A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE BLIND, VEHICLE CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF CRISABOROLE OINTMENT, 2% IN CHINESE AND JAPANESE PEDIATRIC AND ADULT SUBJECTS (AGES 2 YEARS AND OLDER) WITH MILD TO MODERATE ATOPIC DERMATITIS

Investigational Product Number:	PF-06930164
Investigational Product Name:	Crisaborole
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	Not applicable
Protocol Number	C3291032
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	17 October 2017	Not applicable (N/A)
Amendment 1	15 November 2019	Section 1: Update of additional study information of studies completed after the original protocol of 17 October 2017 Rationale: To reflect updated Crisaborole knowledge. Section 2: Update of the primary and key secondary efficacy endpoints to align with global clinical development program, including: • Change primary endpoint from ISGA (Investigator's Static Global Assessment) to EASI (Eczema Area and Severity Index). • Addition of ISGA as a key secondary endpoint. • Addition of age specification for Pruritus assessments. • CCI [redacted] Section 4.2 and Section 7.2.4: Addition of C-SSRS assessment at screening visit to exclude the subject with suicidal ideation. Rationale: To align with global development program. Section 5.8.1: Addition of requirement that prior dupilumab use is exclusionary. Rationale: To minimize confounding factors on efficacy and safety assessment. Section 5.8.1, 5.8.2 and 5.8.3: Unified requirements on the washout periods of non-sedating and sedating systemic antihistamines as 7 days prior to Baseline/Day 1; clarified a stable systemic

		antihistamine regimen with at least 7 days of consistent use prior to Baseline/Day 1 is permitted to continue but must not alter or stop their regimen during the study. Section 7.1.4: addition of table Handprint Determination of Body Region Surface Area to provide more instruction about EASI. Section 7.1.6: Modify instructions for PROs (Patient Reported Outcomes) and remove all questionnaires in text. Rationale: For the purpose of compliance with legal requirements for use of copyrighted questionnaires while required processes are carried out for obtaining licenses for their use according to this Amendment and current study timelines. This will also provide for more simple and clear instructions in protocol. Section 7.2.1: Extend the longest acceptable interval period between Screening visit and Day 1 for serum chemistry & hematology tests from 7 days to 14 days. Section 9: Update of sample size justification and statistical analyses after the change in primary efficacy endpoint specified in Section 2.
Amendment 2	28 August 2020	● Only for Japan: Japan participants who complete the study intervention period in Study C3291032 will be offered participation in the long-term safety extension study C3291027 if eligibility criteria are met. The participants who roll over into study C3291027 without a Post Treatment Follow Up period will be considered completers in this study. Rationale: This change is made to allow Japan subjects who complete the study intervention period in Study C3291032 and roll over into the long-term safety extension study C3291027 to be

		considered completers in C3291032. The following sections of the protocol are affected: Protocol Summary, Schedule of Activities, Section 3, and Section 6.4.3. ● All female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use an appropriate method of contraception consistently and correctly for the screening period, the duration of the active treatment period and for at least 28 days after the last dose of investigational product. Male condom or female condom used with or without a spermicide product (ie, foam, gel, film, cream, or suppository) is viewed as an appropriate contraceptive method. Rationale: As the crisaborole label does not require contraceptive precautions and there is no suspicion of human teratogenicity based on the intended pharmacology, male condom or female condom used without a spermicide product will be acceptable in this study. The following sections of the protocol are affected: Section 4.2, and Section 4.4.1. ● Subjects who had previous treatment with Crisaborole ointment, 2%, or other topical or oral PDE-4 inhibitor will be excluded. Rationale: To enroll PDE-4 inhibitor treatment naïve subjects to avoid inclusion of participant who has a potential lack of efficacy to PDE-4

		inhibitor. The following section of the protocol is affected: Section 4.2. ● Medications Prohibited 28 Days Prior to Baseline/Day 1: Use of systemic JAK inhibitor, within 28 days prior to Baseline/Day 1. Rationale: To avoid potential impact of systemic JAK inhibitor on AD lesions, which may interfere with crisaborole efficacy and safety evaluation. The following section of the protocol is affected: Schedule of Activities and Section 5.8.1. ● As the documentation of treatable areas will be updated for any new AD lesions that appear after the Baseline/Day 1 Visit. The subject and parent/legal guardian (if applicable) will be provided with documentation of the designated treatment areas after the Baseline/Day 1 Visit, to ensure that previously treated areas which have resolved continue to be treated as required. The following sections of the protocol are affected: Schedule of Activities and Section 6.4.2. ● If the screening serum chemistry and hematology tests are performed within ~~14 days~~ 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. Rationale: 14 days is revised to 15 days as if a subject happens to take a medication that needs to be washed-out for 14 days at Day 1, the next possible date to start Day 1 is 15 days later. In

		such case, clinical laboratory tests need to be repeated as per the current description. The following section of the protocol is affected: Schedule of Activities note l. ● Use of emollients, not only non-medicated but also medicated emollients should also be prohibited within 1 day prior to Baseline/Day 1. Rationale: medicated emollients should also be prohibited as it has clear effect on AD and may interfere with the efficacy and safety evaluation of study drug. The following section of the protocol is affected: Section 5.8.1. ● Further clarify the definition of medication error. Rationale: Explain clearly to avoid misunderstanding. The following section of the protocol is affected: Section 8.4.4.1. ● Rationale: Age could differ at screening visit vs. inform consent. Age at time of inform consent is chosen for the cutoff consistently in the protocol. The following sections of the protocol is affected: Schedule of Activities note j, Section 4.1, Section 7.1.4, and Section 7.1.6. ● Delete “BL” in the Appendix 1. Abbreviations. Rationale: The wording “BL” is not used in the protocol. The following section of the protocol is

		affected: Appendix 1. Abbreviations. ● The protocol changes specified in Protocol Administrative Change Letter (29 May 2020) have been incorporated in Section 4.4.1, Section 5.8.1, Section 5.8.2, Section 6.3, Schedule of Activities endnote (q), Section 6.4.2, Section 6.4.3, Section 6.4.5, Schedule of Activities endnote (r), Section 7.1.4, and Section 7.1.6.1.
Amendment 3	18 Dec 2020	● Change wording "Asia regional/Asia" to "China and Japan" and Change wording "Asian" related to C3291032 study to Chinese and Japanese" Rationale: To make the study description more precise as only China and Japan will participate the study. The following sections of the protocol are affected: Protocol title, Protocol summary, Section 1.4, Section 3. ● In this China and Japan study, a similar study design to the two global pivotal studies (AN2728-AD-301 and AN2728-AD-302) will be used to investigate the efficacy and safety of Crisaborole Ointment, 2% twice daily (BID) in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD, to support the registration of Crisaborole in China and Japan. Rationale: According to current decision, only China and Japan will participate the study. The following sections of the protocol are affected: Protocol summary and Section 1.4.1. ● Delete the content: Only for Japan: Japan participants who complete the

		study intervention period in Study C3291032 will be offered participation in the long-term safety extension study C3291027 if eligibility criteria are met. ● Replacement for the deleted content: The 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. Rationale: This change is made based on current termination decision on C3291027 study for Japan. After 21 Oct 2020, participants who complete study C3291032 will no longer participate in C3291027 study. The following sections of the protocol are affected: Protocol Summary, Schedule of Activities note t, Section 3, Section 6.4.3 and Study Design Schematic ● Update the sample size and power: The total sample size of 384 subjects in this study with a 2:1 randomization ratio (256:128) will provide approximately 90% power to detect a 12% difference of percent change from baseline in EASI total score at Day 29 between crisaborole arm and vehicle arm at the 0.05 (2-sided) significance level[redacted] Rationale: Sample size is being reduced from 510 to 384 to ensure adequate recruitment time within the new country footprint while maintaining adequate statistical power which will still have a ~90% power to detect the 12% difference of primary endpoint between

		2 arms. The following sections of the protocol are affected: Protocol Summary, Study Design Schematic, Section 3 and Section 9.1. ● Other secondary efficacy endpoints including change from Baseline in % BSA, percent change from baseline in EASI total score at all time points other than Day 29, change from 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. 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. Rationale: The analysis of other secondary endpoints is updated to include Patient Reported Itch Severity Scale and Observer Reported Itch Severity Scale, and to make the wording more precise. ● The following section of the protocol is affected: Section 9.2.3.After the Baseline/Day 1 Visit, use of emollient(s), moisturizer or sunscreen is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD involved areas until Day 29. ● Use of emollient(s), moisturizer or

		sunscreen is permitted in the skin of whole body after Day 29 telephone contact. Rationale: To clarify that emollient(s), moisturizer or sunscreen could not be used on treatable area until Day 29. After Day 29 telephone visit completed, emollient(s), moisturizer or sunscreen could be used on treatable area. The following section of the protocol is affected: Section 5.8.1 ● Calculate subject's Treatable %BSA. ● Update the documentation of treatable areas for any new AD lesions that appear after the Baseline/Day 1 Visit. The subject and parent/legal guardian (if applicable) will be provided with documentation of the designated treatment areas, to ensure that previously treated areas which have resolved continue to be treated as required. Rationale: Divide above content into 2 paragraphs as to clearly explain the separate actions. The following section of the protocol is affected: Section 6.4.2 ● Calculate subject's Treatable %BSA based on all AD lesions present at Day 29, excluding the scalp. Rationale: Adjust the wording to make it more concise The following section of the protocol is affected: Section 6.4.3 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 Rationale: Explain clearly the approach of AE recording after informed consent/assent obtained while investigational invention has not been initiated. The following section of the protocol is affected: Section 8.1.4. ● Typos correction in below sections: Section 1.3.2, Section 3, Section 6.3, Section 6.4.1, Section 7.1.1,Section 7.2.1, Section 8.1.1 and Section 8.1.3.

