TITLE PAGE

Protocol Title: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Maintenance Treatment and Flare Reduction with Crisaborole Ointment, 2%, Once Daily Over 52 Weeks in Pediatric and Adult Participants (Ages 3 Months and Older) with Mild-to-Moderate Atopic Dermatitis, who Responded to Twice Daily Crisaborole Ointment, 2%, Treatment

Protocol Number: C3291035

Amendment Number: 1

Compound Number: PF-06930164/AN2728

Study Phase: Phase 3

Short Title: Study Evaluating Long-Term Maintenance Treatment and Flare Reduction with Crisaborole Ointment 2% in Pediatric and Adult Participants with Mild-to-Moderate Atopic Dermatitis

Acronym: CrisADe Control

Sponsor Name: Pfizer, Inc

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	ID
IND	77,537
EudraCT	2019-000443-28

Approval Date: 19 May 2020

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	19 May 2020
Original Protocol	04 April 2019

Amendment 1 (XX May 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Protocol Title, Section 1.1. Synopsis, Section 2.1. Study Rationale, Section 3. Objectives, Estimands, and Endpoints, Section 5.1. Inclusion Criteria, Section 8.1.3. Eczema Area and Severity Index (EASI), Section 8.1.6. Patient Reported Outcomes (PROs), Section 9.4.1.1. Testing Procedures for Multiple Comparisons, Section 10.8. Appendix 8: Country-Specific Requirements	The age of the study participant population was extended to 3 months of age and older.	This is in alignment with an FDA recommendation and the agreed initial Pediatric Study Plan in the US. The inclusion of the age group of 3 months to <24 months to the C3291035 study is supported by the recently completed Study C3291002 in 3 months to <24 months in participants with mild and moderate atopic dermatitis. The C3291002 study showed a comparable benefit risk profile as that observed in the pivotal Phase 3 clinical trials in participants aged 2 years and older.
Section 1.1. Synopsis, Section 9.2. Sample Size Determination	It was clarified that to yield a total of 162 first flares in the double-blind maintenance period of the study, it is estimated that approximately 700 participants will be enrolled in the open-label period for responder identification and that 250 participants will be randomized into the double-blind maintenance period. It is possible that less than 700 or up to 860	Administrative update to improve on clarity pertaining to explicit description of the event-driven design of the trial, for which the numbers of study participants enrolled into run-in treatment and further randomized into double-blind study will be driven by 162 events (first flares during double-blind study) achieved.

Section # and Name	Description of Change	Brief Rationale
	participants will be enrolled in the open-label period.	
Section 1.3. Schedule of Activities (SoA), Section 10.9. Appendix 9: Alternative Study Procedures during COVID-19 Pandemic	Alternative study visit procedures pertaining to the COVID-19 pandemic period of the study were provided.	Administrative update to incorporate Protocol Administrative Change Letter dated 25 March 2020.
Section 2. Introduction	The introduction was modified to reflect approval of crisaborole in the United States as a topical treatment therapy in patients 3 months of age and older with mild to moderate atopic dermatitis (AD) and in the European Union as a topical treatment therapy in patients 2 years of age and older with mild-to-moderate AD. In addition, text was added to describe the mode of action of crisaborole study (C3291001).	Administrative update to current marketing authorization approvals and to incorporate information from the C3291001 mode of action study.
Section 2.2.1.2. Pharmacokinetics	Text was added to state that the PK of crisaborole ointment in infants of 3 to <24 months of age was similar to that observed for participants 2 years of age and older.	Administrative update to reflect current Investigator's Brochure.
Section 2.2.1.3. Clinical Experience, Section 2.3. Benefit/Risk Assessment, Section 4.3. Justification for Dose	Text was added noting that in a Phase 4 open-label safety study of crisaborole ointment in participants 3 to <24 months of age (C3291002), the safety profile CCI results were consistent with the Phase 3 studies	Administrative update to reflect current Investigator's Brochure.
Section 5.2. Exclusion Criteria	It was clarified that either a history of cancer or cancer treatment within 5 years is exclusionary.	Administrative update to improve clarity and readability.
Section 6.1.1. Dosing Application	Additional dosing application instructions added.	To provide additional guidance on dosing application for caregivers.
Section 7.2. Participant Discontinuation/ Withdrawal from the Study,	Additional clarification and procedure information have been added.	To provide further clarification and guidance on participant discontinuation and withdrawal of consent.

Section # and Name	Description of Change	Brief Rationale
Section 7.2.1. Withdrawal of Consent		
Section 8.1.6. Patient Reported Outcomes (PROs)	Recall periods for Patient Reported Outcomes were updated to match recall periods on questionnaires provided to participants.	Administrative update to reflect the correct recall periods.
Section 8.2.5. Clinical Safety Laboratory Assessments	This section was not modified per the Protocol Administrative Change Letter dated 28 August 2019.	The changes outlined in this Protocol Administrative Change Letter are already incorporated in Appendix 2 of the original protocol.
Section 8.3.5.1. Exposure During Pregnancy	Text updated to add female family members and healthcare providers to pregnancy reporting after study intervention exposure.	To include female family members and healthcare providers in pregnancy reporting after study intervention exposure.
Section 8.4. Treatment of Overdose	The treatment of overdose was updated to state that if excess crisaborole is applied, it can be wiped off.	Administrative update to incorporate Protocol Administrative Change Letter 07 May 2019.
Section 9. Statistical Considerations	The Enrolled and Safety – Double-Blind populations were added. "Duration of the BID treatment in open-label period" was added as a stratification factor for the primary and secondary analyses. Sensitivity/supplementary analyses for the primary analysis were added.	Administrative updates to Section 9 'Statistical Consideration' to improve overall clarity and readability. Additional updates made per FDA recommendations following review of the protocol.
Section 10.2. Appendix 2: Clinical Laboratory Tests	Updated to provide specific requirements for repeat laboratory assessments for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and creatinine in the event of ≥30% increase from baseline value.	Update on additional safety laboratory monitoring requirements.
Section 10.8. Appendix 8: Country-Specific Requirements	An Appendix was added to clarify that enrollment for study participants of 3 months to <24 months will be open to all participating sites except for those in Europe (Austria, France, Spain).	To specify the exclusion of European Union (EU) countries from enrollment of age group 3 months to <24 months due to the competing study C3291031 in a similar age group. C3291031 is an agreed study in the EU Paediatric Investigational Plan.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study to Evaluate the Efficacy and Safety of Maintenance Treatment and Flare Reduction with Crisaborole Ointment, 2%, Once Daily Over 52 Weeks in Pediatric and Adult Participants (Ages 3 Months and Older) with Mild-to-Moderate Atopic Dermatitis, who Responded to Twice Daily Crisaborole Ointment, 2%, Treatment
Short Title: Study Evaluating Long-Term Maintenance Treatment and Flare Reduction with Crisaborole Ointment 2% in Pediatric and Adult Participants with Mild-to-Moderate Atopic Dermatitis

Rationale:
Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor and is being developed as a topical treatment for patients with mild-to-moderate atopic dermatitis (AD).

This study will specifically evaluate crisaborole therapy once daily (QD) as a long-term topical maintenance therapy for the reduction of flare in responders to crisaborole twice daily (BID) treatment.

Objectives, Estimands and Endpoints

Primary Objectives	Primary Endpoints
Efficacy: To evaluate the long-term efficacy of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate AD who responded to crisaborole ointment, 2%, BID treatment.	- Flare-free maintenance until onset of first flare during the 52-week double-blind period
Safety: To evaluate the safety and local tolerability of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate AD	- Incidence of treatment emergent adverse events

The primary and secondary estimands are hypothetical estimands defined according to the primary and secondary objectives and are in alignment with the primary endpoint and secondary endpoints.

Log-rank test and product limit approach will be used for analysis of the primary endpoint flare-free maintenance and secondary endpoint pruritus response maintenance. An analysis of covariance (ANCOVA) model will be used for the analysis of secondary endpoint of flare-free days. Wilcoxon rank sum test will be used for the analysis of the secondary endpoint of number of flares.

Overall Design:
Eligible participants will be enrolled to receive crisaborole BID in an open-label run-in period of up to a maximum of 8 weeks in duration. Responders to run-in treatment at any time during this period will be randomized into the double-blind maintenance period in a 1:1 ratio to receive QD crisaborole or vehicle for 52 weeks. Non-responders at the end of the 8-week run-in period will be discontinued from the study. To yield a total of 162 first flare events in the double-blind maintenance period of the study, it is estimated that approximately 700 participants will be enrolled in the open-label period for responder identification and that approximately 250 participants will be randomized into the double-blind maintenance period. Once adequate participants have been randomized, recruitment will stop; it is possible that less than 700 or up to 860 participants will be enrolled in the open-label period.

Participants will be instructed to contact their study site as soon as possible to arrange an unscheduled clinic visit if a flare is suspected (eg, recurring or worsening AD signs or symptoms). In the maintenance period, all confirmed flare(s) will be treated with crisaborole BID in an open-label setting for up to 12 weeks (flare treatment period). Responders to flare treatment will resume double-blind treatment with the same allocation, until completion at 52 weeks. Non-responders to flare treatment period will discontinue from the study.

An end-of-study (EOS) safety follow-up by phone will be required 4 weeks after the discontinuation of last study dose of any treatment period.

CCI [redacted]

Disclosure Statement:
This is a Parallel Treatment study with 2 Arms that are Participant, Investigator, and Sponsor blinded.

Number of Participants:
Approximately 700 participants will be enrolled in the run-in period for responder qualification. Approximately 250 participants will be randomized into the maintenance period of the study.

CCI [redacted]

Intervention Groups and Duration:

For the run-in period, all participants will receive crisaborole BID for up to 8 weeks.

