏn-**spir**-ă-see
28. **deny**
    di-**nī**
29. **miscellaneous**
    mis-ĕ-**lay**-ni-ŭs
30. **quarantine**
    kwor-ăn-teen
31. **deteriorate**
    di-**teer**-i-ŏ-rayt
32. **concoct**
    kŏn-**kokt**
33. **coincide**
    ko-in-**sid**
34. **mosaic**
    moh-**zay**-ik
35. **debris**
    dĕ-**bree**
36. **rudimentary**
    roo-di-**men**-tĕ-ree
37. **novice**
    nov-is
38. **longevity**
    lon-**jev**-i-tee
39. **rescinded**
    ri-**sind**-ed
40. **audacious**
    aw-**day**-shŭs
41. **extemporaneous**
    ik-stem-po-**ray**-ni-ŭs
42. **protuberance**
    proh-**too**-bĕ-răns
43. **diminutive**
    di-**min**-yŭ-tiv
44. **factitious**
    fak-**tish**-ŭs
45. **regime**
    rĕ-**zheem**
46. **predilection**
    pred-ĭ-**lek**-shŏn
47. **lucubration**
    loo-kyuu-**bray**-shŏn
48. **sanguine**
    sang-gwin
49. **puerile**
    pyoo-ĕ-rĭl
50. **internecine**
    in-tĕr-**nee**-seen, -**nes**-een
51. **ubiquitous**
    yoo-**bik**-wi-tŭs
52. **regicidal**
    rej-i-**sī**-dăl
53. **inefficacious**
    in-ef-i-**kay**-shŭs
54. **epithalamion**
    ep-i-thă-**lay**-mi-ŏn
55. **synecdoche**
    si-**nek**-dŏ-kee

Letter Reading Raw Score	/15
+ Word Reading Raw Score*	/55
Word Reading Total Raw Score	/70

Next administer the Sentence Comprehension subtest, if applicable.

*Use this value for determining starting point on Sentence Comprehension subtest.

SPELLING SUBTEST

AGES 7 OR YOUNGER: Administer Part 1: Letter Writing first, followed by Part 2: Spelling. The Spelling section must be administered individually for participants ages 7 and younger. On the Spelling section, the test should be discontinued after the Participant spells 10 consecutive words incorrectly (*10 RULE*).

AGES 8 OR OLDER: Administer Part 2: Spelling first. Discontinue if 10 consecutive errors have been made (*10 RULE*). If the Participant has correctly spelled 5 or more items on the Spelling section before meeting the discontinue criterion, the preliminary Letter Writing section should not be administered. If the Participant does not spell at least 5 words correctly on the Spelling section, then administer Part 1: Letter Writing (*5 RULE*).