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

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PROTOCOL SUMMARY

Background and Rationale:

Crisaborole, also referred as PF-06930164 and AN2728, is a low molecular weight benzoxaborole antiinflammatory phosphodiesterase4 (PDE4) inhibitor that penetrates into the skin to the sites of inflammation. The primary mechanism of the anti-inflammatory effect of crisaborole is through inhibition of PDE-4. Crisaborole has demonstrated in vitro inhibition of a range of cytokines implicated in the pathogenesis of atopic dermatitis (AD). Crisaborole inhibits the release of chemokines that are also important inflammatory mediators. Crisaborole applied to human skin ex vivo or on AD lesions on a subject reduces expression of key drivers of atopic inflammation including T-cell derived cytokines IL-13, IL-31, and interferon gamma (IFNγ) as well as innate markers of inflammation such as matrix metalloproteinase (MMP)12.

Supporting evidence of the safety and efficacy of this product in patients 2 years and older represent a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the treatment limiting effects of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in the two Phase 3 registration studies. Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment related Serious Adverse Events (SAEs) and with the majority of Adverse Events (AEs) being mild and deemed unlikely or not related to investigational product.

In this China and Japan study, a similar study design to the two global pivotal studies (AN2728-AD-301 and AN2728-AD-302) will be used to investigate the efficacy and safety of crisaborole ointment, 2% twice daily (BID) in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD, to support the registration of crisaborole in China and Japan.

Objectives and Endpoints:

Primary Objectives	Primary Endpoint(s)
• To evaluate the efficacy of crisaborole ointment, 2% applied BID versus Vehicle in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD. • To evaluate the safety and tolerability of crisaborole ointment, 2% applied BID versus Vehicle in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.	• Efficacy endpoint: Percent Change from Baseline (BL) in Eczema Area and Severity Index (EASI) total score at Day 29. • Safety endpoint: TEAEs (including application site reactions) & SAEs, and clinically significant changes in vital signs and clinical laboratory parameters.

Secondary Objectives	Secondary Endpoints

• To evaluate the effect of crisaborole ointment, 2% applied BID versus Vehicle on additional efficacy endpoints over time in Chinese and Japanese pediatric and adults subjects (Ages 2 years and older) with mild to moderate AD.
• To evaluate the effect of crisaborole ointment, 2% applied BID versus Vehicle on patient/observer reported outcomes over time in Chinese and Japanese pediatric and adults subjects (Ages 2 years and older) with mild to moderate AD.
	• Efficacy endpoints
	  • Key secondary efficacy endpoints:
	  • Achievement of Improvement in Investigator's Static Global Assessment (ISGA) (defined as ISGA score of clear (0) or almost clear (1)) at Day 29.
	  • Achievement of Success in ISGA (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline) at Day 29
	  • Change from Baseline in Peak Pruritus Numeric Rating Scale (NRS) at Week 4 - for subjects ≥12 years.
	  • Other secondary efficacy endpoints:
	  • Success in ISGA over time.
	  • Improvement in ISGA over time.
	  • Percent Change from BL in EASI total score over time.
	  • Change from Baseline in % body surface area (BSA) over time.
	  • Achievement of EASI-50 (≥50% improvement from baseline) over time.
	  • Achievement of EASI-75 (≥75% improvement from baseline) over time.
	  • Change from baseline in Peak Pruritus NRS over time - for subjects ≥12 years.
	  • Change from baseline in Patient Reported Itch Severity Scale over time - for subjects ≥6 years and <12 years.
	  • Change from baseline in Observer Reported Itch Severity Scale over time - for subjects <6 years.
	  • DLQI, CDLQI, IDQOL, DFI, POEM, PGIS/OGIS, PGIC/OGIC over time.

CCI [redacted]	[redacted]
[redacted]	[redacted]

	CCI [redacted]

Study Design:

This is a Phase 3, multicenter, randomized, double blind, vehicle controlled study to evaluate the efficacy and safety of crisaborole ointment, 2% in Chinese and Japanese pediatric and 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. Primary efficacy endpoint percent change from baseline in EASI total score will be assessed at Day 29.

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/subjects' legally acceptable guardians on Day 36 and Day 60 (see Section 6.4.5).

The 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.

Refer to the Schedule of Activities for a complete list of assessments to be performed during the study.

Statistical Methods:

Sample Size Determination

The total sample size of 384 subjects in this study with a 2:1 randomization ratio (256:128) will provide approximately 90% power to detect a 12% difference of percent change from baseline in EASI total score at Day 29 between crisaborole arm and vehicle arm at the 0.05 (2-sided) significance level [redacted]

Analysis of the Primary Endpoint

The primary efficacy endpoint, percent change from baseline in EASI total score at Day 29, will be analyzed using a linear mixed-effect model for repeated measures that includes treatment group, visit, and treatment group by visit interaction as factors and baseline value as a covariate. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Day [relative to start of study treatment (Day 1)]	**Within 35 days prior to Day 1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29[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]**
Informed consent, including assent	X							
Demographics	X							
Height and weight	X	x						
Review of Inclusion and Exclusion Criteria	X	x						
Medical history	X	x						
Prior and concomitant medications	x[a]	x	X	x	x	X	x	x
Vital signs[b]	X	x		x		X		
Physical examination	x[c]	x[d]				x[c]		
Calculate Treatable %BSA	X	x	X	x	x	x		
Serious and non-serious adverse event monitoring	X	x	X	x	x	x	x	X
ISGA[e]	X	x	X	x	x	x		
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
EASI[e]		x	X	x	x	x		
Record treatable AD areas (excluding scalp) in source and provide subjects and/or parent(s)/legal guardian with documentation of the designated treatment areas[u]		x	X	X	X	X		
Body Site checklist of AD lesions		x						

Day [relative to start of study treatment (Day 1)]	**Within 35 days prior to Day 1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 29[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			

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]**
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.

m. Urine pregnancy testing (β-hCG) is required only for women of childbearing potential: test may be repeated as per request of IRB/IECs, if required by local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected or at the discretion of the investigator or his/her designee. Urine pregnancy testing will be performed at the site. 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.

n. In special situation if the subject come to the clinic in the afternoon, two doses (8-16 hours apart) or single dose could be administered on Day 1, if single dose is administered on Day 1, a morning dose will be applied at Day 29 for these special subjects.

o. In the event the scheduled Day 29 (End of Treatment) Visit does not occur on Day 29, eg, due to an unavoidable scheduling conflict, the subject and/or parent/legal guardian will be instructed to continue investigational product application BID through the evening before the day that the rescheduled End of Treatment Visit is to occur.

p. During study visits at Day 8, Day 15, and Day 22, re-educate subject and/or parent/legal guardian if any investigational product doses were missed during the interval since the previous study visit.

q. Peak Pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale, PGIS/OGIS, DLQI, CDLQI, IDQOL, DFI, POEM and ISGA 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.

r. The follow up telephone contact will be performed 7 (±3) days and 31 (±3) days after the End of treatment/Early Termination visit.

s. POEM will be completed by subject (POEM for self-completion for subjects ≥12 years) or observer (POEM for proxy completion for subjects 2-11 years).

t. The 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.

u. Before the Day 1 initial investigational product application is performed, the designated areas for treatment will be identified at the Baseline/Day 1 Visit and documented in the subject's source document study records. The subject and parent/legal guardian (if applicable) will be provided with documentation of the designated treatment areas, to ensure that previously treated areas which have resolved continue to be treated as required. The documentation of treatable areas will be updated for any new AD lesions that appear after the Baseline/Day 1 Visit.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase 4(PDE 4) inhibitor that penetrates into the skin to the sites of inflammation and is currently being investigated for topical treatment in patients with mild to moderate atopic dermatitis. The primary mechanism of the anti-inflammatory effect of crisaborole is through inhibition of PDE-4. Crisaborole has demonstrated in vitro inhibition of a range of cytokines implicated in the pathogenesis of AD. Crisaborole inhibits the release of chemokines that are also important inflammatory mediators. Crisaborole applied to human skin ex vivo or on AD lesions on a subject reduces expression of key drivers of atopic inflammation including T-cell derived cytokines IL-13, IL-31, and IFNγ as well as innate markers of inflammation such as MMP-12.

Crisaborole ointment, 2% (weight by weight) (20 mg/g) (referred to as crisaborole hereafter), is an approved therapy in the United States (US) and Canada (EUCRISA®), and Israel and Australia (STAQUIS®) as a topical treatment therapy in patients 2 years of age and older with mild-to-moderate AD. It is currently being developed worldwide as a topical therapy for patients with mild to moderate AD.