For the maintenance period:

Group 1 (N=125): Crisaborole ointment, 2% (weight by weight) QD for 52 weeks

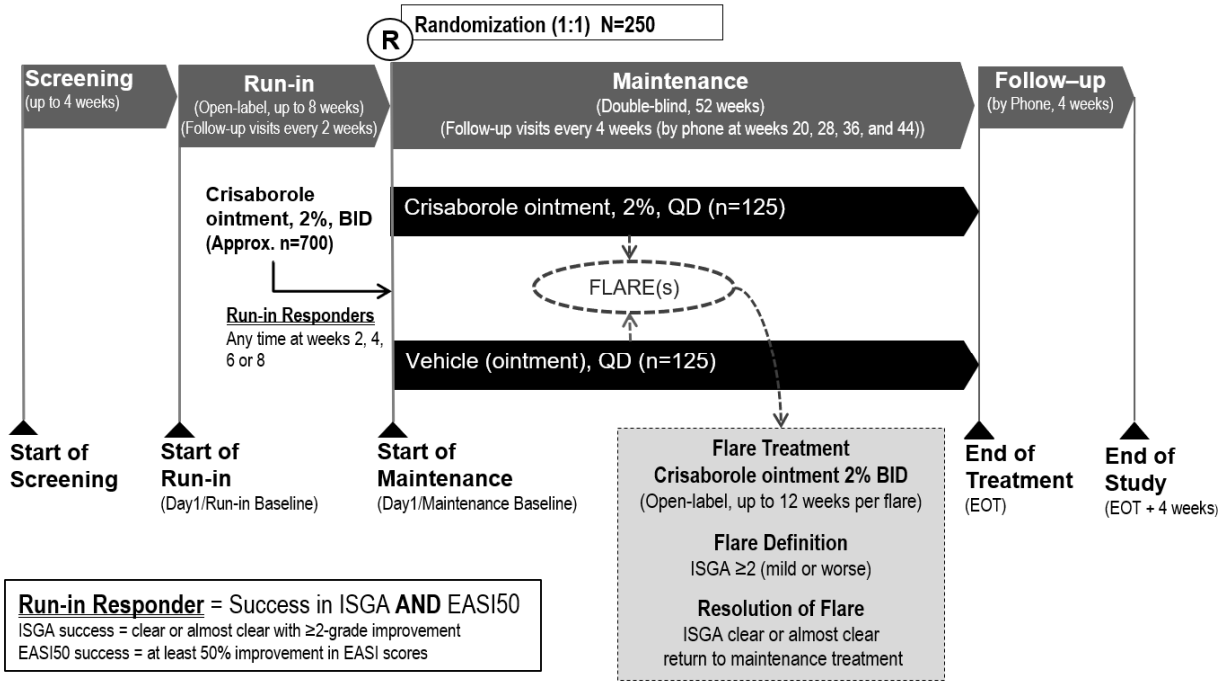
Group 2 (N=125): Vehicle (ointment) QD for 52 weeks

The total duration of participation in the study, CCI [redacted] is up to 68 weeks, including up to 4 weeks for screening, run-in period of up to

8 weeks, 52-week double-blind maintenance period, and follow-up period 4 weeks after treatment completion.

Data Monitoring Committee: Yes

1.2. Schema



BID = twice daily; QD = once daily; ISGA = Investigator's Static Global Assessment; EASI = Eczema Area and Severity Index; EOT = End of treatment

1.3. Schedule of Activities (SoA)

Participants can become responders at any of the end of run-in (EORI) visits. For responders entering into the maintenance period, the Randomization Day 1 is the same day as the last EORI visit; all assessments including the additional assessments required for Day 1 are mandatory.

The in-clinic visits can be both scheduled and unscheduled. Visits on weeks 20, 28, 36, and 44 will be conducted by phone calls. Alternative study visit information pertaining to the COVID-19 pandemic is described in Appendix 9.

Table 1. Schedule of Activities

Period	Screening	Run-in (Open-label)					Maintenance (Double-Blind)													End-of-Study (Follow-up)	Notes
Day	-28 to -1	1	15 (End of Run-in)	29	43	57	1	29	57	85	113	141 ☎	169	197 ☎	225	253 ☎	281	309 ☎	337	365	By phone at least 28 days after last study dose of any period	☎ Phone visits at weeks 20, 28, 36, and 44 (Section 8).
Week(s)		0	2	4	6	8	0	4	8	12	16	20	24	28	32	36	40	44	48	52		
Window(days)			±1	±3				±3 / visit					±3	±3 / visit						±3	+3	
ENROLLMENT PROCEDURES																						
Informed consent / assent	X																					See Appendix 10.1.3
Demographics, and medical history including AD history and prior AD treatment (incl. reasons of stop)	X																					Up to run-in Day 1, pre-dose
Inclusion and exclusion criteria	X	X					X															Confirmation required at Run-in baseline and Maintenance baseline. See Section 5
Register enrollment using IRT	X																					See Section 6.3
Randomization using IRT							X															See Section 6.3
MEDICAL PROCEDURES																						
Vital signs	X	X ---------- every in-clinic visit ---------- X																				See Section 8.2.3

Table 1. Schedule of Activities

Period	Screening	Run-in (Open-label)					Maintenance (Double-Blind)												End-of-Study (Follow-up)	Notes
Day	**-28 to -1**	**1**	**15** (End of Run-in)	**29**	**43**	**57**	**1**	**29**	**57**	**85**	**113**	**141** ☎	**169**	**197** ☎	**225**	**253** ☎	**281**	**309** ☎	**337**	**365**	By phone at least 28 days after last study dose of any period	☎ Phone visits at weeks 20, 28, 36, and 44 (Section 8).
Week(s)		**0**	**2**	**4**	**6**	**8**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
Window(days)			**±1**	**±3**				**±3 / visit**					**±3**	**±3 / visit**						**±3**	**+3**	
Physical examination (PE)	X	X ---------- every in-clinic visit ---------- X																				Complete PE for screening, targeted PE for all follow-up. See Section 8.2.2
Height and weight	X	X					X						X							X		See Section 8.2.2
LABORATORY TESTING																						
Serum chemistry and hematology	X	Only if clinically indicated																				See Appendix 2, Section 8.2.5
Serum pregnancy test	X	For pregnancy status confirmation																				For all WOCBP (Appendix 4)
Urine dipstick pregnancy test		X	X ---------- every in-clinic visit ---------- X																			For all WOCBP. See Section 8.2.5.1 and Appendix 4.
Follicle-stimulating hormone	X																					WONCBP confirmation (Appendix 4)
CLINICAL ASSESSMENTS																						
Investigator's Static Global Assessment (ISGA)	X	X	X ---------- every in-clinic visit ---------- X																			See Section 8.1.2
Eczema Area and Severity Index (EASI)		X	X ---------- every in-clinic visit ---------- X																			See Section 8.1.3
Treatable AD %BSA	X	X	X ---------- every in-clinic visit ---------- X																			See Table 4
Record most commonly affected AD %BSA							X						X							X		See Section 6.1.1, Table 4

Table 1. Schedule of Activities

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Week(s)		**0**	**2**	**4**	**6**	**8**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
Window(days)			**±1**	**±3**				**±3 / visit**					**±3**	**±3 / visit**						**±3**	**+3**	
Record and review AD lesion checklist including new lesions		X	X ---------- every in-clinic visit ---------- X																			See Section 8.1.4
Record and review body map of AD lesions		X	X ---------- every in-clinic visit ---------- X																			See Section 8.1.4
PATIENT REPORTED OUTCOMES (PROs)																						
Columbia Suicide Severity Rating Scale (C-SSRS)	X																					See Section 8.2.6 and exclusion criterion 4
Pruritus and itch assessments		X ---------- daily ---------- X																				See Section 8.1.6.1
Night Time Itch																						See Section 8.1.6.2
AD Skin Pain																						See Section 8.1.6.3
Patient/Observer Global Impression of Severity (PGIS/OGIS)																						See Section 8.1.6.4
Dermatology Quality of Life Assessments		X ---------- weekly---------- X																				See Section 8.1.6.5
Patient-Oriented Eczema Measure (POEM)																						See Section 8.1.6.6
Patient/Observer Global Impression of Change (PGIC/OGIC)		X ---------- all in-clinic and phone visits ---------- X																				See Section 8.1.6.7
Medical Outcomes Study (MOS) Sleep Scale																						See Section 8.1.6.8
EuroQoL - 5 Dimensions (EQ-5D)		X ---------- all in-clinic and phone visits ---------- X																				See Section 8.1.6.9
Work and Classroom Productivity																						See Section 8.1.6.11

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Week(s)		**0**	**2**	**4**	**6**	**8**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
Window(days)			**±1**	**±3**				**±3 / visit**					**±3**	**±3 / visit**						**±3**	**+3**	
Hospital Anxiety and Depression Scale (HADS)		X	X (last EORI)				X	X At or nearest to weeks 8, 16, and 32												X		Participants who do not enter maintenance period will complete assessment only once at last EORI. See Section 8.1.6.10
SAFETY																						
Serious and non-serious AE monitoring and contraception check	X ---------- X																					See Section 8.3 and Appendix 3
STUDY INTERVENTION																						
Concomitant medications / therapies	X ---------- X																					See Section 6.5
In-clinic dose application training		X					X	If required														See Section 6.1.1
At-home dosing		X ---------- daily ---------- X																				Unless applied in-clinic
Issue and review eDiary for treatment compliance		X ---------- every in-clinic visit ---------- X																				
Drug dispensing		X ---------- every in-clinic visit ---------- X																				
Drug accountability		X ---------- every in-clinic visit ---------- X																				

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Week(s)		**0**	**2**	**4**	**6**	**8**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		
Window(days)			**±1**	**±3**				**±3 / visit**					**±3**	**±3 / visit**						**±3**	**+3**	
Flare treatment		• Unscheduled visits may be required **instead** of scheduled visits. It should include a start of flare treatment followed by monthly visits until flare resolution for up to 12 weeks. • Flare treatment visits will include all assessments/procedures as required on Day 29 of the maintenance period. • For week 24 scheduled assessments, if interrupted by flare visits, the assessments are performed at the nearest unscheduled visit within ±14 days [instead of ±3 days]) • Photography of AD lesions (see below)																				See Section 4.1 for Flare treatment See Section 8.1.5 for photography details
PHOTOGRAPHY (SELECTED STUDY SITES)																					
Photography of AD lesions		X	X (last EORI)				X (once at start and once at end of each flare)														See Section 8.1.5
CCI [redacted]																					
CCI [redacted]	[redacted]																				[redacted]

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Period	Screening	Run-in (Open-label)					Maintenance (Double-Blind)												End-of-Study (Follow-up)	Notes
Day	-28 to -1	1	15 (End of Run-in)	29	43	57	1	29	57	85	113	141 ☎	169	197 ☎	225	253 ☎	281	309 ☎	337	365	By phone at least 28 days after last study dose of any period	☎ Phone visits at weeks 20, 28, 36, and 44 (Section 8).
Week(s)		0	2	4	6	8	0	4	8	12	16	20	24	28	32	36	40	44	48	52		
Window(days)			±1	±3				±3 / visit					±3	±3 / visit						±3	+3	

☎ = phone visit; AD = atopic dermatitis; AE = adverse event; BSA = body surface area; C-SSRS = Columbia Suicide Severity Rating Scale; EASI = Eczema Area and Severity Index; EORI = end of run-in; EQ = EuroQoL; HADS = Hospital Anxiety and Depression Scale; IRT = interactive response technology; ISGA = Investigator's Static Global Assessment; MOS = Medical Outcomes Study; OGIC = Observer Global Impression of Change; OGIS = Observer Global Impression of Severity; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PE = physical examination; POEM = Patient Oriented Eczema Measure; PRO = patient reported outcome; WOCBP = women of childbearing potential, WONCBP = women of non-child bearing potential

2. INTRODUCTION

Crisaborole, also referred to as PF-06930164 or AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase (PDE)-4 inhibitor that penetrates into the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate levels, which suppresses inflammation and secretion of certain cytokines, such as tumor necrosis factor-α, interleukin (IL)-2, IL-4, IL-5, and interferon (IFN)-γ, implicated in the pathogenesis of AD. Crisaborole applied to human skin ex vivo or on atopic dermatitis (AD) lesions of patients reduces expression of key drivers of atopic inflammation, including T-cell derived cytokines IL-13, IL-31, and IFN-γ as well as innate markers of inflammation such as matrix metalloproteinase-12. The specific mechanism(s) by which crisaborole exerts its therapeutic action for AD is not well defined.[1] A Phase 2 clinical trial (C3291001) evaluating the mode of action of crisaborole ointment, 2%, showed that crisaborole significantly reduced all 7 prespecified key skin biomarkers involved in AD pathophysiology (S100A12, chemokine [C-C motif] ligand [CCL] 17, CCL18, CCL22, Keratin 16, elafin/peptidase inhibitor 3, and IL-13).

