4.1. Inclusion Criteria

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

1. Is male or female and the appropriate age in years (2 years and older) at time of informed consent/assent.

2. Has a clinical diagnosis of AD according to the criteria of Hanifin and Rajka (See Appendix 2).

3. Has AD involvement of ≥5% Treatable BSA (excluding the scalp) at Baseline/Day 1.

4. Has an ISGA score of Mild (2) or Moderate (3) (excluding the scalp) at Baseline/Day 1.

5. Has adequate venous access to permit venipuncture for clinical safety laboratory sampling.

6. Female subjects of childbearing potential who have a negative urine pregnancy test at the screening visit and negative urine pregnancy test at the baseline visit prior to randomization. A female is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having Children (includes any female who has experienced menarche and does not meet the criteria for females not of childbearing potential. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; have a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

7. Evidence of a personally signed and dated informed consent/assent document indicating that the subject [or parent(s)/legal guardian] has been informed of all pertinent aspects of the study.

8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

Day [relative to start of study treatment (Day 1)]	**Within 35 days prior to Day 1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29[t]**	**Day 36**	**Day 60**
Window			**±1 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**
Visit	**Screening[q]**	**Baseline**				**End of Treatment/ Early Termination**	**Follow up telephone Contact[r]**	**Follow up telephone contact[r]**
Peak Pruritus Numerical Rating Scale (NRS), Patient Reported Itch Severity Scale OR Observer Reported Itch Severity Scale[g]	Daily During Screening	To be captured daily from Day 1 to Day 29						
Patient Global Impression of Severity (PGIS) OR Observer Reported Global Impression of Severity (OGIS)[h]	Daily During Screening	To be captured daily from Day 1 to Day 29						
Patient Global Impression of Change (PGIC) OR Observer Reported Global Impression of Change (OGIC)[i]			x	x	x	x		
CDLQI/DLQI/IDQOL, DFI[j]	X	x		x		x		
Patient Oriented Eczema Measure (POEM)[s]	X	x		x		x		
Columbia Suicide Severity Rating Scale (C-SSRS)[k]	X							
Serum chemistry and hematology	X	x[l]				x		
Urine pregnancy test (in female subjects of childbearing potential only)[m]	X	x				x		
FSH (to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months)	X							
Randomization		x						
In-clinic dosing instruction		x	x	x	x			
In-clinic dose application by study staff (1st dose [preferred AM][n])		x						
At-home dosing, applied by subject or parent/legal guardian, as appropriate[o]		2nd dose (PM) on Day 1, then BID through Day 28[n]						
Dispense Dosing Diary		x	x	x	x			
Obtain and review Dosing Diary data and assess compliance			x	x	x	x		
Weigh investigational product tube(s) and dispense for at-home dosing		x	x	x	x			

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adult subjects (ages 2 years and older) with mild to moderate atopic dermatitis involving at least 5% treatable BSA.

A total of approximately 384 subjects (approximately 50% for age ≥12 years old and approximately 50% for age <12 years old) will be enrolled in the study from multiple sites in China and Japan. Following the screening period (up to 35 days prior to Baseline/Day 1), eligible subjects will be randomized at the Baseline/Day 1 visit in a 2:1 ratio to one of 2 treatment groups (crisaborole ointment, 2% BID; vehicle BID, respectively), the investigational product will be applied BID for 28 days to the Treatable BSA identified at Baseline/Day 1 and new AD lesions that appear after the Baseline/Day 1. The primary efficacy endpoint, percent change from baseline in EASI total score, will be assessed at Day 29.

Scale/Observer Reported Itch Severity Scale that would be completed once daily during screening period.

The following procedures will be performed at the Screening Visit:

- Obtain written informed consent (from adult subject or parent/legal guardian of pediatric subjects) and assent (from pediatric subjects, as applicable) before any study procedures are performed.

- Register subjects with IRT. The IRT must be contacted before screening assessments begin in order to obtain a subject screening identification number (SSID).

- Peak pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale and Patient Global Impression of Severity (PGIS)/Observer Global Impression of Severity (OGIS) will be completed by subject or observer when applicable once daily during screening prior to Day 1 regardless of whether the subject continues to randomization. If a subject is screen failed before above procedures are completed, then related data will not be collected.