1.2. Background

AD, also referred to as eczema, is a chronic and relapsing disease affecting an increasing number of patients. Although AD affects patients of all ages, it is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the United States (US) with 85% of affected individuals showing signs of the disease before 5 years of age.[1,2] Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US and Japan.[3,4] The prevalence rate of atopic dermatitis is gradually increasing in recent 20 years in China and the total prevalence rate in the school age population 6-20 years old was 0.69% in 1998[5] and the prevalence rate in the preschool age children (1-7 years) in 10 cities was 2.78% in 2002,[6] however, the epidemiological survey in Shanghai district in 2012 revealed that the prevalence rate was up to 8.3% in the 3-6 years old children,[7] a recent national survey revealed that the prevalence of AD was 12.94% in the 1-7 years old children by clinical diagnosis of dermatologists.[8]

AD is a distinctive inflammatory, highly pruritic, chronic eczematous condition that usually occurs in people who have a personal or family history of other atopic conditions such as asthma or allergic rhinitis.[1,4] The majority of patients (up to 90%) with AD present with mild to moderate disease.[9] Manifestation of the disease includes intense pruritus, erythematous papules, excoriation, exudation, lichenification, and bacterial colonization.[10] Continuous

scratching during exacerbations can lead to lichenification, excoriations, and serious skin infections. AD is often associated with other conditions including asthma, allergic rhinitis, and food allergy.[11,12] The burden of the clinical symptoms of AD coupled with the stigma associated with highly visible skin lesions correlates with significant morbidity and extensive impairments on health related quality of life measures (HRQOL) for patients, especially in children, and caregivers.[1,13,14,15] Psychosocial problems, depression, and anxiety are associated with AD in both adults and children.[16]

The negative impact on HRQOL caused by childhood AD exceeds that in asthma, epilepsy, and diabetes, is comparable to that in renal disease or cystic fibrosis, and is equal (child) or exceeds (parents) that in psoriasis.[2,14,17] The hallmark symptom of itching causes scratching which is associated with sleep disturbance in greater than 60% of patients. Sleep deprivation leads to physical and mental exhaustion in patients and other family members resulting in loss of concentration and impaired performance at school or work.[18,19] AD is often associated with significant childhood behavioral problems and psychological disorders including depression, attention deficit hyperactivity disorder, anxiety, stress, and autism.[16] Preschool children with AD show a significant increase in behavioral symptoms compared with matched controls.[21] Absolon et al[22] reported that the rate of psychological disturbance in school age children with AD doubled compared with matched controls. For older children with AD, in addition to problems associated with itching and sleep disturbance, their social and school life may be substantially affected. Social embarrassment, due to visible signs of the disease (crusted, excoriated, oozing, bleeding lesions), teasing, and bullying, often results in social isolation leading to depression.[2]

AD has a significant impact on day to day functioning, as evidenced by its impact on the overall wellbeing of the patient and their family on multiple levels; medical management and treatment, HRQOL, and psycho social implications. In summary, AD is a disease with multiple comorbidities and significant impact on the health, day to day functioning, and HRQOL of AD patients, their caregivers, and family members.

AD may also be a source of significant economic burden[23] as this relapsing disease is often misdiagnosed, misunderstood, and ineffectively treated.[4]

AD is a condition associated with significant morbidity. Currently, there is no cure for AD. AD is a chronic disease with treatment focused on the management of flares and maintenance of remissions. Due to the chronic, relapsing nature of the disease, treatment may be needed for many years.

Crisaborole Ointment, 2% was developed by Anacor Pharmaceuticals, Inc. (Anacor), Palo Alto, California, USA, which became a wholly owned subsidiary of Pfizer Inc. on 24 June 2016.

Crisaborole is a novel, non-steroidal, topical anti-inflammatory PDE 4 inhibitor that will serve an unmet need in the treatment of AD. Supporting evidence of the safety and efficacy of this product in patients 2 years and older represent a major advancement in the treatment of AD given the challenges of managing this common, chronic dermatologic condition and the treatment limiting effects of currently available therapies. All primary and secondary efficacy endpoints were statistically significant in favor of crisaborole ointment, 2% BID versus vehicle ointment BID in the two Phase 3 pivotal studies.[24] Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment related SAEs (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related), and the majority of AEs were mild and deemed unlikely or not related to investigational product.

1.3. Drug Development

Crisaborole ointment, 2% is an oxaborole compound developed as a topical antiinflammatory- agent. It demonstrates in vitro inhibition of a wide range of proinflammatory cytokines implicated in the pathogenesis of AD and other inflammatory skin diseases. Crisaborole has been formulated as a topical ointment. The formulation ingredients for crisaborole ointment, 2% are listed in Section 5.

Crisaborole inhibits a range of cytokines implicated in the pathogenesis of inflammatory skin diseases, including TNF-α, IFN-y, IL-2, IL-5, IL-6, IL-10, IL-12, and IL-23.[25] The level of inhibitory activity, ie, the concentrations needed to produce 50% inhibition, ranges from the high nanomolar to the low micromolar concentrations. Crisaborole also inhibits the release of chemokines that are important inflammatory mediators. One mechanism of the anti-inflammatory effect of crisaborole is through inhibition PDE-4. Crisaborole proved efficacious against an inflammatory challenge in vivo, in a mouse model of ear edema induced by phorbol 12-myristate 13-acetate (PMA). Crisaborole formulated as ointment and cream formulations for topical use has demonstrated clinical benefit in nine psoriasis clinical studies and seven AD clinical studies. Safety has been evaluated in a total of 23 completed clinical studies.

The Investigator's Brochure (IB) contains summaries of nonclinical and clinical studies performed with crisaborole.[25] A brief summary as background to this study protocol is presented here.

1.3.1. Nonclinical Studies

Crisaborole demonstrated inhibitory capacity against human leukocyte cytokine release with half maximal effective concentration (EC_{50}) values ranging from high nanomolar to low micromolar concentrations. Crisaborole also inhibits the release of chemokines that are important inflammatory mediators. The primary mechanism of the antiinflammatory effect of crisaborole is through inhibition of PDE4, which causes elevation of cAMP in leukocytes and subsequent protein kinase A (PKA)mediated phosphorylation of transcription factors that are important for cytokine, chemokine, or prostaglandin forming enzyme synthesis and release from cells. Crisaborole proved efficacious against an inflammatory challenge in vivo in a mouse PMA induced ear edema model. AN8323, a metabolite of crisaborole, lacks antiinflammatory activities against PDE4 and a panel of cytokines.

Based on the nonclinical safety studies conducted to date, crisaborole ointment, 2% has an acceptable safety profile. Refer to the IB for further information on the nonclinical experience with crisaborole ointment, 2%.

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1.3.3. Cutaneous Sensitization, Irritancy Potential and Tolerability

1.3.3.1. Local Tolerability in Sensitive Skin Areas

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

course of the study between subjects who received crisaborole ointment, 2% or Vehicle. Overall, crisaborole ointment, 2% was well tolerated over 21 days of dosing in sensitive skin areas of healthy subjects.

1.3.3.2. Sensitizing and Cumulative Irritation Potential

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

In addition, the similar results were observed from Japan study C3291029 Cohort 1. In this study, crisaborole ointment 2% and vehicle were applied topically to 1-side of the intrascapular area of the back once on Day 1 and remained under occlusion for 48 hours (Cohort 1 in Study C3291029) to Japanese healthy participants. The skin irritancy was to be evaluated approximately 30 minutes after removal of the patches on Day 3 and 24 hours after removal of the patches on Day 4. The degree of erythema, edema and other signs of skin irritation at the application site was evaluated using the visual scale. All participants for the crisaborole ointment 2% patch had a maximum irritation score of 0 (No reaction) or 0.5 (Mild erythema) except for the 3 participants with a maximum irritation score of 2 (Erythema + edema, papule).

Overall, Crisaborole ointment, 2% and vehicle showed no evidence of sensitization and only very minimal irritation.

1.3.4. Clinical Experience

Eight (8) clinical trials of topical formulations of crisaborole have been completed to date in subjects 2 years of age and older with mild to moderate AD. Key study information is summarized below.

[redacted]

[redacted]

- In a 6-week bilateral comparison trial of subjects with mild to moderate AD, 68% of AD lesions treated with crisaborole ointment, 2% BID showed greater improvement in atopic dermatitis severity index (ADSI) than vehicle treated lesions (20%) at 4 weeks (primary endpoint). These response rates were similar at Day 14 and Day 42 (end of treatment).

- In a 6-week, randomized, vehicle-controlled intra-subject efficacy and biomarker study of adult subjects with mild to moderate AD (C3291001), crisaborole ointment, 2% applied BID statistically significantly improved lesion Target Sign Scores (TSS) more than vehicle at Day 15 (primary efficacy endpoint). Crisaborole significantly reduced 7 key skin biomarkers of AD from Baseline to Day 15 (primary biomarker endpoint).

- In a 4-week bilateral comparison trial of 86 adolescent subjects with mild to moderate AD, crisaborole ointment, 2% BID showed greater improvement than the lower concentration of crisaborole ointment, 0.5% applied BID for 29 days, and was more efficacious than either concentration applied once daily (QD).