Crisaborole ointment, 2% (weight by weight) (20 mg/g) (referred to as crisaborole hereafter), is approved in the United States (US; EUCRISA®) as a topical treatment therapy in patients 3 months of age and older with mild to moderate AD; and in Canada (EUCRISA®), Israel, the European Union (EU), and Australia (STAQUIS®) as a topical treatment therapy in patients 2 years of age and older with mild-to-moderate AD.[1, 2] It is currently being developed worldwide as a topical therapy for patients with mild to moderate AD.

Additional information can be found in the Investigator's Brochure (IB).

2.1. Study Rationale

Crisaborole is being developed worldwide as a topical therapy for patients with mild-to-moderate AD based on its mechanism of action and the results obtained from 10 AD clinical trials to date (Section 2.2.1.3). This study will specifically evaluate crisaborole once daily (QD) regimen as a long-term maintenance therapy for the reduction of flares in patients 3 months of age and older with mild-to-moderate AD who respond to crisaborole twice daily (BID) treatment.

2.2. Background

AD, often known as eczema, is a chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life (QoL). AD flares occur at variable and unpredictable intervals. Patients with moderate AD may experience approximately 8 flares per year, each lasting approximately 14 days.[3]

Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US.[4, 5] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood. Earlier reports indicated that, in up to 70% of cases, the disease greatly improved or resolved by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of

7157 patients enrolled in the Pediatric Eczema Elective Registry study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[6] The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[7] Adult-onset AD does also occur, though it is less common. The prevalence of AD in adults is estimated to be 10%.[8]

Other treatment options for mild-to-moderate AD include regular use of emollients, topical corticosteroids (TCSs) of low-to-moderate potency, and topical calcineurin inhibitors (TCIs) (eg, pimecrolimus, tacrolimus) as a second line treatment. TCSs and TCIs have limitations for long term use due to safety concerns of TCS (striae rubrae, skin atrophy, telangiectasia, skin burning, erythema, and acneiform or rosacea-like eruptions) and TCI (inhibition of immune surveillance in the skin or systemically and warnings regarding potential for malignancies) adverse effects.[9, 10] Additional treatments generally reserved for more severe AD include phototherapy (eg, ultraviolet (UV)-A light with or without psoralen, UV-B light narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant interferon-γ, mycophenolate mofetil, methotrexate, azathioprine, intravenous immunoglobulin and dupilumab).[11] Of the currently available therapies, none offers a long-term maintenance solution without long-term use safety concerns for mild-to-moderate AD.[12, 13]

The AD skin is often immunologically abnormal even when it appears clinically normal.[5] Despite adherence to treatment, treatment modalities often fail to achieve stable long-term disease control, hence the significant impact on the QoL. Being proactive to prevent flares is recommended by guidelines,[14] but safety concerns have limited the long-term use of many available therapies. Based on the safety and efficacy data to date, crisaborole offers a potential option for long-term maintenance use and for the reduction in the occurrence of AD flares.

2.2.1. Drug Development

Crisaborole has been formulated as a topical ointment. Crisaborole has demonstrated clinical benefit in Phase 1, 2, and 3 AD clinical studies. Details of the non-clinical and clinical data are provided in the current IB.

2.2.1.1. Nonclinical Studies and Phase 1 Data

Data from nonclinical and Phase 1 programs support the ongoing and planned clinical development of crisaborole in Phase 2, Phase 3, and Phase 4 studies. Further information is provided in the current IB.

2.2.1.2. Pharmacokinetics

The efficacy of crisaborole for the topical treatment of AD is dependent on local skin absorption and not on systemic exposure. Following topical application, crisaborole penetrated through the stratum corneum, epidermis, and dermis of human skin. Based on observed systemic exposures observed in healthy adults, in children and adolescent participants (3 months-17 years of age) with AD, and in adult participants with psoriasis, at

similar % treated body surface area (BSA), crisaborole systemic exposures across age groups are expected to be in a similar range. Systemic absorption does not cause any clinically relevant pharmacological effects.

Of note, AD participants 2-17 years of age in Study AN2728-AD-203 treated with crisaborole ointment, 2% BID at a dose of approximately 3 mg/cm2 to a mean 17.6% BSA for up to 28 days showed that the overall plasma levels of crisaborole were low and similar to those observed in adults (BSA-adjusted). An analysis of variance showed no statistically significant differences in pharmacokinetic (PK) parameters between the age cohorts (12-17 years; 6-11 years and 2-5 years). Absorption across the skin was rapid with median time to reach maximum observed plasma concentration (T_{max}) of 3.0 hours on both Day 1 and Day 8. The extent of systemic exposure (plasma maximum observed plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) of crisaborole and its 2 main metabolites, AN7602, and AN8323, increased as the amount of crisaborole applied increased. There was minimal accumulation of crisaborole and AN7602 over 8 days of dosing, whereas AN8323 displayed moderate accumulation, consistent with its long half-life ($t_{1/2}$) (33.5 hours). Steady state was achieved within 4-6 days for crisaborole, AN7602, and AN8323. PK of crisaborole ointment was also evaluated in infants of 3 months to <24 months of age with mild to moderate disease with treatable BSA of ≥35%. The C_{max} and AUC in 3 month to <24 month infants was in the same range as that observed for participants 2 years of age and older.

Of note, no PDE4 inhibitory activity was detected in vitro for AN7602 and AN8323 and no off-target pharmacology was observed for AN8323. Both metabolites have toxicological coverages (ie, higher concentrations at the no-observed-adverse-effect level doses of crisaborole) in nonclinical studies.

Further information is provided in the current IB.

2.2.1.3. Clinical Experience

Ten clinical trials of topical crisaborole have been completed to date in participants with mild-to-moderate AD.

Clinical efficacy of a BID regimen of crisaborole ointment 2% was demonstrated in two Phase 3, randomized, double-blind, vehicle-controlled studies in participants 2 years of age and older (AN2728-AD-301 and AN2728-AD-302), and a Phase 3 open-label long-term safety study up to 48 weeks in participants 2 years of age and older (AN2728-AD-303). A Phase 4 open-label safety study of crisaborole ointment 2% in participants 3 to <24 months of age (C3291002) with the BID regimen showed a safety profile and exploratory efficacy results consistent with the Phase 3 studies (Section 4.2). In addition, a Phase 2 study (AN2728-AD-204) also demonstrated efficacy of a QD regimen of crisaborole ointment 2%, albeit with a slower onset of action and lower magnitude of clinical efficacy compared with the BID regimen.

In summary, crisaborole has been well-tolerated across completed clinical studies. No clinically important systemic safety signals have been identified in adults and children as

young as 3 months of age. Most adverse events (AEs) have been mild, and most considered unrelated or unlikely to be related to investigational product (IP). The most common drug-related AEs were application site reactions, such as application site pain (stinging or burning) and application site pruritus.

Full details of crisaborole clinical trial data are provided in the current IB.

2.3. Benefit/Risk Assessment

This study will evaluate crisaborole at a dose strength and regimen that has been demonstrated to be well tolerated and efficacious based on the completed clinical development program data.

The crisaborole dose strength and regimen (2% BID) of crisaborole for this study has been shown to have a favorable safety profile and to be well tolerated in participants 3 months of age and older who participated in previously conducted studies. Crisaborole ointment, 2% BID regimen was studied in two Phase 3, randomized, double-blind, vehicle-controlled studies in participants 2 years of age and older (AN2728-AD-301 and AN2728-AD-302), a Phase 3 open-label long-term safety study in participants 2 years of age and older (AN2728-AD-303) up to 48 weeks, and a Phase 4 open-label safety study in participants 3 to <24 months of age (C3291002).

Data from the 2 controlled studies (AN2728-AD-301 and AN2728-AD-302) showed no systemic safety concerns in participants aged 2 years and older. The safety profile from the open-label long-term clinical study (AN2728-AD-303) was consistent with that of the 2 controlled pivotal clinical studies with no new clinically important safety signals identified. The safety profile observed in the Phase 4 open-label study in participants 3 to <24 months of age (C3291002) was consistent with previous studies in participants 2 years of age and older with no new clinically important safety signals identified.

The most common drug-related AEs from the 2 controlled studies were application site reactions (5.6% and 3.6% for crisaborole and vehicle groups, respectively) and most were classified as mild. Of these drug-related application site reactions, application site pain (eg, burning or stinging) was the only treatment-related AE that showed a clinically relevant difference in rates between the treatment groups (4.4% and 1.2% for crisaborole and vehicle groups, respectively). Generally, application site pain was noted early in the treatment period and was transient in nature, resolving spontaneously.

A review of the post marketing safety data, to date, has shown that the type and occurrence of adverse event reports are consistent with the known safety profile of crisaborole. No new safety signals or unusual trends have been identified.

Adequate and well controlled clinical studies of pregnant women have not been performed for crisaborole and there is a limited amount of data from the use of crisaborole in pregnant women. As per protocol, women who are pregnant or intending to become pregnant are excluded from the study and women of child bearing potential must use a highly effective method of contraception.

Studies in renal or hepatic impaired patient populations have not been conducted. Studies to date did not include sufficient numbers of participants aged 65 years and over to determine whether they respond differently from younger participants.

Hypersensitivity, including contact urticaria, has occurred in participants treated with crisaborole. As per protocol, participants with a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the IPs are excluded.