- Complete the Patient Oriented Eczema Measure (POEM) (completed by subject or observer), Dermatology Life Quality Index (DLQI) (for subject >= 16 years old, completed by subject) Children's Dermatology Life Quality Index (CDLQI) (for subject 4-15 years old, completed by subject or observer), Infants' Dermatitis Quality of Life Index (IDQOL) (for subject 2-3 years old, completed by observer) and Dermatitis Family Impact Questionnaire (DFI) (for subject 2-17 years old, completed by observer).

  Note: DLQI, CDLQI, IDQOL, DFI, POEM will be collected at screening for all subjects including screen failure subjects. If a subject is screen failed before above procedures are completed, then related data will not be collected.

- Ask C-SSRS questions for subjects ≥7 years of age. Subjects meeting any of the criteria specified in Exclusion Criterion 12 will be ineligible for participation (See Section 4.2).

- Collect demographic information (sex, date of birth, race, ethnicity).

- Obtain vital signs (temperature, respiratory rate, pulse rate, and blood pressure [BP]) in the seated position or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes.

6.4.5. Follow-up Contact/Follow Up Period

Follow-up contact will be done via a phone call on 7 (±3) days and 31 (±3) days after the End of Treatment/Early Termination Visit to capture any potential adverse events and to review (see the Time Period for Collecting AE/SAE Information section) and record concomitant medications and to confirm appropriate contraception usage (see the Contraception section).

6.5. Subject Withdrawal/Early Termination

Withdrawal of consent:

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

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

throughout the study; a backup experienced and qualified, protocol trained evaluator will only be allowed and documented in case of emergency or special situation when the designated evaluator is unable to perform the evaluation. Identity (eg, initials) of the evaluator will be captured on the source documentation (eg, scale worksheet).

7.1.1. Calculation of Subject's Treatable %Body Surface Area (BSA)

The Treatable %BSA will be calculated for each subject at Screening, Baseline/Day 1, Days 8, 15, 22 and Day 29. The Treatable %BSA should be evaluated based on all AD lesions present on the day of the visit, excluding the scalp. Score 0 in the ISGA definition will not be evaluated as BSA while Score 1-4 will be.

Treatable %BSA is defined as the percentage of the subject's total BSA that is AD involved, excluding the scalp. To estimate the subject's Treatable %BSA, the investigator or his/her designee will use "handprint method", by which the area represented by the palmar (ie, outstretched) surface of the subject's hand with all five digits adducted together is approximately 1% of the subject's BSA, regardless of the subjects age.

7.1.2. Investigator's Static Global Assessment

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

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

ISGA assessment during the study must be done by the investigator or his/her designee. Every effort should be made to ensure that all ISGA assessments for a given subject are done by the same qualified individual throughout the study.

Table 1. Investigator's Static Global Assessment

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

This single item instrument uses a 7-point rating scale. The PGIS/OGIS will be used as an anchor for defining a 'clinical important difference' on the pruritus and itch assessments and can also be used to create severity categorization for pruritus and itch assessments to enhance interpretation.

- The PGIS will be completed by all participants ≥12 years of age.
- The OGIS will be completed by the observer for participants 2-11 years of age.

7.1.6.3. Patient Global Impression of Change (PGIC) and Observer Reported Global Impression of Change (OGIC)

The PGIC and OGIC are an one item- question to rate change in a patient's overall status. This single item instrument is a 7-point rating scale and will be used to determine global improvement. It will be used as an anchor to define a responder definition for the pruritus and itch assessments for 'clinically important responder' and as a sensitivity analysis for defining a 'clinical important difference' for pruritus and itch assessments.

- The PGIC will be completed by participants ≥12 years of age.
- The OGIC will be completed by the observer for participants 2-11 years of age.

7.1.6.4. Patient Oriented Eczema Measure (POEM)

The POEM[28,29,30] is a validated 7-item measure used to assess the impact of AD over the past week.

- The POEM will be completed by participants ≥12 years of age.
- The proxy POEM will be completed by observers for participants 2-11 years of age.

7.1.6.5. Dermatology related Quality of Life Questionnaires

Dermatology related quality of life (QoL) scores will be descriptively summarized by treatment group for each collection time point defined in the Schedule of Activities.