- In two Phase 3 multicenter, randomized, doubleblind, vehicle controlled studies in subjects ≥2 years of age and older with AD, crisaborole ointment, 2% outperformed the vehicle in the primary efficacy analysis, proportion of subjects achieving success in ISGA at Day 29. Success was defined as an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement over baseline. Proportion of success was 32.8% and 25.4% for crisaborole ointment, 2% and vehicle, respectively in AN2728-AD-301 and 31.4% and 18.0%, respectively in AN2728-AD-302. Differences from vehicle were statistically significant in both studies.

- An additional Phase 3 multicenter, open label, long term extension study (AN2728-AD-303) of crisaborole ointment, 2% for the treatment of mild to moderate AD in adults and children as young as 2 years of age evaluated the long term safety of topical crisaborole. No clinically important safety signals were identified by this study.

Crisaborole has been well tolerated across completed clinical studies. No clinically important safety signals have been identified, including during a Phase 3 multicenter, open label, long term extension study of crisaborole ointment, 2% for mild to moderate AD in adults and children as young as 2 years of age. Most AEs have been mild, and most considered unrelated or unlikely to be related to investigational product. The most common drugrelated AEs was application site pain (eg, cutaneous stinging and or burning).

Refer to the Investigator Brochure for further information on the clinical experience with crisaborole ointment, 2%.[25]

1.4. Rationale

1.4.1. Study and Dose Rationale

In this China and Japan study, a similar study design to the two global pivotal studies (AN2728-AD-301 and AN2728-AD-302) will be used to investigate the efficacy and safety of Crisaborole Ointment, 2% twice daily (BID) in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD, to support the registration of Crisaborole in China and Japan.

Dose selection for the global pivotal clinical studies was based on safety and efficacy results from Phase 2 studies, and the dose selected was later confirmed to be safe and effective for commercialization by the results of the Phase 3 studies.

Phase 2 Study AN2728-AD-204 compared two concentrations of crisaborole (2% and 0.5%) applied QD or BID in adolescents with mild to moderate AD. The largest dose-related response and the greatest improvement in all 5 component signs and symptoms of AD occurred in the crisaborole 2% BID group, with a notable reduction from baseline in the pruritus score.

The 2% dosage strength of the crisaborole ointment formulation administered BID was selected for study in Phase 3 as the highest well-tolerated dose to maximize the potential for efficacy with minimal safety risk. Results from the Phase 3 trials in which subjects aged 2 years and older with mild to moderate AD were dosed BID for 28 days with Crisaborole

Ointment, 2% confirm the safety and efficacy of this formulation strength and dosing regimen in subjects with mild to moderate AD (AN2728-AD-301, AN2728-AD-302).

Long-term (up to 12 months) intermittent use in this patient population was shown to be safe in a 48-week long -term safety study (AN2728-AD-303).

The safety of the 2% dosage strength was confirmed in additional studies, including maximal use systemic exposure (MUSE) studies (pediatric subjects with AD and adult subjects with psoriasis) and with supra-therapeutic dosing in a TQT study (healthy adult subjects). In the pooled Phase 3 registration studies, higher rates of success in ISGA at Day 29 were observed in the crisaborole group than in the vehicle group for the subgroups of sex, age, race, and ethnicity. The proportion of Asian subjects is around 5%, similar trend was observed in the Asian subgroup of the pooled global pivotal studies, with a success in ISGA of 17.3% in the crisaborole group and 11.1% in the vehicle group. The safety profile of crisaborole was not affected by age, sex, ethnicity, or race.

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This China and Japan Phase 3 study will evaluate the same dosing regimen which was investigated in the global pivotal Phase 3 studies.

1.4.2. Single Reference Safety Document

Additional information for crisaborole may be found in the Single Reference Safety Document (SRSD), which for this study is the crisaborole Investigator's Brochure.

1.5. Anticipated Benefits and Risks

The benefit/risk balance of crisaborole ointment, 2% application in this study is considered favorable and supported by the following:

- The expected efficacy of crisaborole ointment, 2% for the treatment of atopic dermatitis based on the results of clinical studies conducted to date.
- The expected limited crisaborole systemic exposure when applied topically based on the results of clinical studies conducted with crisaborole ointment, 2% to date.

- The satisfactory safety and local tolerability demonstrated in non-clinical and clinical studies conducted with crisaborole ointment, 2% to date.

The main benefit for subjects participating in this study is based on access to regular clinical assessments and active atopic disease management as well as expected efficacy of treatment with crisaborole during the study, in which the safety will be monitored appropriately. Based on the favorable clinical safety profile as well as the limited systemic exposure of crisaborole, the risk to subjects treated with crisaborole is deemed to be minimal.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoint(s)
• To evaluate the efficacy of crisaborole ointment, 2% applied BID versus Vehicle in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD. • To evaluate the safety and tolerability of crisaborole ointment, 2% applied BID versus Vehicle in Chinese and Japanese pediatric and adult subjects (ages 2 years and older) with mild to moderate AD.	• Efficacy endpoint: Percent Change from Baseline in Eczema Area and Severity Index (EASI) total score at Day 29. • Safety endpoint: TEAEs (including application site reactions) & SAEs and clinically significant changes in vital signs and clinical laboratory parameters.
Secondary Objectives	**Secondary Endpoints**

• To evaluate the effect of crisaborole ointment, 2% applied BID versus Vehicle on additional efficacy endpoints in Chinese and Japanese pediatric and adults subjects (Ages 2 years and older) with mild to moderate AD.
• To evaluate the effect of crisaborole ointment, 2% applied BID versus Vehicle on patient/observer reported outcomes over time in Chinese and Japanese pediatric and adults subjects (Ages 2 years and older) with mild to moderate AD.
	• Efficacy endpoints.
	  • Key secondary efficacy endpoints.
	  • Achievement of improvement in ISGA (defined as ISGA score of clear (0) or almost clear (1)) at Day 29.
	  • Achievement of Success in ISGA (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline) at Day 29.
	  • Change from Baseline in Peak Pruritus Numeric Rating Scale (NRS) at Week 4 - for subjects ≥12 years.
	  • Other secondary efficacy endpoints.
	  • Success in ISGA (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline) over time.
	  • Improvement in ISGA (defined as ISGA score of clear (0) or almost clear (1)) over time.
	  • Percent Change from BL in EASI total score over time.
	  • Change from Baseline in % BSA over time.
	  • Achievement of EASI-50 (≥50% improvement from baseline) over time.

	• Achievement of EASI-75 (≥75% improvement from baseline) over time. • Change from baseline in Peak Pruritus NRS over time - for subjects ≥12 years. • Changes from baseline in Patient Reported Itch Severity Scale over time - for subjects ≥6 years and <12 years. • Change from baseline in Observer Reported Itch Severity Scale over time - for subjects <6 years. • DLQI, CDLQI, IDQOL, DFI, POEM, PGIS/OGIS, PGIC/OGIC over time.
CCI	

3. STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-blind, vehicle-controlled study to evaluate the efficacy and safety of crisaborole ointment, 2% in Chinese and Japanese pediatric and

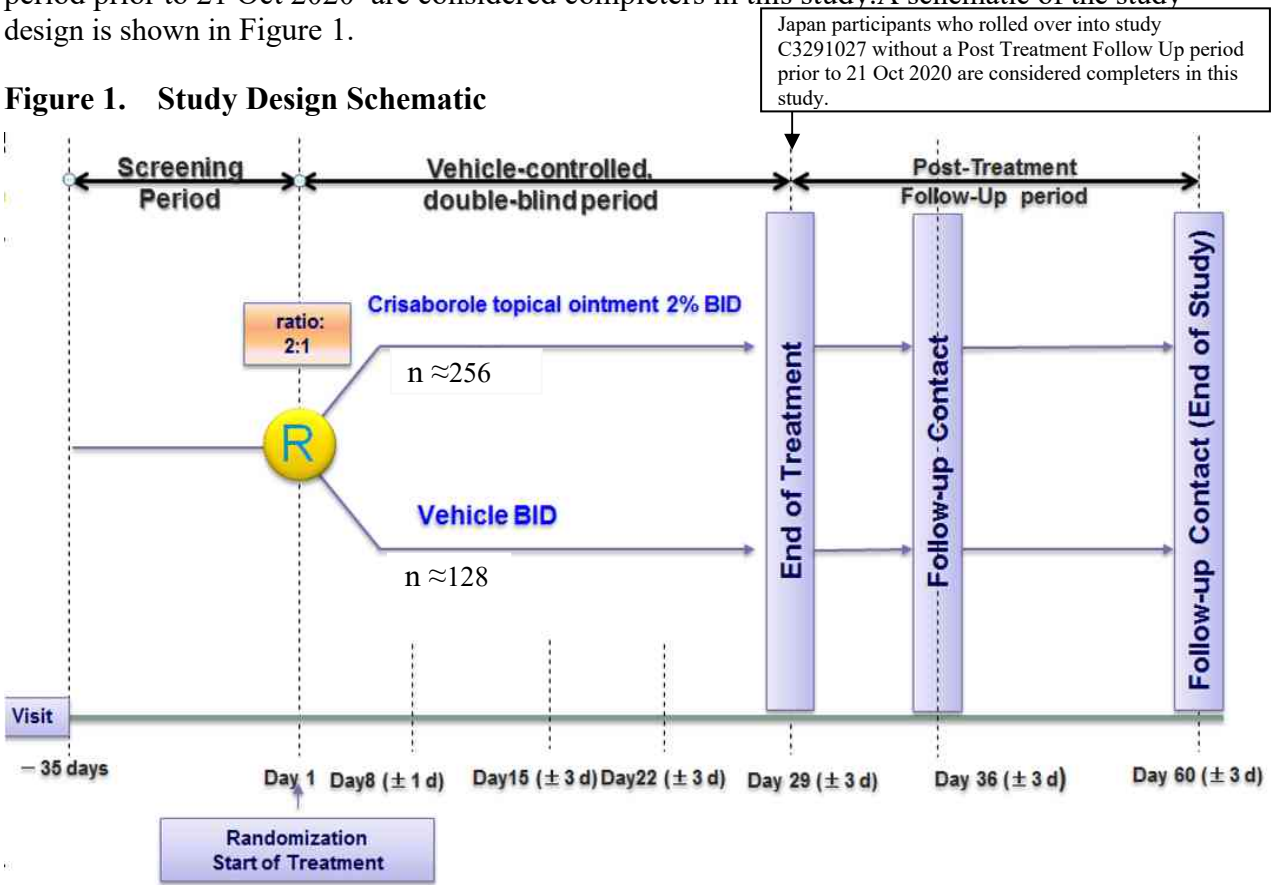
adult subjects (ages 2 years and older) with mild to moderate atopic dermatitis involving at least 5% treatable BSA.