In conclusion, the clinical experience obtained to date with crisaborole, support the continued development of crisaborole for the treatment of AD and support the initiation of this Phase 3 clinical Study C3291035. Participants will be monitored closely during the study for safety and local tolerability AEs of the IPs by the Investigators, Sponsor, and external Data Monitoring Committee (DMC) to ensure participant safety.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of crisaborole ointment, 2%, is provided in the current IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• **Efficacy:** To evaluate the long-term efficacy of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate AD who responded to crisaborole ointment, 2%, BID treatment.	• Flare-free maintenance until onset of first flare during the 52-week double-blind period
• **Safety:** To evaluate the safety and local tolerability of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate AD	• Incidence of treatment emergent adverse events
Secondary	
• To evaluate other long-term efficacy parameters for maintenance therapy and flare reduction of crisaborole ointment, 2%, QD in pediatric and adult participants ≥3 months of age	Key secondary endpoints during the 52-week double-blind period: • Number of flare-free days • Number of flares

with mild-to-moderate AD who responded to crisaborole ointment, 2%, BID treatment	• Pruritus response maintenance until onset of first flare Other secondary endpoints during the 52-week double-blind period: • ≥50% reduction in Eczema Area and Severity Index (EASI)50 response maintenance • Maintenance of Dermatology Quality of Life Assessments • Maintenance of Patient Oriented Eczema Measure (POEM) The following will be assessed during flare treatment period: • Severity of flare on Investigator's Static Global Assessment (ISGA) and EASI • Duration of flare episode
Additional Secondary	
• To evaluate the long-term efficacy of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in participants ≥3 months of age with mild-to-moderate AD	The following will be assessed as change from baseline of each respective treatment period (run-in, double-blind, and flare treatment): • EASI scores • ISGA scores • Treatable AD %BSA • Most commonly affected AD %BSA
• To evaluate the long-term health impact of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in participants ≥3 months of age with mild-to-moderate AD	The following patient reported outcomes (PROs) will be assessed: • Night Time Itch • AD Skin Pain • Patient Global Impression of Severity • Patient Global Impression of Change • Medical Outcomes Study Sleep Scale • EuroQoL EQ-5D • Work and Classroom Productivity • Hospital Anxiety and Depression

The primary and secondary estimands are hypothetical estimands defined according to the primary and secondary objectives and are in alignment with the primary endpoint and secondary endpoints.

Log-rank test and product limit approach will be used for analysis of the primary endpoint flare-free maintenance and secondary endpoint pruritus response maintenance. An analysis of covariance (ANCOVA) model will be used for the analysis of the secondary endpoint of flare-free days. Wilcoxon rank sum test will be used for the analysis of secondary endpoint number of flares.

Section 9 provides further details on statistical consideration on primary and secondary endpoints.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, vehicle-controlled study to assess the efficacy and safety of crisaborole ointment, 2%, QD as maintenance treatment and for the reduction of flare occurrence in participants (3 months of age and older) with mild-to-moderate AD.

To yield a total of 162 first flare events in the double-blind maintenance period of the study, it is estimated that approximately 700 participants will be enrolled in the open-label run-in period to receive crisaborole, BID for up to a maximum of 8 weeks to identify crisaborole responders. Approximately 250 participants will be randomized into the double-blind maintenance period. Once adequate participants have been randomized, recruitment will stop; it is possible that less than 700 or up to 860 participants will be enrolled in the open-label period.

Participants (approximately n=250) identified as responders at any study visit (i.e., 2, 4, 6 or 8 weeks) of the run-in period will be randomized (1:1 ratio) to enter the double-blind maintenance period to receive crisaborole QD or vehicle QD for 52 weeks. Non-responders at the end of the 8-week run-in period will be discontinued from the study. During the maintenance period, participants will return to the clinic or have phone contact with the investigative site once per month. However, at any time of the maintenance period, if a flare is suspected (eg, recurring or worsening AD signs or symptoms) by a participant or caregiver of a participant, the participant/caregiver should contact their study site as soon as possible to arrange an unscheduled clinic visit. If the participant meets the criteria for having a flare (Investigator's Static Global Assessment [ISGA] ≥2), the participant will switch to enter a flare treatment period during which the participant will receive open-label crisaborole ointment, 2%, BID for up to 12 weeks. During flare treatment periods, a participant will return to the investigative site after 4 weeks for assessment. If the flare has resolved (ISGA clear or almost clear), the participant will resume treatment with their original assigned blinded QD therapy and return to the maintenance period visit schedule. A flare treatment period may comprise up to 3 consecutive 4-week treatment courses with crisaborole BID. If a

flare does not resolve after 3 consecutive treatment courses with crisaborole BID, the participant will be withdrawn from the study.

During the open-label run-in period, a responder is defined as a participant who achieves both ISGA success (achieving a score of clear [0] or almost clear [1] with a ≥2 grade improvement from the run-in baseline) and at least 50% improvement from the run-in baseline in Eczema Area Severity Index (EASI) score (EASI50).

An end of study (EOS) safety follow-up by phone is required for participants who discontinue from the study at any study period (run-in, maintenance, or flare treatment), 4 weeks after the last study treatment.

Flare Treatment Period

When flares occur during the maintenance period, the participants assigned to either QD treatment arm will be switched to receive flare rescue treatment with crisaborole BID in an open-label setting until resumption of double-blind maintenance treatment. The flare treatment is for up to a maximum of 3 treatment courses each lasting 4 weeks (maximum of 12 weeks).

Flare definition: ISGA ≥2

Resolution of flare: ISGA clear (0) or almost clear (1)

During treatment of flares, participants will be assessed every 4 weeks for the following outcomes:

- If ISGA of clear (0) or almost clear (1) is achieved at the end of any of the 4-week treatment courses with crisaborole BID, the participant will resume treatment with their assigned double-blind maintenance therapy.
- If ISGA of clear (0) or almost clear (1) is NOT achieved at the end of 12 weeks of treatment with crisaborole BID, the participant will be discontinued from the study.

For flare treatments that cannot be completed by Week 52 or flares that begin at Week 52, then a maximum of one treatment course (4 weeks) is allowed. Any flare occurring after Week 52 will not be treated for flare treatment by protocol, and the participants should discontinue from the study. EOS follow-up is required in both situations.

The total duration of participation in the study, CCI [redacted] including up to 4 weeks for screening, run-in period of up to 8 weeks, 52-week double-blind maintenance period, and follow up period 4 weeks after treatment completion.

See Schema for overall study design (Section 1.2).

See Schedule of Activities (SoA) and details of study assessments in Section 8.

CCI [redacted]

[redacted]

[redacted]

4.2. Scientific Rationale for Study Design

This study will specifically evaluate if the crisaborole ointment, 2%, QD regimen is safe and efficacious for maintenance therapy and flare reduction during long-term treatment for 52 weeks. The primary and key secondary endpoints are based on the comparison of flare events between crisaborole and vehicle treatments.

The rationale for a QD regimen of crisaborole ointment, 2%, as a maintenance and flare reduction therapy is supported by the efficacy observed in a Phase 2 study (AN2728-AD-204). In Study AN27278-AD-204, crisaborole QD demonstrated that the efficacy onset of response was slower after 1, 2, and 3 weeks of treatment and did not show the same magnitude of AD signs and symptom improvement as BID at the end of 4 weeks of treatment. It was therefore considered that the BID regimen was more suitable for acute treatment of mild-to-moderate AD than the QD regimen. If a flare occurs during the double-blind maintenance period, then BID crisaborole will be provided as a rescue therapy for each flare episode. In the long-term open-label study (AN2728-AD-303) the median time to regain an ISGA score of clear or almost clear after AD relapse following no crisaborole treatment was 84 days. In this study each episode of flare will be treated with crisaborole BID for up to 12 weeks to ensure opportunity for participants to regain the treatment response status before resuming blinded QD maintenance treatment.

The long-term safety of crisaborole ointment, 2%, BID was demonstrated in an open-label extension study (AN2728-AD-303) where participants were treated with on-treatment and off-treatment cycles (corresponding to relapsing-remitting status of AD) for up to 52 weeks. In this study 7 and 8 participants received continuous crisaborole treatment for the entire 48 and 52 weeks, respectively. In this long-term study, no new clinically important safety signal was identified that had not already been identified in the short-term pivotal Phase 3 studies AN2728-AD-301 and AN2728-AD-302. It is therefore considered suitable to evaluate the long-term safety for 52 weeks in this study with crisaborole ointment, 2%, QD.

4.3. Justification for Dose

The crisaborole dose strength and regimens selected for this study have been demonstrated to be well-tolerated and efficacious in mild-to-moderate AD patients of 3 months of age and older in previous 8 clinical trials (see IB).

The crisaborole ointment, 2%, BID dose regimen was evaluated in 2 pivotal Phase 3 studies in patients 2 years of age and older with mild-to-moderate AD (AN2728-AD-301 and AN2728-AD-302) and was confirmed to be well-tolerated and efficacious. A long-term

safety study (AN2728-AD-303) of crisaborole BID demonstrated the long-term safety of intermittent use of crisaborole for up to 48 weeks. In a Phase 4 open-label safety study (C3291002) of crisaborole BID in participants 3 to <24 months of age, exploratory efficacy assessments showed results consistent with those in the Phase 3 studies and a consistent safety profile was observed. There were no new clinically important safety signals identified. The Phase 2 study (AN2728-AD-204) showed that the QD regimen demonstrated efficacy although onset of response was slower and did not achieve the same magnitude of AD signs and symptom improvement as the BID regimen.

Therefore crisaborole 2% BID has been selected in this study for treatment of active AD signs and symptoms during the run-in period as well as a rescue treatment to treat flares during the double-blind maintenance period.

This study will specifically evaluate if crisaborole ointment, 2%, QD is suitable for maintenance treatment and flare reduction of mild-to-moderate AD following an initial response to crisaborole BID treatment.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the Day 393 phone follow-up of the maintenance period.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 3 months of age or older at the time of signing the informed consent/assent (see Appendix 8 for country-specific requirements).

Type of Participant and Disease Characteristics

2. Participant who meets the following AD criteria:
    a. Confirmed clinical diagnosis of AD according to the criteria of Hanifin and Rajka (see Appendix 6).
    b. AD treatment naïve, prior non-responder to emollient use, or has been previously treated with TCSs or TCIs.
    c. AD involvement of ≥5% Treatable % BSA (excluding the scalp) (see Table 4) at entry into the run-in period.

d. ISGA score of Mild (2) or Moderate (3) at entry into the open-label run-in period.

Sex

3. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

No contraception methods are required for male participants in this study.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

    OR

  - Is a WOCBP and using an acceptable contraceptive method as described in Appendix 4 during the intervention period (at a minimum until after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test (urine or serum as required by local regulations) within 7 days before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

4. Capable of giving signed informed consent/assent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant 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 investigator's/designee's opinion may interfere with study objectives (eg, expose participant to unacceptable risk by study participation, confound evaluation of treatment response or AEs, or interfere with participant's ability to complete the study)
2. Participant has unstable AD or any consistent requirement for high-potency TCS to manage AD signs and symptoms
3. Participant has a significant active systemic or localized infection, including known actively infected AD
4. History of or active suicidal ideation or behavior, or chronic psychiatric abnormality that may increase the risk associated with study participation or study intervention or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study including the following:
    a. For participants 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) (Section 8.2.6) or a previous history of suicidal behaviors in their lifetime: "Yes" answer to any of the suicidal behavior items of the C-SSRS.
    b. For participants ≥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 (Section 8.2.6) 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.
5. Participant has a history of cancer or has undergone treatment for any type of cancer within 5 years (except squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only).
6. Participant has a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the IPs.
7. Participant has a known lack of efficacy to crisaborole.