- The Dermatology Life Quality Index (DLQI) will be completed by all subjects aged 16 years and older, based on the age at time of informed consent/assent.
- The Children's Dermatology Life Quality Index (CDLQI) will be completed by the subject or observer for subjects aged 4–15 years, based on the age at time of informed consent/assent.
- The Infants' Dermatitis Quality of Life Index (IDQOL) will be completed by observer for subjects aged 2–3 years, based on the age at time of informed consent/assent.

- The Dermatitis Family Impact Questionnaire (DFI) will be completed by all observer for subjects aged 2–17 years, based on the age at time of informed consent/assent.

7.2. Safety Assessments

7.2.1. Clinical Laboratory Evaluations

The following safety laboratory tests will be performed at times defined in the Schedule of Activity section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

The clinical laboratory test parameters that will be reviewed for safety evaluation are presented in Table 5. Hematology, Chemistry and FSH will be done at a central laboratory.

Table 5. Clinical Laboratory Test Parameters

Hematology	Chemistry	Pregnancy	FSH[a]
Hemoglobin Hematocrit Red blood cell count Platelet count White blood cell count (% and absolute) • Neutrophils; • Eosinophils; • Monocytes; • Basophils; • Lymphocytes.	Blood urea nitrogen/Urea Glucose Creatinine Sodium Potassium Chloride Bicarbonate or Total CO_2 Alanine aminotransferase Aspartate aminotransferase Total bilirubin Alkaline phosphatase Albumin Total protein	At Screening, Baseline/Day 1, and Day 29 (End of treatment)/Early termination visit: Urine pregnancy test[b] (female subjects of childbearing potential only).	At Screening

a. At Screening only, to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months.

b. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). In the case of a positive urine β-hCG test during the treatment period, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study; if the serum β-hCG test is negative and investigator judged that the subject is not pregnant, the subject may resume investigational product.

Baseline clinical laboratory tests will be drawn during the Baseline/Day1 visit, after assessment of vital signs and prior to the first investigational product application.

If the screening serum chemistry and hematology tests are performed within 15 days prior to Baseline/Day 1, whether the Day 1 serum chemistry and hematology tests are to be performed will be at the discretion of the investigator or his/her designee.

At the discretion of the investigator or his/her designee, a lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the subject provided the anesthetic does not contain propylene glycol. However, the skin must be thoroughly cleansed prior to blood sample collection.

The Investigator will review all clinical laboratory test results for safety evaluation upon receipt. After reviewing the laboratory reports and evaluating the results for clinical significance, the investigator or his/her designee must sign and date the laboratory report. Clinically significant laboratory abnormalities are defined as abnormal values that have clinical manifestations or require medical intervention. Clinically significant laboratory abnormalities noted from the Screening Visit will be recorded in the medical history.

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

7.2.2. Physical Examination, including Height, and Weight

Physical examinations, including height, and weight will be performed at times specified in the Schedules of Activities section of this protocol.

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

A full physical examination will be performed at Screening and Day 29 (End of treatment)/Early termination visit which will include, but is not limited to the following organ or body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, musculoskeletal, abdomen (liver, spleen), and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin.

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

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

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent/assent as described in Section 8.1.4, will be recorded on the AE section of the CRF.

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.4.3. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- For subjects with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

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

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

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability**

baseline in weekly average of peak pruritus NRS of weeks other than Week 4, change from baseline in weekly average of Patient Reported Itch Severity Scale, and change from baseline in weekly average of Observer Reported Itch Severity Scale will be analyzed similarly as the primary efficacy endpoints using a linear mixed effect model for repeated measures.

Other secondary efficacy endpoints including EASI50 and EASI75 at all time points, as well as Success in ISGA and Improvement in ISGA at all time points other than Day 29, will be analyzed using normal approximation to response rates.

DLQI, CDLQI, IDQOL, DFI, POEM, PGIS/OGIS, PGIC/OGIC will be summarized descriptively, missing values will be handled following instrument-specific procedures when available and as per the SAP.

9.3. Safety Analysis

Safety data will be descriptively summarized and will be presented in tabular and/or graphical format. No imputation will be made for missing safety data. The following safety data will be summarized:

- TEAEs, including SAEs;
- Clinically significant changes in vital signs;
- Clinically significant changes in laboratory parameters.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study.