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.

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.

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.

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.

11. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

12. Other acute or chronic medical or psychiatric condition including history of or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study including the following:

    - For subjects 7-11 years of age, suicidal ideation associated with actual intent and a method or plan in the past 6 months: “Yes” answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) or a previous history of suicidal behaviors in their lifetime: “Yes” answer to any of the suicidal behavior items of the C-SSRS.

- For subjects ≥12 years of age, suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the C-SSRS or a previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS

- For younger subjects under 7 years of age, subject has suicidal ideation and behavior risks assessed clinically and in consultation with their parents/caregivers

13. Pregnant female subjects; breastfeeding female subjects; and female subjects of childbearing potential who are unwilling or unable to use an appropriate method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

4.3. Randomization Criteria

Subject will be randomized into the study provided that the subject [or parent(s)/legal guardian] has signed an informed consent (or assent, if applicable) document to participate in the study, and the subject has undergone all screening procedures, and meets all inclusion and exclusion criteria for participation in the study at the baseline visit. A centralized computer generated randomization schedule will be used to assign subjects to the treatment groups. Subjects will be randomized in a 2:1 ratio to one of the 2 parallel treatment groups (Crisaborole ointment, 2% BID or Crisaborole placebo vehicle ointment BID).

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

4.4. Lifestyle Requirements

4.4.1. Contraception

All female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use an appropriate method of contraception consistently and correctly for the screening period, the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or his/her designee will inform the subject of the need to use an appropriate contraceptive method consistently and correctly and document the conversation and the subject's affirmation in the subject's

chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Contraceptives allowed during the study include:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used with or without a spermicide product (ie, foam, gel, film, cream, or suppository).

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

4.4.2. Other Lifestyle Requirements

- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation.

- Subjects should not swim, be bathed or have treatment areas washed for at least 4 hours after application of investigational product.

- Use of sunscreen is permitted, but only on areas without AD involvement.

- The parent(s)/legal guardian should avoid wiping the investigational product off the skin and investigational product should not be reapplied to wiped areas until the next scheduled dose.

- When applying investigational product, the parent(s)/legal guardian will not be required to wear gloves when applying investigational product at home. However, they must be instructed to wash their hands with mild soap and water before and after each application.

4.5. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, investigational products are the following:

- Crisaborole ointment, 2%, also referred to as active.

- Crisaborole placebo vehicle ointment, referred to as vehicle.

Crisaborole ointment, 2%, is formulated to contain PF-06930164 (2% wt/wt), white petrolatum, propylene glycol, mono and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

Vehicle (no active drug in the formulation) contains white petrolatum, propylene glycol, mono- and diglycerides, paraffin wax, butylated hydroxytoluene, and edetate calcium disodium.

5.1. Allocation to Treatment

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

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

5.2. Breaking the Blind

- The study will be subject, and investigator blinded.

- At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

Subject/a parent/legal guardian will apply crisaborole ointment, 2% or Vehicle to the subject at home; compliance will be captured and completed by the subject/parent/legal guardian/legally acceptable representative using a dosing diary provided by the site. The subject and parent/legal guardian (if applicable) will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1, then BID through Day 28 (ie, each time investigational product is applied) for the investigational product doses applied at home. In special situation if the subject come to the clinic in the afternoon, two doses (8-16 hours apart) or single dose could be administered on Day 1, if single dose is administered on Day 1, a morning dose will be applied at Day 29 for these special subjects in order to keep 56 doses. Subjects and parents/legal guardians (if applicable) will be instructed to bring the Dosing Diary and all dispensed investigational product supplies to the clinic at Days 8, 15, 22, and 29.

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected applications during the investigational product application period and has not missed 6 or more consecutive doses. This will be verified by the dosing records. Subjects having missed doses of IP will be re-educated on the importance of compliance.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Crisaborole Ointment, 2% and vehicle ointment will be supplied in 60 g tubes for topical administration. The tubes will be provided in cartons and labeled in a blinded fashion according to local regulatory requirements.

5.4.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

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

For doses to be administered at home, the caregiver (parents/legal guardians) should be instructed to maintain the product in the package provided throughout the course of dosing and return the product (including empty, partial used and unused tubes) to the site at the next study visit.

5.5. Administration

Ointment should be applied as an even layer of approximately 3 mg/cm2.

The tool to standardize the calculation of the amount of ointment required for each participant will be provided by the sponsor to the study sites, which is based on each participant’s own AD %BSA adjusted by height and weight.

Before the Day 1 initial investigational product application is performed, the designated areas for treatment will be identified at the Baseline/Day 1 Visit and documented in the subject's source document study records. The subject and parent/legal guardian (if applicable) will be provided with documentation of the designated treatment areas. The documentation of treatable areas will be updated for any new AD lesions that appear after the Baseline/Day 1 Visit.

Crisaborole Ointment, 2% is for external use on the skin only. Avoid contact with mucous membranes (ie, inside of nostrils, mouth, vagina, urethra, and rectum), and the eyes.

Wearing gloves, study staff will apply a layer of investigational product ointment to all treatable AD lesions identified at Baseline/Day 1. Subjects and parents/legal guardians (if applicable) will be encouraged to observe and participate in the initial investigational product application on Day 1. All subsequent doses, including the second dose on Day 1, will be applied at home. Those subjects applying IP at home and having difficulty reaching treatment eligible atopic dermatitis areas (eg, back) may be assisted by another person who will need to apply the investigational product to the subject according to the above IP application instructions.

Subjects and/or parents/guardian/legal guardians will be instructed to not wipe investigational product off the skin, avoid occluding the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application.

Regimen: Investigational product will be applied BID to all treatable AD involved areas (excluding the scalp) identified at Baseline/Day 1 through Day 28. The initial dose application on Baseline/Day 1 will be applied in the clinic, and all subsequent doses will be applied at home. Subjects and/or parents/legal guardians will be instructed to apply enough investigational product to cover each lesion with a layer of ointment. A total of 56 doses are expected to be applied between Baseline/Day 1 and Day 29, inclusive. In the event the scheduled Day 29 (End of Treatment) Visit does not occur on Day 29, eg, due to an unavoidable scheduling conflict, the subject and parent/legal guardian (if applicable) will be instructed to continue investigational product application BID through the evening before the day that the rescheduled End of Treatment Visit is to occur.

Investigational product will continue to be applied to all treatable AD involved areas (excluding scalp) identified at Baseline/Day 1 regardless of whether they become clinically clear prior to Day 29. Investigational product will also be applied to any new treatable AD involved areas that appear following Baseline/Day 1.

Subjects and parents/legal guardians (if applicable) will be instructed to apply evening (PM) doses approximately 8–16 hours after the morning (AM) doses (eg, if an AM dose is completed at 8:00 AM, the PM dose can be applied anytime between 4:00 PM and 12:00 AM). Caregivers or partners may also be ones to apply investigational product, especially for areas that a subject cannot reach, even in adults. The first dose is preferred to be administered in the morning on Day 1 if applicable. In special situation if the subject come to the clinic in the afternoon, two doses (8-16 hours apart) or single dose could be administered fine to only administer the PM dose on Day 1, if single dose is administered on Day 1, a morning dose will be applied at Day 29 for these special subjects.