Prior/Concomitant Therapy

8. Participant has a history of use of biologic therapy including intravenous immunoglobulin or dupilumab at any time prior to study
9. Participant has recent or anticipated concomitant use of systemic therapies or therapies that might alter the course of AD, as specified in the protocol

10. Participant has received any of the prohibited medications/therapies that may alter the course of AD without the required minimum washout period (see Section 6.5.1) or anticipated concomitant use of any of the prohibited medications/therapy (see Section 6.5.2).
11. Participant has any planned surgical or medical procedure that would overlap with study participation, from Screening through the end of study.

Prior/Concurrent Clinical Study Experience

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

Diagnostic assessments

13. Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Other Exclusions

14. Pregnant female participants, breastfeeding female participants, and female participants of childbearing potential who are unwilling or unable to use a highly effective 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 study intervention.
15. 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

1. Participant must avoid swimming or taking a shower or bath within 4 hours after applying study intervention. Applying moisturizers, sunscreen, or make-up to facial lesions should also be avoided within 60 minutes before and after the applying study intervention.
2. Participant must avoid sunbathing or tanning bed use that may interfere with their AD disease activity.
3. Women of childbearing potential must comply with contraception use required in this study.

5.3.1. Meals and Dietary Restrictions

Participants should refrain from consumption of food they have known allergy to.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants should refrain from excessive caffeine, alcohol, and tobacco consumption that may interfere with their AD disease activity.

5.3.3. Activity

Participants must avoid applying study intervention during exercise-induced sweating.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently entered into the run-in period of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. For the purposes of this protocol, the term IP may be used synonymously with study intervention. The following sections provide details on crisaborole, and permitted and prohibited concomitant medications and therapies. CCI [redacted]

6.1. Study Intervention(s) Administered

ARM Name	Crisaborole Ointment 2%, BID (Run-in and Flare Treatment)	Crisaborole Ointment 2%, QD (Maintenance Treatment)	Crisaborole Vehicle QD (Maintenance Treatment)
Intervention Name	Crisaborole 2%	Crisaborole 2%	Crisaborole Vehicle
Type	Small molecule	Small molecule	Other
Dosage Form	Ointment	Ointment	Ointment
Dose Strength	2% wt/wt, (20 mg/g)	2% wt/wt, (20 mg/g)	Not applicable
Dosage	BID	QD	QD
Route of Administration	Topical	Topical	Topical
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor	Provided centrally by Sponsor

Packaging and Labeling	Study intervention will be provided in 60-gram tubes in cartons in an open label fashion. Each tube and carton will be labeled as required per country requirement.	Study intervention will be provided in 60-gram tubes in cartons in blinded fashion with blinded labels. Each tube and carton will be labeled as required per country requirement.	Study intervention will be provided in 60-gram tubes in cartons in blinded fashion with blinded labels. Each tube and carton will be labeled as required per country requirement.
Aliases	PF-06930164 or AN2728	PF-06930164 or AN2728	Vehicle for PF-06930164

See IB for crisaborole ingredients. Vehicle contains the excipients of crisaborole ointment, and the base of crisaborole ointment has no difference in appearance, texture, color, or odor to crisaborole ointment, 2%.

6.1.1. Dosing Application

Ointment should be applied as an even layer of approximately 3 mg/cm^2.

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 first dosing application the study staff will calculate the amount of ointment required for each participant based on the treatable AD skin areas to be treated. During the maintenance period, the amount of ointment required should be calculated based on the %BSA of the **most commonly affected skin areas** that are identified and recorded on the AD lesion checklist (Section 8.1.4).

During any treatment period, all treatable lesions listed in the AD lesion checklist (Section 8.1.4) should be treated, even when the skin appears normal. During the maintenance period, it is especially important to continue to apply ointment to the **most commonly affected skin areas** even if they appear normal. Any new lesion(s) occurring during any treatment period should also be treated.

When participants are following the BID dosing regimen (ie, during the run-in and flare treatment periods), the dosing application should be at least 8 hours apart within each 24-hour day. When following the QD dosing regimen, it is recommended that dosing application is at the same time each day.

Under no circumstances will the dose regimens described in this protocol be modified.

For dosing application provided by site staff or caregivers, it is recommended that site staff and caregivers wear gloves for application or wash hands following application of dose.

If there are AD lesions in the diaper area, they should be treated with the study intervention; however, following diaper change, any study intervention inadvertently wiped off soiled skin should not be reapplied until the next scheduled dose.

Caregivers who are pregnant, or women of childbearing potential who are trying to become pregnant, should avoid accidental exposure by either avoiding applying the study intervention or wearing gloves during its application.

Caregivers who are breastfeeding the participants where study intervention is applied to the face of the participants, should avoid accidental exposure by either avoiding direct breastfeeding (eg, using a milk pump) or breastfeed at least 60 minutes after the study drug application and use a wet cloth to clean the participant's face prior to breastfeeding and the breast area following breastfeeding.

Use of routine emollients is allowed under restriction during study treatments, as described in Section 6.5.3. Details on lifestyle considerations and use of other topical products are (eg, cream or make-up) are described in Section 5.3.

6.1.2. Preparation and Dispensing

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

The IP will be dispensed in an open label fashion for run-in and flare treatment periods and in a blinded fashion during maintenance period, using an interactive response technology (IRT) system. A qualified staff member will dispense the IP via unique container numbers on the cartons provided, in quantities appropriate for the study visit schedule, based on the total %BSA, adjusted for height and weight, for participants with mild-to-moderate AD.

Further guidance and information are provided in the IP Manual.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator/designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.
4. Study interventions should be stored in their original containers and in accordance with the labels.

5. At a minimum, daily minimum and maximum temperature for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.
6. Any excursion from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the required storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not be used until Pfizer provides further guidance.
7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
8. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
9. All study interventions will be accounted for using an IP accountability form. Detailed IP accountability records, including dispensed and returned (empty or unused), will be maintained at study site and available for the study monitor's review. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.
10. Returned IP tubes by participants must not be re-dispensed to the participants.
11. Further guidance and information for the final disposition of unused study interventions are provided in the IP Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

IRT for enrollment and randomization, and allocation of study intervention	All participants will be centrally enrolled into the open-label run-in period and subsequently randomized into the double-blind maintenance period using an Interactive Response Technology (IRT). The IRT is the source of participant number, randomization number and IP allocation dispensed at the study visits per SoA. The site personnel will be responsible to register participants onto the IRT system. The IRT manual will provide the contact information and further details on the use of the IRT system.
Blind Break	The study site will be instructed on the method for blind breaking. The method will be an electronic process using the IRT system. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' treatment assignment is warranted. Participant safety must

	always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding unless necessary for any emergency treatment. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable. Participants whose code is broken will be discontinued from the study, See Section 7.2 for study discontinuation procedures.

6.4. Study Intervention Compliance

A participant will be considered compliant with the dosing regimen if they receive 80%-120% of the expected number of doses in accordance with the protocol.

Participant adherence with study intervention will be verified and monitored by review of the participant dosing diary. If a participant has missed applications between the previous and the current visit, the investigator/designee is to counsel the participant to improve adherence. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), or any non-medication therapies such as light treatment that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Start and end dates
- Dosage and regimen

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) per Section 6.5.1 and Section 6.5.2, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

6.5.1. Medications Prohibited Prior to Baseline of Run-In Treatment

Classes of medications and non-medication therapies that may alter the course of AD and for which washout is required prior to Run-in Baseline are listed below. If a participant requires

a washout, the investigator/designee will provide instructions on discontinuing the prohibited medication(s) or non-medication therapy at the Screening Visit.

Medications Prohibited 12 weeks or 5 half-lives (whichever is longer) Prior to Run-in Baseline

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

Medications/Therapies Prohibited 28 Days Prior to Run-in Baseline

- Use of systemic (oral, parenteral) corticosteroids

  Note: Participants on a stable (dose and regimen) of intranasal/inhaled/ophthalmic corticosteroids for at least 14 days prior to Baseline are permitted to continue use of intranasal/inhaled/ophthalmic corticosteroids. Participants should maintain a consistent dose and regimen of these treatments during the study

- Use of systemic immunosuppressive agents, including but not limited to, methotrexate, cyclosporin, azathioprine, hydroxychloroquine, and mycophenolate mofetil (MMF)
- Use of sunbathing, tanning bed use, or light therapy (UV, UV-B, psoralen–UV-A)
- Escalating, decreasing, or as-needed (PRN) use of topical retinoids or benzoyl peroxide (BPO) on treatable AD lesions

  Note: Participants on a stable regimen of topical retinoids and/or BPO regimen for at least 14 days of consistent use prior to Baseline are permitted to continue the topical retinoids or BPO regimen (not on the AD lesions). Participants should maintain a consistent dose and regimen of these treatments during the study

Medications Prohibited 14 Days Prior to Run-in Baseline

- Use of systemic antibiotics
- Use of TCS or TCI anywhere on the body
- Use of topical antihistamines anywhere on the body
- Use of any other oral or topical PDE-4 inhibitor
- Use of crisaborole ointment anywhere on the body

Medications Prohibited 7 Days Prior to Run-in Baseline

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body
- Escalating, decreasing, or PRN use of systemic antihistamines

  Note: Participants on stable dose of oral antihistamines for at least 7 days of consistent use prior to Baseline are permitted to continue use with minimum alteration of dose/regimen during the study, except as medically necessary

- Escalating, decreasing, or PRN use of systemic leukotriene inhibitors

Note: Participants on stable dose of oral leukotriene inhibitors for at least 7 days of consistent use prior to Baseline are permitted to continue with minimum alteration of dose/regimen during the study, except as medically necessary

Medications Prohibited 1 Day Prior to Run-in Baseline

- Use of non-medicated emollients on treatable AD lesion areas (see Section 6.5.3 for permitted use of non-medicated emollients)

6.5.2. Medications/Therapies Prohibited During All Study Periods

Classes of medications and non-medication therapies that may alter the AD disease course are prohibited during the study from run-in Baseline (Day 1) through to the end-of-treatment (last dose of study intervention).