Abbreviation	Term
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food And Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HRQOL	Health-Related Quality Of Life
IB	Investigator'S Brochure
ID	Identification
ICH	International Conference On Harmonisation
IDQOL	Infants' Dermatitis Quality Of Life Index
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISGA	Investigator'S Static Global Assessment
IUD	Intrauterine Devicem
IWR	Interactive Web Response
JAK	Janus Kinase
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
LSLV	Last Subject Last Visit
MI	Multiple Imputations
MCMC	Markov Chain Monte Carlo
MMF	Mycophenolate Mofetil
MMP	matrix metalloproteinase
MUSE	Maximal Use Systemic Exposure
N/A	Not Applicable
NRI	Non Responder Imputation
NRS	Numeric Rating Scale
OGIC	Observer Global Impression of Change
OGIS	Observer Global Impression of Severity
PCD	Primary Completion Date
PD	Pharmacodynamics(S)
PDE4	Phosphodiesterase-4
PGIC	Patient Global Impression of Change

4.2. Exclusion Criteria

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

1. Has any clinically significant medical disorder, condition, or disease (including active or potentially recurrent non-AD dermatological conditions and known genetic dermatological conditions that overlap with AD, such as Netherton syndrome) or clinically significant physical examination finding at Screening that in the PI's or designee's opinion may interfere with study objectives (eg, expose subject to unacceptable risk by study participation, confound evaluation of treatment response or AEs, or interfere with subject's ability to complete the study).

2. Has unstable AD or any consistent requirement for high/strong potency or very high/very strong potency topical corticosteroids to manage AD signs and symptoms.

3. Has a history of angioedema or anaphylaxis.

4. Has a significant active systemic or localized infection, including known actively infected AD.

5. Has received any of the prohibited medications/therapies that may alter the course of AD without the required minimum washout (see Section 5.8.1) or anticipated concomitant use of the any of the prohibited medications/therapy (see Section 5.8.2).

6. Has any planned surgical or medical procedure that would overlap with study participation, from Screening through the end of study.

7. Has history of cancer within 5 years or has undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only).

8. Has a known sensitivity to any of the components of the investigational product.

9. Has participated in a previous crisaborole clinical study or had previous treatment with Crisaborole ointment, 2%, or other topical or oral PDE-4 inhibitors.

10. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

	[q]	Baseline				End of Treatment/ Early Termination	Follow up telephone Contact[r]	Follow up telephone contact[r]
Collect and weigh returned investigational product tube(s)			x	x	x	x		
Contraception Check	X	x	x	x	x	x	x	X

a. Record all treatments (including medications and non-medication therapies) used for AD 90 days prior to screening and all other medications (including bland [non-medicated] emollients, over-the-counter drugs, vitamins, and antacids) used within 30 days prior to Screening.

b. Temperature, respiratory rate, pulse rate, and blood pressure taken in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes. Position of recording must be consistent within subject through-out the study. At Baseline/Day 1 and Day 29, assessment of vital signs should precede blood draw for clinical laboratory tests.

c. Full physical examination including, but is not limited to the following organ or body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, musculoskeletal, abdomen (liver, spleen), and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin.

d. Disease focused physical examination of all AD involved skin (in treatable and non-treatable areas) and evaluate any current or reported symptoms for clinically significant changes.

[redacted]

g. Peak Pruritus NRS will be completed by subject (≥12 years), Patient Reported Itch Severity Scale will be completed by the subject (≥6 years and <12 years.), and Observer Reported Itch Severity Scale will be completed by observer [parent/legal guardian/other caregiver] when applicable) for patients <6 years in screening once daily prior to Day 1, and once daily from Day 1 to Day 29 before IP morning dose application preferably at the same time of each day if applicable.

h. PGIS will be completed by the subject (≥12 years) or OGIS will be completed by observer (for subjects 2-11 years) once daily preferably at the same time as the Pruritus NRS.

i. PGIC will be completed by the subject (≥12 years) or OGIC will be completed by observer (for subjects 2-11 years) at the same day when ISGA was assessed post baseline.

j. The CDLQI will be completed by subject or observer for subjects aged 4–15 years, based on the age at time of informed consent/assent. The DLQI will be completed by all subjects aged 16 years and older, based on the age at time of informed consent/assent. IDQOL will be completed by observer for subjects aged 2-3 years based on age at time of informed consent/assent. The DFI will be completed by observer for subjects aged 2–17 years, based on the age at time of informed consent/assent.