5.6. Investigational Product Storage

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

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

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

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

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

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

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

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

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

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

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

The original investigational product accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the Sponsor) when the study is complete.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

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

5.8. Prior and Concomitant Treatment(s)

- All prior medications, including all medications and non-medication therapies used for AD within 90 days prior to Screening and all other treatments, including bland (non-medicated) emollients, over the counter drugs, vitamins, and antacids, used within 30 days prior to Screening will be recorded at the screening visit. Any changes in concomitant medications or dosage will be recorded at Baseline/Day 1 and at each subsequent visit. Medication entries should provide the correctly spelled drug

or therapy name and the dose, units, frequency, route of administration, start and stop date, and reason for use. The use of any concomitant medication must relate to the subject's medical history or to an AE, except for vitamins/nutritional supplements and routine immunizations.

5.8.1. Medications Prohibited Prior to Baseline/Day 1

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

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

- Biological drugs. (Note: prior dupilumab use is exclusionary).

Medications Prohibited 28 Days Prior to Baseline/Day 1

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

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

- Use of systemic immunosuppressive agents, including but not limited to, methotrexate, cyclosporine, azathioprine, hydroxychloroquine, and mycophenolate mofetil (MMF), within 28 days prior to Baseline/Day 1.

- Use of systemic JAK inhibitor, within 28 days prior to Baseline/Day 1.

- Use of sunbathing, tanning bed use, or light therapy (UV, UV-B, psoralen–UV-A [PUVA]), within 28 days prior to Baseline/Day 1.

- Escalating, decreasing, or as needed (PRN) use of topical retinoids or benzoyl peroxide (BPO) on treatable AD lesions, within 28 days prior to Baseline/Day 1.

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

- Systemic Traditional Chinese Medicine/herbal preparation that might alter the course of atopic dermatitis, for example Lei Gong Teng.

Medications Prohibited 14 Days Prior to Baseline/Day 1

- Use of systemic antibiotics, within 14 days prior to Baseline/Day 1.
- Use of topical corticosteroids, or topical calcineurin inhibitors, anywhere on the body, within 14 days prior to Baseline/Day 1.
- Use of a topical JAK inhibitor, anywhere on the body within 14 days prior to Baseline/Day1.
- Use of topical antihistamines anywhere on the body, within 14 days prior to Baseline/Day 1.
- Topical traditional Chinese medicine/herbal preparation that might alter the course of atopic dermatitis, within 14 days prior to Baseline/Day 1

Medications Prohibited 7 Days Prior to Baseline/Day 1

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body, within 7 days prior to Baseline/Day 1.
- Escalating, decreasing, or PRN use of systemic antihistamines.

  Subjects on a stable systemic antihistamine regimen with ≥7 days of consistent use prior to Baseline/Day 1 are permitted to continue but must not alter or stop their regimen during the study.

  Medications Prohibited 1 Day Prior to Baseline/Day 1

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

After the Baseline/Day 1 Visit, use of emollient(s), moisturizer or sunscreen is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD involved areas until Day 29. Use of emollient(s), moisturizer or sunscreen in the skin of whole body is permitted after Day 29 telephone contact.

5.8.2. Medications Prohibited During the Study (Days 1–36)

Classes of medications and non-medication therapies that may alter the course of AD and that are prohibited during the study (from Baseline/Day 1 through the post-treatment follow-up visit on Day 36) are listed below.

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

  Subjects on a stable topical retinoid and/or BPO regimen with ≥14 days of consistent use prior to Baseline/Day 1 are permitted to continue the topical retinoid or BPO regimen (not on AD lesions) but must not alter or stop their regimen during the study.
- Use of systemic antihistamines, unless on stable ≥regimen (see note in Section 5.8.1).
- Use of systemic or topical traditional Chinese medicine/herbal preparation that might alter the course of atopic dermatitis
- Use of systemic antibiotics for more than 14 consecutive days.

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

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body.

- Use of sunbathing, tanning bed use, light therapy (UV, UV-B, PUVA) anywhere on the body.

- Use of topical antihistamines anywhere on the body.

- Participation in another drug or device research study.

5.8.3. Medications Allowed During the Study (Days 1–29)

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

- After the Baseline/Day 1 Visit, use of bland emollient(s) is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD-involved areas.

- Subjects on a stable regimen of inhaled, intranasal, or ocular corticosteroids, with ≥14 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study

- Short courses (≤14 days) of systemic antibiotics may be given during the course of the study, if clinically necessary for the treatment of new onset infections.

- Subjects on a stable systemic antihistamine regimen, with at least 7 days of consistent use prior to Baseline/Day 1, are permitted to continue but must not alter or stop their regimen during the study.

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

- Nonsteroidal anti-inflammatory drugs are allowed throughout the study.

- Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation in study.

- Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception are permitted during the study, for female subjects of childbearing potential.

- Concomitant medications for other chronic medical conditions are permitted during the study unless the medication/therapy is specifically prohibited by the protocol.

6. STUDY PROCEDURES

6.1. Study Visits

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

6.2. Time Windows for Study Procedures

Allowable time windows for visits/contacts are as follows:

- Screening visit: up to 35 Days prior to Day 1/baseline;
- Day 1 Visit: Day 1;
- Day 8 Visit: Day 8 ±1 day;
- Day 15 Visit: Day 15 ±3 day;
- Day 22 Visit: Day 22 ±3 day;
- Day 29 End of Treatment Visit: Day 29 ±3 day;
- Follow up telephone contact 1: Day 36 ±3 day;
- Follow up telephone contact 2: Day 60 ±3 day.

Refer to the Schedule of Activities for a complete list of assessments to be performed during the study.

6.3. Screening period

Screening procedures must be completed within 35 days (inclusive) before the baseline/Day 1 Visit. If necessary, the screening procedures may be completed over several days, with the exception of the Peak Pruritus NRS and Patient Reported Itch Severity

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.

- 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.

- If a subject is using a prohibited medication (or non-medication therapy) at the time of Screening, the investigator or his/her designee will provide instructions on discontinuing the prohibited medication or therapy (ie, a washout period) at Screening.

- If a subject will be undergoing washout of a prohibited medication as directed by the investigator or his/her designee, the subject's tentative eligibility will be confirmed pending successful completion of the washout (to be confirmed at Baseline/Day 1 Visit).

- Assess for AEs/SAEs, starting from the time of informed consent and assent, as applicable.

- Urine pregnancy test (female subjects of childbearing potential only).

- Serum chemistry and hematology.

- FSH (to confirm postmenopausal status in females who are amenorrheic for at least 12 consecutive months).

- Complete the ISGA (will be completed 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).

- Calculate subject's Treatable %BSA.

- Review subject's tentative eligibility according to the Inclusion and Exclusion Criteria.

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

- Contraception check: Confirm and document in source documents that proper contraception has been reviewed for the female subject of child bearing potential and their partner as appropriate, and the subject's agreement to use appropriate contraception methods throughout the study.

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

6.4. Study Period/Treatment Period

6.4.1. Baseline/Day 1 Visit

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

- Ask the subject or observer (parent/legal guardian/other caregiver) when applicable to complete the Peak Pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale and PGIS/OGIS QD (preferably same time of day each day if applicable) before IP morning dose applied starting at Baseline/Day 1 and continuing through Day 28 and at Day 29.

- Ask the subject or observer when applicable to complete the POEM, DLQI, CDLQI, IDQOL, and DFI.

- Assess and record any changes in the subject's prior and concomitant medications since the Screening Visit (if Screening and Baseline are 2 visits); see Section 5.8 for medications prohibited prior to Baseline/Day 1 and during the study.

- Obtain and record medical history.

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes; assessment of vital signs should precede blood draw for clinical laboratory tests.

- Measure height and weight.

- Perform a 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.

- Complete the ISGA. ISGA must be completed prior to CCI [redacted] the EASI assessment (Note: The ISGA score must be 2 or 3 at Baseline/Day 1 for subject to be eligible for the study).

CCI [redacted]

- Complete the EASI assessment, after completing the ISGA CCI [redacted]

- Calculate subject's Treatable %BSA.

- Confirm subject's eligibility based on the Inclusion Criteria and Exclusion Criteria, including confirming acceptable methods of birth control for female subjects of childbearing potential.

- Assess and record any AEs/SAEs.

- Draw blood for clinical laboratory tests on Day 1 prior to initial dosing; assessment of vital signs should precede blood draw for clinical laboratory tests; testing includes serum chemistry and hematology.

  Note: If the screening serum chemistry and hematology tests are performed within 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 Principle Investigator (PI) or designee.

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

- Perform a urine pregnancy test (female subjects of childbearing potential only) and confirm the subject has a negative urine pregnancy test result prior to randomization.

- Mark the subject's source documents to record the treatable AD areas (excluding the scalp) as identified by the investigator or his/her designee at Baseline/Day 1 and provide subject and/or parent/legal guardian with documentation of the designated treatment areas.

- A checklist of body areas currently affected by AD will be completed at the baseline/Day 1 visit. Location of skin lesions will be selected from a prepopulated listing of body locations.

- After PI's or designee's documented confirmation of eligibility, access IRT system to randomize subject to investigational product treatment.

- Access into IRT system to dispense the investigational products based on IRT randomization code.

- Weigh investigational product tube(s) before applying first dose; record investigational product tube(s) weight in subject's source documents.