- Use of systemic (oral, parenteral) corticosteroids, unless on stable intranasal/inhaled/ophthalmic regimen (see note in Section 6.5.1)
- Use of TCS or TCI anywhere on the body
- Use of systemic immunosuppressive agents, including but not limited to methotrexate, cyclosporin, azathioprine, hydroxychloroquine, or MMF
- Escalating, decreasing, or PRN use of topical retinoids or BPO on treatable AD lesions, unless on stable regimen (see note in Section 6.5.1)
- Use of systemic antihistamines, unless on stable regimen (see note in Section 6.5.1)
- Use of topical antihistamines anywhere on the body
- Use of any other PDE-4 inhibitor topically or systemically, with the exception of study intervention in this study
- Use of systemic antibiotics for more than 14 consecutive days

  Note: Short courses (≤28 days in total duration) 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, psoralen UV-A) anywhere on the body
- Use of bland (non-medicated) emollients, moisturizers, or sunscreen on AD lesions within 60 minutes before and after dosing with study intervention
- Participation in another drug or device research study

6.5.3. Medications and Therapies Allowed During the Study

Classes of medications/therapies that are allowed during the study are recorded as concomitant medications/therapies on CRF. Participants on certain stable regimens should minimize alteration of the stable regimen during the study. Any changes in stable dosages and/or regimens should be recorded on CRF. The permitted medications/therapies are summarized below:

- Stable regimen of bland (non-medicated) emollient(s) is permitted during the study to manage dry skin, provided that it is not used on the AD lesion areas within 60 minutes before or after dosing with study intervention
- Stable regimen of intranasal/inhaled/ophthalmic corticosteroids
- Stable regimen of oral antihistamine
- Stable regimen of leukotriene inhibitors
- Short courses (≤28 days) of systemic antibiotics if clinically necessary for the treatment of new onset infections
- Stable topical retinoid and/or BPO regimen that is not on AD lesions
- Nonsteroidal anti-inflammatory drugs (except for any other PDE-4 inhibitors)
- Routine preventative immunizations provided that the injection site is not on or near AD lesions
- Oral transdermal, intrauterine, injected, or implanted hormonal methods of contraception for WOCBP
- Concomitant medications for other chronic medical conditions are permitted during the study unless specifically prohibited by the protocol

6.5.4. Rescue Medications

Rescue medications for AD treatment are not permitted in the study, with the exception of crisaborole ointment, 2%, BID during flare treatment periods (Section 4.1).

6.6. Dose Modification

This protocol does not permit any intended dose or regimen modification outside the protocol dosing regimen for each study period.

6.7. Intervention after the End of the Study

Study intervention will not be provided at the end of this study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In certain instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to undergo an end of treatment assessment (Day 365) followed by an end of study safety follow-up.

See the SoA for data to be collected at the time of intervention discontinuation and follow up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent/assent 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 a withdrawal of consent/assent. Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.
- If a participant withdraws from the study, he/she may request destruction of any remaining samples but data already generated from the samples will continue to be available, and may be used to, to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.
- When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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 participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator/designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the consent/assent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant by test parameter is summarized in Appendix 2. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- If blood collection is difficult for individual participants, venipuncture will be limited to 3 attempts, with additional attempts within 3–5 business days unless there is a medical emergency.
- For pediatric participants, low volume pediatric tubes will be used where possible and every effort should be made to ensure that blood volume collections do not exceed 1% of the total blood volume at any single time and 3% of the total blood volume during any period of 4 weeks.
- Urine pregnancy test using dipstick must be performed for all WOCBP (Appendix 4) during the study, if positive, a serum pregnancy test is required to confirm pregnancy (Appendix 2).
- All in-clinic visits, scheduled and unscheduled, will be conducted at study sites.
- Phone visits will occur at Days 141, 197, 253, and 309 (Weeks 20, 28, 36, and 44, respectively), and as a minimum, the participants should be assessed for any AE/SAE, concomitant medications/therapies, study treatment compliance, and any suspected flare (which will require an in-clinic visit for assessment).

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or

experienced medical professional with experience in the conduct of AD clinical trials may be permitted to perform the clinical evaluations of AD when designated by the investigator and with Sponsor approval. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual participant throughout the study whenever possible**. A back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

8.1.2. Investigator's Static Global Assessment

The ISGA is a 5-point scale (0-4), reflecting a global assessment of AD severity based on erythema, induration/papulation, and oozing/crusting (Table 2). ISGA will be assessed at times specified in the SoA to characterize participants' overall disease severity across all treatable AD lesions (excluding the scalp). The assessment will be a static evaluation without regard to the score at a previous visit.

Table 2. 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

*The ISGA will exclude scalp from the assessment/scoring

8.1.3. Eczema Area and Severity Index (EASI)

The EASI[15] quantifies the severity of a participant's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of 4 body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

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

The EASI will be assessed at times specified in the SoA.

Lesion Severity by Clinical Signs: The basic characteristics of AD 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 4 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 3.

Table 3. Clinical Sign Severity Scoring Criteria for 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

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 AD (Table 4).

The handprint as a unit refers to a participant's own hand with fingers in a closed position.

Table 4. 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		3 months-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, palms, and soles from the BSA assessment.

The extent (%) to which each of the 4 body regions is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 5).

Table 5. EASI Area Score Criteria

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

Body Region Weighting: Each body region is weighted according to its approximate percentage of the whole body (Table 6).

Table 6. EASI Body Region Weighting

Body Region	Body Region Weighting for participants ≥8 years of age	Body Region Weighting for participants 3 months-7 years of age
Head and Neck	0.1	0.2
Upper Limbs	0.2	0.2
Trunk (including axillae)	0.3	0.3
Lower Limbs (including buttocks)	0.4	0.3

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

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

Equation 2 (participants aged 3 months-7 years old): EASI =0.2Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+Exu+Lu) + 0.3At(Et+It+Ext+Lt) + 0.3Al(El+Il+Exl+Ll)

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

8.1.4. Checklist of AD Lesions and Body Map

A checklist of treatable AD areas will be completed at run-in baseline (Day 1) and reviewed at each study visit for updates. The **most commonly affected skin areas** must be documented at randomization Day 1, Day 169, and Day 365 of the maintenance period.

Any new lesion should be recorded and updated in the checklist.

Study site staff (or the investigator/designee) will determine whether a new AD lesion is reported as an AE or as part of the underlying disease based on medical judgement (Section 8.3.6).

The AD lesion checklist will be recorded in the participant's source documents and data entered onto CRF.

Body map:

The investigators/designees will be provided with a body map to draw skin areas affected by AD for each participant. The original body map must be kept in the source medical file at the site; a copy of the body map will be provided to the participant and/or caregiver to take home for guidance and the participants must bring the copy back at the next study visit for investigator review and update in the source record. The participants must be instructed to record any new lesion on the body map.

The **most commonly affected skin areas** with the corresponding lesion recorded in AD lesion checklist should be shown in the body map at all time.

8.1.5. Photography of Atopic Dermatitis Lesions (At Selected Study Sites)

Photographs of AD lesions will be obtained during the run-in period and during flare treatment periods. For the run-in period, photographs should be obtained on Day 1 and at the last EORI visit. For the flare treatment period, photographs should be obtained once at the start time of the flare onset and once following resolution of the flare (eg, last flare visit).

AD areas photographed should be consistent across each assessment for the same body region and recorded in study source documents.

Photographic instruments, instruction, and training will be provided by a central photography vendor selected by the sponsor. Detailed procedures will be provided separately in a photography manual.

8.1.6. Patient Reported Outcomes (PROs)

The PROs will be evaluated using questionnaires designed to be completed by participants or by observers (parents/caregivers) about the participant's experience to assess AD symptoms and health impact due to AD.

The PROs to be completed at home are fixed regular time points of daily, weekly, or phone visits. The total time required to complete all questionnaires at each time point is approximately 3-10 minutes. The participants/observers must be instructed on how to complete the questionnaires.

The PROs to be completed at in-clinic visits (scheduled or unscheduled) will be completed at study site and may require approximately 10-15 minutes. The investigator/designee should oversee the first-time PRO completion by the participants/observers and provide further completion instruction as required during the subsequent visits. The PROs should be completed after ISGA assessment but prior to any other clinical assessment.

Note: age-specific PRO instrument must be selected according to age at the time of consent/assent. The instrument must not be changed during the study even if age changes.

See SoA for the PRO schedule.

8.1.6.1. Pruritus and Itch Assessments

Participants will be asked to assess their worst itch or scratching due to AD.

- Peak Pruritus Numerical Rating Scale (NRS)[16] is an 11-point scale and must be completed by participants ≥12 years of age, assessed over the previous 24 hours.
- Patient reported Itch Severity Scale is a 5-point scale must be completed by participants 6-11 years of age, assessed for today.
- Observer reported Itch Severity Scale is an 11-point scale and must be completed by the observers (caregivers of participants) for participants 3 months-5 years of age, assessed over the previous 24 hours.

8.1.6.2. Night Time Itch Scale

The severity and frequency of itch (pruritus) during the night due to AD will be assessed using a horizontal scale. Participants 12 years of age or older will be asked to assess their worst itching and frequency of itching due to AD during their most recent night's sleep on a scale.

8.1.6.3. AD Skin Pain NRS

Participants 12 years of age or older will be asked to assess their worst skin pain due to AD at the present time, (ie, 'AD skin pain right now').

8.1.6.4. Patient/Observer Global Impression of Severity (PGIS/OGIS)

The PGIS/OGIS is a single item patient- or observer-rated measure of the participant'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 'clinically 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 3 months-11 years of age.

8.1.6.5. Dermatology Quality of Life Assessments

The Dermatology Life Quality Index (DLQI) is a validated general dermatology questionnaire that consists of 10 items to assess participant-reported health-related QoL (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment).[17] These instruments are used to assess quality of life over the last week.

- The DLQI will be completed by participants ≥16 years of age.
- The Children's Dermatology Life Quality Index (CDLQI) will be completed by participants 4-15 years of age and assisted by observers, if required.
- The Infant's Dermatitis Quality of Life Index (IDQoL) will be completed by observers for participants 3 months–3 years of age.

8.1.6.6. Patient Oriented Eczema Measure (POEM)

The POEM[18-20] is a validated 7-item measure used to assess the impact of AD over the last week.

- The POEM will be completed by participants ≥12 years of age.
- The proxy POEM will be completed by observers for participants 3 months-11 years of age.

8.1.6.7. Patient/Observer Global Impression of Change (PGIC/OGIC)

This single item instrument is a 7-point rating scale and will be used to determine global improvement at a given point in time since the start of study drug. 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 'clinically 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 3 months-11 years of age.

8.1.6.8. Medical Outcomes Study (MOS) Sleep Scale

The Medical Outcomes Study sleep scale is patient-reported measure consisting of 12 items that assess the key constructs of sleep over the past week. The scale has been found reliable and valid with good overall measurement properties.[21, 22]

Participants 12 years of age or older will be asked to recall sleep-related activities over the past one week.

8.1.6.9. EuroQoL-5 Dimension (EQ-5D)

The EQ-5D-5L is a validated, standardized, generic instrument that is the most widely used preference based health related quality of life questionnaire in cost effectiveness and health technologies assessment.[23-26] Recently, a version was developed and validated for use in children and adolescents, EQ-5D-Youth (EQ-5D-Y).[27-29] For participants 2-7 years, a proxy version of this version will be used. All of the EQ-5D assessments are completed for recall period of today.