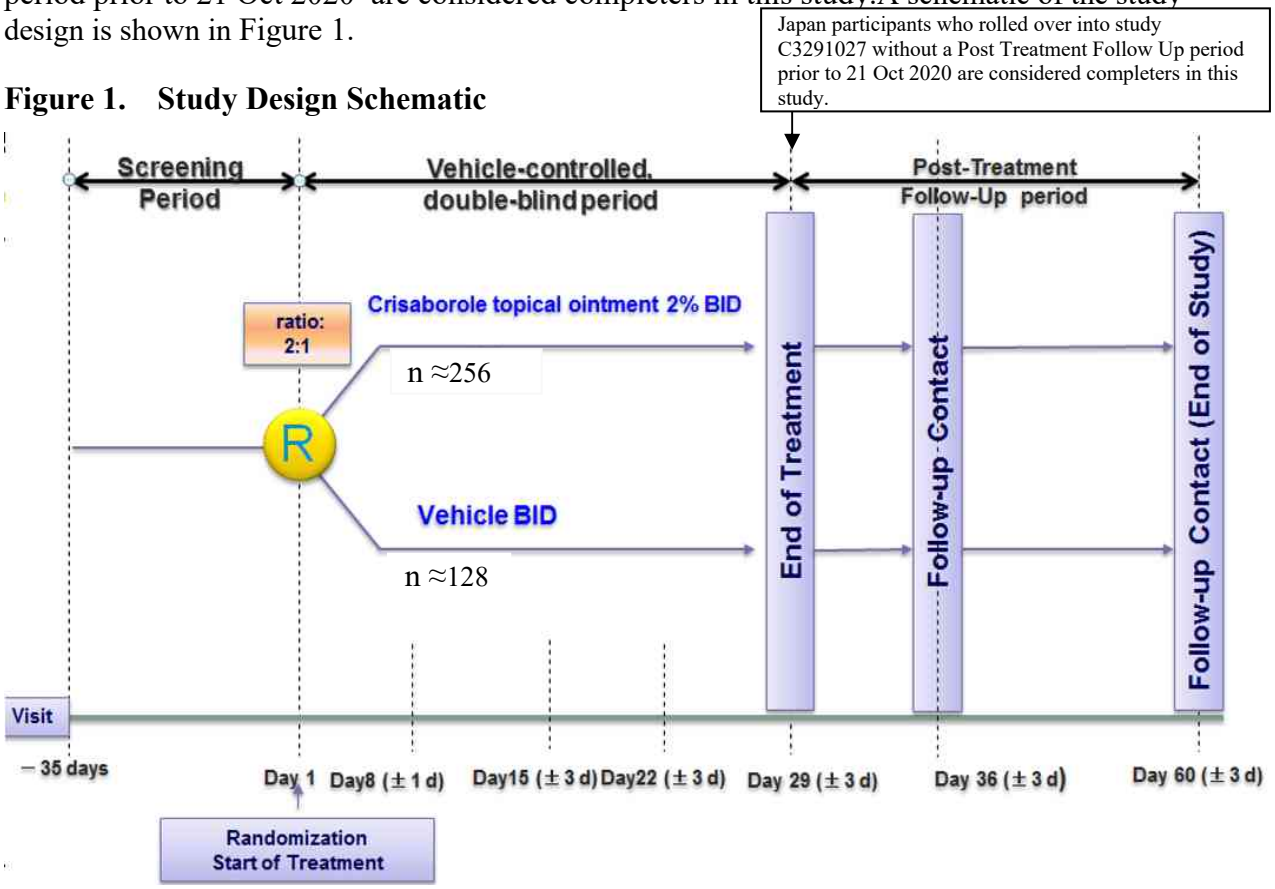
k. Investigator completed C-SSRS for subjects ≥7 years old.

l. Blood draw for clinical laboratory tests (serum chemistry and hematology) on Day 1 will be performed before the in-clinic investigational product application. If the screening serum chemistry and hematology tests are performed within 15 days prior to Day 1, whether the Day 1 serum chemistry and hematology tests are to be performed will be at the discretion of the investigator or his/her designee.