- Wearing gloves, study staff will apply a layer of investigational product ointment (first dose) to all treatable AD lesions identified at Baseline/Day 1.

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

- Assess and record any AEs (including application site reactions) and SAEs.

- Provide to subject and/or parent/legal guardian a sufficient number of tubes of investigational product for 1 week of dosing; ensure that all dispensed tubes are weighed, and weight is recorded in subject's source documents.

- Instruct the subject and/or the parent/legal guardian that subject should not wipe investigational product off the skin, avoid occluding the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application.

- Dispense dosing diary and instruct the subject's parent(s)/legal guardian on use (ie, each time investigational product is applied). Instruct the subject and/or parent/legal guardian regarding all procedures for at home dosing beginning with the evening (PM) dose on Day 1 followed by BID dosing through Day 28, including how to complete the Dosing Diary, which will start at the Baseline/Day 1 Visit and continue BID through Day 28 (ie, each time investigational product is applied).

- Contraception check: Confirm and document that proper contraception is being used for the female subject of childbearing potential and their partner as appropriate.

- Review the schedule of upcoming study visits with the subject and/or parent/legal guardian and instruct them to return at the scheduled time for the Day 8 Visit.

- Remind the subject and/or parent/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the Dosing Diary to their next visit.

6.4.2. Day 8 (±1 day), Day 15 (±3 days) and Day 22 (±3 days) Study Visit

The following procedures will be performed:

- Remind the subject or observer when applicable to complete the Peak Pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale (QD before investigational product is applied).
- Remind the subject or observer when applicable to complete the PGIS/OGIS, Patient Global Impression of Change (PGIC)/Observer Global Impression of Change (OGIC).
- Remind the subject or observer when applicable to complete the POEM, DLQI, CDLQI, IDQOL, DFI (these questionnaires will only be completed for Day 15 visit, not for Day 8 and Day 22 visit).
- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications.
- Assess and record any AEs (including application site reactions) and SAEs. For any AE occurring in the treated area, a body site check list will be used to report the AE locations.
- Obtain vital signs (temperature, respiratory rate, pulse rate, and blood pressure) (only for Day 15 visit, not scheduled for Day 8 and Day 22 visit) in the seated or supine position, after the subject has been sitting or lying calmly for a minimum of 5 minutes.
- Complete the ISGA. ISGA must be completed prior to CCI [redacted] EASI assessment.
- CCI [redacted]
- Complete the EASI assessment, after completing the ISGA CCI [redacted]
- Calculate subject's Treatable %BSA.
- Update the documentation of treatable areas for any new AD lesions that appear after the Baseline/Day 1 Visit. The subject and parent/legal guardian (if applicable) will be

provided with documentation of the designated treatment areas, to ensure that previously treated areas which have resolved continue to be treated as required.

- Review Dosing Diary and assess compliance; re-educate the subject and/or parent/legal guardian if any missed doses have occurred.

- Collect returned tube(s) of investigational product from the subject and/or parent/legal guardian and weigh them. Weights will be recorded in subject's source documents.

- Access into IRT system to assign new tube(s) of investigational product (enough for 1 week of dosing) and weigh them prior to dispensing the tube(s) to subject and/or parent/legal guardian.

- Remind the subject and/or parent/legal guardian that investigational product must continue to be applied at home twice each day (am and pm), as instructed.

- Dispense dosing diary.

- Instruct the subject and/or parent/legal guardian that subject should not wipe investigational product off the skin, avoid occluding the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application.

- Contraception check: Confirm and document that proper contraception is being used for the female subject of child bearing potential and their partner as appropriate.

- Review the schedule of upcoming study visits with the subject and/or parent/legal guardian, and instruct them to return at the scheduled time for the next visit.

- Remind subject and/or parent/legal guardian to bring all investigational product tubes (empty, partially used and unused) and the Dosing Diary to their next visit.

6.4.3. Day 29 (±3 days) (End-of-Treatment)/Early termination Study Visit

In the event the Day 29 Visit must be delayed, eg, due to an unavoidable scheduling conflict, subject and/or parent/legal guardian will be instructed to continue blinded investigational product application BID through the evening before the day on which the rescheduled End-of-Treatment Visit is to occur. The following procedures will be performed at the Day 29/Early Termination Visit:

- Ask the subject or observer when applicable to complete Day 29 Peak Pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale, PGIS/OGIS scale if not already completed.

- Ask the subject or observer when applicable to complete the PGIC/OGIC, POEM, DLQI, CDLQI, IDQOL, DFI.

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications.

- Assess and record any AEs (including application site reactions) and SAEs. For any AE occurring in the treated area, a body site check list will be used to report the AE locations.

- Urine pregnancy test (female subjects of childbearing potential only).

- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, after the subject has been sitting calmly for a minimum of 5 minutes; assessment of vital signs should precede blood draw for clinical laboratory tests.

- Draw blood for clinical laboratory tests including chemistry and hematology (after having assessed vital signs).

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

- Perform a full physical examination, evaluate any current or reported symptoms for clinically significant changes and report relevant AE if applicable.

- Complete the ISGA. ISGA must be completed prior to CCI [redacted] the EASI assessment.

CCI [redacted]

- Complete the EASI assessment, after completing the ISGA CCI [redacted]

- Calculate subject's Treatable %BSA based on all AD lesions present at Day 29, excluding the scalp.
- Review Dosing Diary and assess compliance.
- Collect Dosing Diary.
- Collect returned tube(s) of investigational product from the subject and/or parent/legal guardian and weigh them.
- Contraception check: Confirm and document that proper contraception is being used for the female subject of childbearing potential and their partner as appropriate.
- The 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.

6.4.4. Unscheduled Visit

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

- Assess and record any changes in concomitant medications, including confirming that subject is not taking any prohibited medications, as detailed in Section 5.8.3.
- Obtain vital signs (temperature, respiratory rate, pulse rate, and BP) in the seated or supine position, preferably after the subject has been sitting or lying face up for a minimum of 5 minutes.
- Weigh investigational product tubes; record investigational product tubes weight in subject's source documents.
- Instruct the parent(s)/legal guardian regarding all procedures for at home dosing beginning BID dosing through Day 29 visit, including how to complete the dosing diary.
- Assess and record any AEs, including application site reactions, and SAEs.
- Review the schedule of upcoming study visits with the parent(s)/legal guardian and instruct them to return at the scheduled time.

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.

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

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

CCI [redacted]

7.1.4. Eczema Area and Severity Index (EASI)

The EASI[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.

The extent (%) to which each of the four body regions is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria. See Table 3 on EASI Area Score Criteria.

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

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

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

Table 4. 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, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale
∗ The EASI will exclude scalp from the assessment/scoring		

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

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

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

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

The EASI score can vary in increments of range from 0.0 to 72.0, with higher scores representing greater severity of atopic dermatitis. Considering the scalp will be excluded

from the EASI assessment in the present study, the maximum possible score will be less than 72.0 (modified EASI score).

7.1.5. Body Site Checklist for Atopic Dermatitis

A checklist of body areas currently affected by AD will be completed at the baseline visit. Location of skin lesions will be selected from a prepopulated listing of body locations.

7.1.6. Patient/Observer Reported Outcomes

The Patient/Observer Reported Outcomes questionnaires in this study include: Peak pruritus NRS/Patient Reported Itch Severity Scale/Observer Reported Itch Severity Scale, PGIS/OGIS, PGIC/OGIC, POEM, DLQI, CDLQI, IDQOL, DFI. They will be performed at the time points defined in the Schedule of Activities. The age cut-offs are based on the age at informed consent.

On study visit days, subjects or observer (ie, the one who provides the information to complete the questionnaires other than subject, eg, parent/legal guardian/other caregiver) should complete the patient reported outcomes at the clinic prior to any procedures being performed. The one who completed the questionnaires should be captured and stored in database and available for analysis. It's preferred that all observer reported outcomes for a given subject are completed by same individual throughout the study.

7.1.6.1. Pruritus and Itch Assessment

Participants will be asked to assess their worst itch or scratching due to AD over the past 24 hours. Participants ⩾6 years and <12 years will be asked to assess their worst itch or scratching due to AD for today.

- Peak Pruritus Numerical Rating Scale (NRS)[27] is an 11-point scale and must be completed by participants ≥12 years of age.
- Patient reported Itch Severity Scale is a 5-point scale must be completed by participants ≥6 years and <12 years.
- Observer reported Itch Severity Scale is an 11-point scale and must be completed by the observers (caregivers of participants) for participants <6 years of age.

7.1.6.2. Patient Global Impression of Severity (PGIS) and Observer Reported Global Impression of Severity (OGIS)

The PGIS and OGIS is a single item patient- or observer-rated measure of the subject's AD condition severity at a given point in time.

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.

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.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted at site with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). In the case of a positive urine 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 judges that the subject is not pregnant, the subject may resume investigational product.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

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.

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;

- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

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

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × 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**

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Spontaneous abortion includes miscarriage and missed abortion.

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

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

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

For further clarification, a medication error is:

- Any scenarios leading to inappropriate medication use or participant harm;
- When participant misunderstood, could not read prescription, was not aware of, or not given appropriate dosing instructions.