- The EQ-5D-5L (5 levels) will be completed by participants ≥18 years of age.
- The EQ-5D-Y (3 levels) will be completed by participants 8-17 years of age and assisted by observers, if required.
- EQ-5D-Y Proxy (3 levels) will be completed by observers for participants 2-7 years of age.

8.1.6.10. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week.[30] The HADS must be completed by participants ≥12 years of age.

8.1.6.11. Work and Classroom Productivity

The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Atopic Dermatitis, Version 2 (WPAI+CIQ:AD, V2)[31] will be used to collect participant reports on burdens with respect to possible impact of AD on work/school performance during the past 7 days. The WPAI+CIQ:AD is validated for respondents 12 years of age and older and must only be completed by participants ≥12 years of age.

CCI [redacted]

[redacted]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Medical History

- Medical history includes diagnosis and disease duration, intolerance/allergy to any drug or food, history of any significant alcohol, tobacco, controlled substance use.
- Complete AD disease history: AD diagnosis; the use of topical treatments, systemic treatments, and other treatments for AD (within 90 days prior to Screening); and reason for discontinuation.
- Medication history will be recorded on the concomitant medication CRF page and will include all prescription or non-prescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose; and for vaccines and biological drugs taken within 12 weeks prior to the planned first dose.

8.2.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance, skin, head, ears, eyes, nose, throat, mouth, skin, heart, lung, breast, lymph nodes, extremities, abdomen, external genitalia (optional), and neurological function. In addition, an assessment will be made for skin abnormalities other than AD, including scalp.
- A targeted physical examination will include, at a minimum, assessments of the skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the participant.
- Height and weight will also be measured and recorded. For both measurements, the investigator or examiner should be trained in measuring height/length and weight as well as in calibration procedures.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3. Vital Signs

- Temperature and pulse rate will be assessed. Ideally, the same method should be used consistently throughout the study.
- Temperature and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Participants should refrain from smoking or ingesting caffeine 30 minutes before the measurements.

8.2.4. Electrocardiograms

- Not required.

8.2.5. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- Details on sampling collection, labeling, storage, and shipment to the central laboratory can be found in the laboratory manual.
- The skin must be thoroughly cleansed prior to blood sample collection. At the discretion of the investigator/designee, a lidocaine based topical aesthetic (eg, lidocaine 4% cream) may be used prior to blood sample draws to decrease potential discomfort to the participant provided with the anaesthetic. The use of topical lidocaine based anesthetics must be recorded in the CRF.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5.1. Pregnancy Testing

For all WOCBP (see definition in Appendix 4), a serum or urine pregnancy test will be required for eligibility, with a test sensitivity of at least 25 mIU/mL. Serum pregnancy test will be performed in central lab. Urine pregnancy tests will be conducted at site with the test kit provided by the central laboratory in accordance with instructions provided in its package insert.

During the study, pregnancy tests will be done using urine pregnancy test kit for all WOCBP.

Urine pregnancy tests will also be done whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ independent ethics committees (IECs) or if required by local regulations.

Participants who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress with the study treatment until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test.

If the investigator judges that the participant is not pregnant, the participant may resume study treatment.

In the case of a positive confirmed pregnancy, the participant will be withdrawn from the study.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

For study exclusionary purposes (Section 5.2, Exclusion Criterion #4), participants 7 years of age or older will be assessed for suicidal ideation and behavior risks using the Columbia Suicide Severity Rating Scale (C-SSRS).[32] The C-SSRS is a validated PRO tool to evaluate suicidal ideation and behavior in this age range. 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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3. For AD-related AEs, see Section 8.3.6.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention/study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent/assent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a

minimum of 28 calendar days; except as indicated below after the last administration of the IP.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

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.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the Clinical Trial (CT) SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

SAEs occurring in a participant 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 IP must be reported to Pfizer Safety.

8.3.1.2. 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.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

- Details of all pregnancies in female participants, female partners of male participants, female family members, and healthcare providers who have been exposed to study intervention will be collected after the start of study intervention and until the end of the active collection period.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. 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.

8.3.5.3. 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 participant 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.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs

The following disease related events are common in participants with AD:

- AD
- Eczema
- Flare of AD

Because these events are expected in this remitting and relapsing disease, they will not be reported as AEs. These events should be documented and recorded on the appropriate CRF as occurrence of a flare of AD during the maintenance period represents the efficacy outcome measure.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE:

- In the investigator's opinion, the event is of greater intensity or severity than the individual participant's condition at baseline (Day 1 of the run-in period).

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.7. Wearable Device Incidents

A wearable device incident is an incident associated with a study device, including any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.

Reporting of wearable device incidents will follow AE and SAE reporting procedures.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.8. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention 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

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 participating participant.

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**.

8.4. Treatment of Overdose

While overdose following topical administration is unlikely, there is a possibility that an excess of crisaborole may be applied. If too much crisaborole has been applied, the excess can be wiped off. The investigator should monitor participant for any AEs/SAEs.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (or specified genetics) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

See Section 8.1.6.9 and Section 8.1.6.11 for assessments of EQ-5D and WPAI+CIQ:AD, V2, respectively.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

Estimand 1: The primary estimand of the main study is a hypothetical estimand, defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Participants who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria;
- Variable: Duration of flare-free maintenance up until the onset of the first flare during the maintenance period.
- Intercurrent events: If an event (eg, death, dropout, loss to follow up, or end of study) occurs before the first flare, the duration of flare-free maintenance is the time from randomization to the first intercurrent event and is censored. When a flare occurs first, or a prohibited treatment is used before a flare, the duration of flare-free maintenance is the time from randomization to the earlier one of first flare or a prohibited treatment use and is not censored.
- Population-level summary: Median duration of flare-free maintenance during the double-blind period, proportion of participants who are flare-free by time point in each treatment group.

Estimand 2: The second estimand of the study for the secondary endpoint of number of flare-free days during the double-blind period is a hypothetical estimand. It includes the following 4 attributes:

- Population: Participants who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria;
- Variable: Flare-free days during the double-blind period. It is the sum of the duration of flare-free maintenance of all QD periods during the maintenance period for each participant.
- Intercurrent events: Addressing of events for the duration of flare-free maintenance at each QD period is the same as that for the primary endpoint during the first QD period.
- Population-level summary: Difference in least-square means between crisaborole ointment, 2%, QD and vehicle QD for flare-free days over 52 weeks.

Estimand 3: The third estimand of the study for the secondary endpoint of number of flares during the double-blind period is a hypothetical estimand. It includes the following 4 attributes:

- Population: Participants who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria;
- Variable: number of flares during the maintenance period.
- Intercurrent events: It will be counted as a flare if a prohibited treatment is used during a QD period.
- Population-level summary: Median difference between crisaborole ointment, 2%, QD and vehicle QD for number of flares over 52 weeks.

Estimand 4: The fourth estimand of the study for the secondary endpoint of pruritus response maintenance up until the onset of the first flare (ISGA ≥2) is a hypothetical estimand. It includes the following 4 attributes:

- Population: Participants who are treated with crisaborole 2% BID up to 8 weeks and achieve pruritus response defined by the criteria;
- Variable: Duration of pruritus response maintenance up until the onset of the first flare (ISGA ≥2).
- Intercurrent events: If an event (eg, death, prohibited treatment, dropout, first flare [ISGA ≥2], lost to follow up, or end of study) occurs before loss of pruritus response for the first QD period, the duration of pruritus response maintenance is the time from randomization to the first intercurrent event and is censored. When loss of pruritus response occurs first, the duration of pruritus response maintenance is not censored.
- Population-level summary: Median duration of pruritus response maintenance up until the onset of the first flare during the double-blind period, proportion of participants who maintain pruritus response by time point in each treatment group.

9.2. Sample Size Determination

A total of 162 events will provide approximately 96% power to detect a 1.8 ratio of median time of being flare-free (hazard ratio of 0.556) in the first QD period between crisaborole and vehicle at a significance level of 0.05 (2-sided, log-rank test). To get 162 events (first flare), approximately 250 participants who are eligible responders will be randomized (ratio=1:1) into the double-blind maintenance period of the study. When 162 events are observed, the randomization will be stopped even if less than 250 participants are randomized. On the other hand, if 250 participants are randomized, but 162 events cannot be reached, more participants will be randomized.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Evaluable – Open Label (Evaluable-OL)	All participants receiving at least 1 dose of study intervention in the open-label run-in period
Evaluable – Double-Blind (Evaluable-DB)	All randomized participants receiving at least 1 dose of study intervention in the double-blind maintenance period. Participants will be analyzed according to the intervention they are randomized to.
Safety – Double-Blind (Safety-DB)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention in the double-blind maintenance period. Participants will be analyzed according to the intervention they actually received.
Safety – Double-Blind Maintenance Period (excluding data from flare treatment period) (Safety-QD)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention in the double-blind maintenance period (excluding data from the flare treatment period). Participants will be analyzed according to the intervention they actually received. Safety data from flare treatment periods will be summarized separately.
Safety – flare treatment period (Safety-flare)	All participants who receive at least 1 dose of study intervention in the flare treatment period during the double-blind maintenance period. Participants will be analyzed according to the intervention they received in QD period.

9.4. Statistical Analyses

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 and key secondary endpoints definitions or their analyses will also be reflected in a protocol amendment.

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

9.4.1.1. Testing Procedure for Multiple Comparisons

A step-down closed testing procedure and Bonferroni's method will be used for Type I error control for testing the primary endpoint and the secondary endpoints. The order of testing is as follows:

1. Flare-free maintenance up until the onset of the first flare during the maintenance period

2. Number of flare-free days over 52 weeks

3. Number of flares over 52 weeks

4. Pruritus response maintenance up until the onset of the first flare (ISGA ≥2), defined as the maintenance of improvement ≥50%. Analysis will be performed for 5 subgroups:
   a) ≥12 years of age: ≥3 points reduction for responders
   b) ≥12 years of age: ≥4 points reduction for responders
   c) 6-11 years of age: ≥2 points reduction for responders
   d) 3 months-5 years of age: ≥3 points reduction for responders
   e) 3 months-5 years of age: ≥4 points reduction for responders

The statistical significance can be claimed for a given endpoint only if the prior endpoint is significant. For the endpoints of 1-3, the significance level is 0.05. For pruritus response maintenance, Bonferroni's method is used to adjust the significance level. The significance level is 0.01 for each subgroup, there is no testing order. Only the subgroup with p-value ≤0.01 can claim significance after the primary endpoint and other two secondary endpoints are statistically significant.