Scheduled study visits for all subjects will occur at Screening, Baseline/Day 1, Day 8, Day 15, Day 22, Day 29 (End of treatment/Early termination). A follow up telephone call will be made by site staff to the subjects and/or parents/legal guardians on Day 36 and Day 60 (See Section 6.4.5).

Japan participants who rolled over into study C3291027 without a Post Treatment Follow Up period prior to 21 Oct 2020 are considered completers in this study.A schematic of the study design is shown in Figure 1.

Figure 1. Study Design Schematic



4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

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

- Collect complete medical history, including onset of AD (date of diagnosis, as specifically as known).
- Measure height and weight.
- Perform a complete physical examination and confirm clinical diagnosis of AD per Hanifin and Rajka criteria (Appendix 2).
- Record all prior and concomitant medications (including all medications and non-medication therapies) used for AD used within 90 days prior to screening and all other treatments, including bland emollients, over-the-counter- drugs, vitamins, and antacids, used within 30 days prior to Screening.

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

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

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

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Efficacy Assessments

Clinical evaluations of atopic dermatitis will be performed by an experienced and certified physician, dermatologist, or medical professional. The evaluator must have received documented training to conduct the protocol AD specific clinical evaluations prior to performing these evaluations. To assure consistency and reduce variability, the same evaluator must assess all clinical evaluation of atopic dermatitis for any individual subject

CCI [redacted]

[26] quantifies the severity of a subject's atopic dermatitis 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.

Percent BSA with Treatable AD: The number of handprints of AD skin in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 2).

Table 2 Handprint Determination of Body Region Surface Area

Body Region	**Total Number of Handprints in Body Region***	**Surface Area of Body Region Equivalent of One Handprint**	**Total Number of Handprints in Body Region***	**Surface Area of Body Region Equivalent of One Handprint**
	≥8 years of age		2-7 years of age	
Head and Neck	10	10%	20	5%
Upper Limbs	20	5%	20	5%
Trunk (including axillae)	30	3.33%	30	3.33%
Lower Limbs (including buttocks)	40	2.5%	30	3.33%

*The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp from the BSA assessment.
Note: The age of cut-off is based on the age at time of informed consent.

A disease focused physical examination of all AD involved skin (in treatable and non-treatable areas) will be performed at Baseline/Day 1.

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

7.2.3. Vital Signs

Vital sign measurements (temperature, respiratory rate, pulse rate, and BP) will be performed at Screening, Baseline/Day 1, Day15 and Day 29. Vital sign measurements should be performed with the subject in the seated or lying position and after the subject has been sitting or lying calmly for a minimum of 5 minutes. The position of recording must be consistent within subject through-out the study. On study day visits when clinical laboratory tests are performed, assessment of vital signs should precede blood draw.

7.2.4. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior and will be completed at the Screening for subjects ≥7 years of age. This is investigator completed. For younger participants under 7 years of age, the investigator/designee should assess the suicidal ideation and behavior risks clinically in consultation with their parents/caregivers.

7.3. Pregnancy Testing

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

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

Pediatric female subject who has not experienced menarche is not required to perform pregnancy testing. If the pediatric female subject starts menarche during the study, pregnancy testing will be performed.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/[parent(s)/legal guardian]. In addition, each study subject/[parent(s)/legal guardian/] will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal/Early Termination section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.4. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

9.5. Data Monitoring Committee

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

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Abbreviation	Term
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic
PM	Evening
PMA	Phorbol 12-myristate 13-acetate
POEM	Patient-Oriented Eczema Measure
PKA	Protein Kinase A
PPAS	Per Protocol Analysis Set
PRN	As Needed
PT	Prothrombin Time
PUVA	Psoralen–UV-A
QD	Once Daily
QoL	Quality of Life
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
SSIN	Subject Screening Identification Number
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TBili	Total Bilirubin
T_{max}	Time to Reach Maximum Observed Plasma Concentration
TQT	Thorough QT/QTc
TSS	Target Sign Scores
ULN	Upper Limit of Normal
US	United States