A medication error is any unintentional error. Intentionally missing a dose or use of extra dose of study medication by a participant, who understands dosing instructions, is a compliance issue.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

Efficacy analyses will be performed on the Full Analysis Set (FAS) which includes all subjects who are randomized and dispensed investigational product. Analyses based on the Per Protocol Analysis Set (PPAS) will be considered supportive. The PPAS includes all subjects in the FAS who complete the Day 29 evaluation without any major protocol deviations. Safety analyses will be performed on the Safety Analysis Set (SAFETY) which includes all subjects who are randomized and received at least one confirmed dose of investigational product.

Major protocol deviations will be summarized. Noncompliance with investigational product administration requirement will be summarized in terms of number of applications, number of days dosing, amount of drug used, and compliant status. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected applications during the investigational product application period, and has not missed 6 or more consecutive doses.

9.1. Sample Size Determination

The total sample size of 384 subjects in this study with a 2:1 randomization ratio (256:128) will provide approximately 90% power to detect a 12% difference of percent change from baseline in EASI total score at Day 29 between crisaborole arm and vehicle arm at the 0.05 (2-sided) significance level, CCI [redacted]

Comparative EASI data relative to vehicle was not collected in previous crisaborole studies. The 12% treatment effect in EASI percent improvement was converted from the ISGA response in the Phase 3 studies using a linear regression equation that evaluated the relationship between ISGA response rate and EASI percent improvement from historical trial

data of other topical products (data on file). From the crisaborole Phase 3 pooled data, the ISGA response rate is 32.1 % for crisaborole and 21.8% for vehicle. The converted EASI percent improvement is 38.9% and 26.8% respectively. The difference of EASI percent improvement between crisaborole and vehicle is approximately 12%.

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

The primary efficacy endpoint, percent change from baseline in EASI total score at Day 29, will be analyzed using a linear mixed-effect model for repeated measures that includes treatment group, visit, and treatment group by visit interaction as factors and baseline value as a covariate. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix.

9.2.2. Analysis of Key Secondary Endpoints

Type I error rate will be strictly controlled for the analyses of the key secondary efficacy endpoints with sequential testing in the following order: Improvement in ISGA (defined as ISGA score of Clear (0) or Almost Clear (1)) at Day 29, Success in ISGA (defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2 grade improvement from Baseline) at Day 29, and change from baseline to Week 4 in weekly average of peak pruritus Numeric Rating Scale (NRS). The percentage of subjects with Improvement in ISGA at Day 29 will be compared between crisaborole arm and vehicle arm and the difference will be tested based on normal approximation to response rates. Missing Day 29 ISGA scores will be derived for the analysis using the method of multiple imputations (MI) based on Markov Chain Monte Carlo (MCMC).

The percentage of subjects with Success in ISGA at Day 29 will be analyzed in the same way as Improvement in ISGA. The same sets of imputed ISGA scores will be used for both Success in ISGA and Improvement in ISGA.

The change from baseline to Week 4 in weekly average of peak pruritus NRS will be analyzed using a linear mixed-effect model for repeated measures that includes treatment group, visit, and treatment -group by visit interaction as factors and baseline value as a covariate. Within-subject variability will be accounted for using a random effect with the first order autoregressive (AR(1)) covariance matrix.

9.2.3. Analysis of Other Secondary Endpoints

Other secondary efficacy endpoints including change from Baseline in % BSA, percent change from baseline in EASI total score at all time points other than Day 29, change from

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.

9.5. Data Monitoring Committee

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

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The

study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent[/assent] documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will

maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent[/assent] documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent[/assent] documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or parent(s) or legal guardian if a minor is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies preferably at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

1. Bieber T. Atopic dermatitis. N Engl J Med 2008;358(14):1483–94.

2. Lewis Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract. 2006 Aug;60(8):984 92.

3. Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. Semin Cutan Med Surg 2012;31(3 Suppl):S3 5.

4. Leicht S, Hanggi M. Atopic dermatitis. How to incorporate advances in management. Postgrad Med 2001;109(6):119–27.

5. Gu Heng, YAN Yan, CHEN Kun, et al. Survey on Atopic Dermatitis in China. Chin J Dermatol. 2000 Dec 33 (6):379-382.

6. GU Heng, You Li-ping, LIU Yong-sheng, et al. Survey on the Prevalence of Childhood Atopic Dermatitis in Ten Cities of China. Chin J Dermatol.2004 Jan 37 (1):29-31.

7. Feng Xu, Shuxian Yan, Fei Li, et al. Prevalence of Childhood Atopic Dermatitis: An Urban and Rural Community-Based Study in Shanghai, China. PLoS ONE. 2012 May 7(5): e36174.

8. Guo Y, Li P, Tang J, et al. Prevalence of Atopic Dermatitis in Chinese Children aged 1-7 ys. Sci Rep. 2016 Jul 19;6:29751.

9. Arkwright PD, Motala C, Subramanian H, et al. Management of difficult to treat atopic dermatitis, 2013. J Allergy Clin Immunol Pract. 2013 Mar;1(2):142 51.

10. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. Allergol Int. 2013 Jun;62(2):151 61.

11. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol. 2014 Apr;5(2).

12. Saunes M, Oien T, Dotterud C, et al. Early eczema and the risk of childhood asthma: a prospective, population based study. BMC Pediatr. 2012 Oct 24;12:168.

13. Garg N, Silverberg J. Epidemiology of childhood atopic dermatitis. Clin Dermatol. 2015 May Jun;33(3):281 8.

14. Beatti PE, Lewis Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. Br J Dermatol. 2006 Jul;155(1):145 51.

15. Carroll CL, Balkrishnan R, Feldman S, et al. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatr Dermatol. 2005 May Jun;22(3):192 9.

16. Halvorsen J, Lien L, Dalgard F, et al. Suicidal ideation, mental health problems, and social function in adolescents with eczema: a population based study. J Invest Dermatol. 2014 Jul;134(7):1847 54.

17. Su JC, Kemp AS, Varigos GA, et al. Atopic eczema: its impact on the family and financial cost. Arch Dis Child. 1997 Feb;76(2):159 62.

18. Lawson V, Lewis Jones MS, Finlay AY, et al. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. Br J Dermatol. 1998 Jan;138(1):107 13.

19. Dahl RE, Bernhisel Broadbent J, Scanlon Holdford S, et al. Sleep disturbances in children with atopic dermatitis. Arch Pediatr Adolesc Med. 1995 Aug;149(8):856 60.

20. Kim S, Hur J, Jang J, et al. Psychological Distress in Young Adult Males with Atopic Dermatitis: A Cross Sectional Study. Medicine (Baltimore). 2015 Jun;94(23):e949.

21. Daud LR, Garralda ME, David TJ. Psychosocial adjustment in preschool children with atopic eczema. Arch Dis Child. 1993 Dec;69(6):670 6.

22. Absolon CM, Cottrell D, Eldridge SM, et al. Psychological disturbance in atopic eczema: the extent of the problem in school aged children. Br J Dermatol. 1997 Aug;137(2):241 5.

23. Watson W, Kapur S. Atopic dermatitis. Allergy Asthma Clin Immunol. 2011 Nov 10;7 Suppl 1:S4.

24. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016 Sep;75(3):494-503.

25. Pfizer Investigator Brochure for Crisaborole, February 2017.

26. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, Wang C, Purohit V, Mamolo C, Papacharalambous J, Ports WC. Br J Dermatol. 2016 Nov;175(5):902-911. doi: 10.1111/bjd.14871. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial.

27. Yosipovitch G, Reaney M, Mastey V, et al. Peak Pruritus Numerical Rating Scale: Psychometric Validation and Responder Definition for Assessing Itch in Moderate-To-Severe Atopic Dermatitis. Br J Dermatol. 2019.

28. 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.

29. Ersser SJ, Cowdell F, Latter S, et al. Psychological and educational interventions for atopic eczema in children. Cochrane Database Syst Rev. 2014(1):CD004054.

30. Schmitt J, Langan S, Williams HC, et al. What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol. 2007;120(6):1389-98.

31. Hanifin JM and Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92(suppl):44-7.

Appendix 1. Abbreviations

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

Abbreviation	Term
AD	Atopic Dermatitis
ADSI	Atopic Dermatitis Severity Index
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Morning
AR	Autoregressive
AST	Aspartate Aminotransferase
BBS	Biospecimen Banking System
BID	Twice Daily
BP	Blood Pressure
BPO	Benzoyl Peroxide
%BSA	Percent Body Surface Area
cAMP	Cyclic Adenosine Monophosphate
CI	Confidence Interval
CK	Creatine Kinase
C_{max}	Maximum Observed Plasma Concentration
CDLQI	Children'S Dermatology Life Quality Index
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CTA	Clinical Trial Application
DFI	Dermatitis Family Impact Questionnaire
DILI	Drug-Induced Liver Injury
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DU	Dispensable Unit
EASI	Eczema Area And Severity Index
EC	Ethics Committee
EC_{50}	Half Maximal Effective Concentration
E-DMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy
EU	European Union

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

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

Appendix 2. Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[31]

Table 6. Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

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

Food intolerance
Course influenced by environmental and emotional factors
White demographism, delayed blanch

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