9.4.1.2. Analysis Methods

Endpoint	Statistical Analysis Methods
Primary	Primary Analysis Time of flare-free maintenance in the first QD period up until the onset of the first flare during the 52-week maintenance period will be analyzed using a log-rank test, stratified by age group, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization to test the difference between crisaborole QD versus vehicle QD. The proportion of participants maintaining flare-free at each month until the first flare onset in the maintenance period will be estimated by the product limit method; the median time of flare-free up until the first flare onset will also be estimated by this method. This analysis will be based on Estimand 1 using the Evaluable-DB population (see Section 9.1 and Section 9.3 for estimands and populations). Sensitivity/Supplementary Analysis For the above primary analysis, the flare is based on the investigator assessment of ISGA; time of flare is ISGA assessment time. Before investigator assessment, the flare may already have occurred. As a sensitivity analysis, flare is defined as participants reported AD worsening event. Analysis method and intercurrent events handling are the same as above for the primary analysis. Another sensitivity analysis is interval censoring survival analysis. Time of flare is between the time of participants reported AD worsening and the time of investigator confirmed ISGA ≥2. This analysis will be based on Estimand 1 using the Evaluable-DB population.
Secondary	Number of flare-free days will be analyzed using an analysis of covariance model, with treatment, age, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization as factors. The number of flare-free days is total duration across the double-blind QD periods in the study for each participant. This analysis will be based on Estimand 2 using the Evaluable-DB population.

Endpoint	Statistical Analysis Methods
	Number of flares, will be analyzed using Wilcoxon rank sum test stratified by age group, duration of the BID treatment in open-label period, and ISGA score (clear [0], almost clear [1]) at randomization. Participants will be ranked according to the number of flares adjusted for length of time in the maintenance period (ie, if participants have same number of flares: the participant with longer time in maintenance period will receive a higher rank; if participants have the same time in maintenance period as well, the participant with longer time in QD period will receive a higher rank; participants who prematurely discontinue the study for efficacy reasons will be ranked below others). This analysis will be based on Estimand 3 using the Evaluable-DB population. Time of pruritus response maintenance up until the first flare onset during the 52-week maintenance period will be analyzed separately for each age and responders subgroup using the same approach as the analysis for the primary endpoint. For PROs: Dermatology Quality of Life Assessments, POEM, and EASI50 response, time of maintaining of each response will be analyzed using the same approach as the analysis for the primary endpoint. Dermatology Quality of Life Assessments and POEM response maintenance is defined as the response that does not lose more than Minimal Clinical Important Difference. EASI50 response maintenance is defined as EASI score that does not lose more than 50% of achieved reduction from the Day 1/Baseline run-in EASI score. This analysis will be based on Estimand 4 using the Evaluable-DB population. Analysis of other secondary endpoints will be summarized in the SAP.
Additional Secondary	Additional secondary endpoints will be descriptively summarized by QD period, flare treatment period, and double-blind treatment assignment.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	AEs, SAEs, local tolerability, discontinuations, and clinically significant changes in vital signs will be descriptively summarized and will be presented in tabular and/or graphical format by open-label run-in period, flare treatment period in the maintenance period, and QD period. No imputation will be made for missing safety data.

CCI [redacted]

9.5. Interim Analyses

There is no planned interim analysis.

9.5.1. Data Monitoring Committee (DMC)

This study will use a data monitoring committee (DMC). The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- In the event of any prohibition or restriction imposed (i.e., 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 IP, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate local regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements, where applicable, of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, and the IRB/IEC or study center.
- The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent/assent for the processing of his or her personal data.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented/re-assented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the Day 1 run-in treatment.

CCI [redacted] Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. CCI [redacted]

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study 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 addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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 product, regardless of the geographical location in which the study is conducted. US Basic Results are generally 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 participant 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 pre-specified 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 [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials

24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No

records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.

- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the clinical research organization if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.
- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.
- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.
- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. 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, participants are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, participant 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 participant'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. For sites other than a Pfizer Clinical Research Unit, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by a central laboratory. Urine pregnancy test will be performed at the site, with test kits provided by the central laboratory.

- Local laboratory results can be used for medical decision making if the central laboratory results are not available in time. The local laboratory reports must be kept in source documents and made available for medical review as required. It is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Table 7. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	White blood cell (WBC) count (% and absolute: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Albumin Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Sodium Glucose (non-fasting)	Blood urea nitrogen (BUN) Potassium Alkaline phosphatase Total bilirubin Total Protein Calcium Creatinine Chloride Bicarbonate or total CO_2
	Note: During the study, if any ALT, AST, total bilirubin, or creatinine value is ≥30% higher than the baseline value at screening, a repeat clinical laboratory sample must be collected and analyzed by the central laboratory and the event must be followed until resolution.	
Urine Pregnancy	• For all WOCBP: Test kit (dipsticks) provided by the central laboratory. The results of the urine dipstick test must be recorded in the source document and made available for study review.	
Other Tests	• Follicle-stimulating hormone (only for post-menopausal status confirmation at screening) • Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (for all WOCBP at screening, and for pregnancy status confirmation if urine dipstick pregnancy test is positive or if a urine dipstick test cannot be confirmed as negative [eg, an ambiguous result])	

Investigators must document their review of each laboratory safety report.

Table 8. Maximum Blood Volume by Test Parameter

Test Parameter	Volume (mL)
Serum Pregnancy Test (β-hCG), if applicable	1.1
Hematology	1.2
Serum Chemistry	1.1
Follicle-Stimulating Hormone, if applicable	2.0

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, 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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial 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 IP under study during pregnancy or breastfeeding, and occupational exposure.

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

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 IP under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (And exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Pfizer Safety. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pfizer Safety.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor" and "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.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Pfizer Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone. • Contacts for SAE reporting can be found in the investigator site file.
SAE Reporting to Pfizer Safety via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the investigator site file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.
3. Postmenopausal female
   - A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS) [b]
4. Bilateral tubal occlusion
5. Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
7. Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
8. Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
ACCEPTABLE METHODS[d]
9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
10. Male or female condom with or without spermicide[e]
11. Cervical cap, diaphragm, or sponge with spermicide
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

e) Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information:
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 IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP;
  - 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 IP prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the IP, 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 participant 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 (i.e., 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 IP.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants 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 (i.e., 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 participant’s individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 Hepatic Injury Council (HIC) should be informed if such a situation occurs during the study; the HIC will provide the necessary support to the study team. The participant 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 for suspected cases of Hy's Law, additional 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, and alkaline phosphatase. 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) and collection of serum sample for acetaminophen drug and/or protein adduct levels 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.

10.6. Appendix 6: Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis[33]

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 immunoglobulin E
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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10.8. Appendix 8: Country-Specific Requirements

Enrollment for participants 3 months of age and older will be open to all participating sites, except for those in Europe (Austria, France, and Spain), where a separate pediatric crisaborole study is planned in participants 1 month to <24 months of age (C3291031). Sites in Austria, France, and Spain will continue to enroll participants 2 years of age and older.

10.9. Appendix 9: Alternative Study Procedures during COVID-19 Pandemic

In response to the COVID-19 pandemic, associated local or regional travel restrictions, and public health concerns, the following changes were incorporated into this protocol to clarify study procedures during the COVID-19 pandemic. These changes apply to the time period of the COVID-19 pandemic only when an in-clinic visit is not possible; after this time period normal study procedures should resume.

- In the event that the in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study participants by phone contact at the scheduled or unscheduled visits per the protocol Schedule of Activities. Video contact can be used if permitted by local regulations. During the phone (or video) contact, the following assessments should be performed:

    a. Review and record study treatment including compliance and missed doses.
    b. Review and record any AEs and SAEs since last contact, including but not limited to COVID-19 related events. The AE and SAE reporting process should be followed per protocol (Section 8.3 and Appendix 3).
    c. Review and record contraceptive method and results of urine pregnancy tests for female participants who are women of childbearing potential (See protocol Appendix 4).
    d. Review and record any changes or new concomitant medications since last contact.
    e. Record the review of the Bodymap with the participants, including information on any new lesions, and collect the Bodymaps in the participant's medical record when possible (See protocol Section 8.1.4).
    f. Review eDiary for completion.

    Note: For the participant to be randomized into the double-blind maintenance period of the study, the Randomization Day 1 visit must be an in-person visit with study site staff, which could be conducted as an in-home visit or an in-person visit at an alternative clinic, provided that these are permitted according to local regulations.

- If courier delivery of the study medication from study sites is allowable by law and local guidance, the study participants must provide verbal consent for providing the contact details for shipping purposes. The verbal consent should be documented in the source document. Tracking records of shipment including the chain of custody of the study medication must be kept in the participant's medical records.

- If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframe needs to be reported on a CRF, this will be requested.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
β-hCG	beta human chorionic gonadotropin
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BPO	benzoyl peroxide
BSA	body surface area
CCL	chemokine (C-C motif) ligand
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
C-SSRS	Columbia Suicide Severity Rating Scale
C_{max}	maximum observed plasma concentration
CRF	case report form
CSR	clinical study report
CT	clinical trial
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EASI	Eczema Area and Severity Index

Abbreviation	Term
EASI50	≥50% improvement in Eczema Area and Severity Index score
eDiary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ED-5D-Y	EuroQol-5 Dimensions-Youth
EORI	end of run-in
EOS	end of study
EU	European Union
EudraCT	European Clinical Trials Database
Evaluable-DB	Evaluable – Double-Blind
Evaluable-OL	Evaluable – Open-Label
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
HIC	Hepatic Injury Council
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IDQoL	Infant's Dermatitis Quality of Life Index
IFN	interferon
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

Abbreviation	Term
IRB	institutional review board
IRT	interactive response technology
ISGA	Investigator's Static Global Assessment
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LFT	liver function test
MMF	mycophenolate mofetil
MOS	Medical Outcomes Study
NIMP	non-investigational medicinal product
NRS	numerical rating scale
OGIC	Observer Reported Global Impression of Change
OGIS	Observer Reported Global Impression of Severity
PCD	primary completion date
PDE-4	phosphodiesterase 4
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POEM	Patient Oriented Eczema Measure
PP-NRS	Peak Pruritus Numerical Rating Scale
PRN	as needed
PRO	patient reported outcome
PT	prothrombin time
QD	once daily
QoL	quality of life
SAE	serious adverse event
Safety-DB	Safety – Double-blind
Safety-flare	Safety – flare treatment period
Safety-QD	Safety – Double-Blind Maintenance Period (excluding data from flare treatment period)

Abbreviation	Term
SAP	statistical analysis plan
SoA	schedule of activities
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reactions
TBili	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
$t_{1/2}$	half-life
T_{max}	time to reach maximum observed plasma concentration
ULN	upper limit of normal
US	United States
UV	ultraviolet
WASO	wake after sleep onset
WOCBP	women of childbearing potential
WPAI+CIQ:AD, V2	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Atopic Dermatitis, Version 2

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