TITLE PAGE

Protocol Title: A Phase 2, Randomized, Double-Blind, Vehicle-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, and Local Tolerability of Crisaborole Ointment, 2%, in Adult Participants with Stasis Dermatitis without Active Skin Ulceration

Protocol Number: C3291038

Amendment Number: 2

Compound Number: PF-06930164/AN2728

Study Phase: Phase 2a

Short Title: STUDY EVALUATING THE EFFICACY AND SAFETY OF CRISABOROLE OINTMENT, 2% IN ADULT PARTICIPANTS WITH STASIS DERMATITIS WITHOUT ACTIVE SKIN ULCERATION

Acronym: N/A

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	CCI

Approval Date: 19 July 2021

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	26 Sep 2019
Amendment 1	10 Jan 2020
Amendment 2	19 July 2021

Amendment 1 (10 January 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Protocol Summary; Section 3 Objectives, Estimands and Endpoints	Updated the following secondary CCI [redacted] endpoints: • Achievement of an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline at all time points; • Achievement of an ISGA score of Clear (0) or Almost Clear (1) at all time points; CCI [redacted]	For binary and categorical endpoints, "proportion" is not an endpoint, it is summary for binary and categorical endpoints.
Protocol Summary, 1.2 Schema, 4.1 Overall Design; 9.2 Sample Size Determination	Updated sample size to 92 participants.	The in-person assessment will be used for the primary analysis. Because there is only one postbaseline assessment, completers will be used for the primary analysis (ie, observed cases data). If a 10% dropout is assumed, 92 participants are required (total, 46 per arm).

Section # and Name	Description of Change	Brief Rationale
Protocol , Section 3 Objectives, Estimands and Endpoints Summary	Updated objectives and endpoints to clarify that the primary endpoint is based on the in-person assessment.	CCI [redacted] Agreement will be evaluated between the efficacy assessments made in person by the HVP at home visits and the corresponding assessments completed by a Central Reader using standardized static digital images. These supportive analyses will contribute to validation of the imaging device technology.
1.3.1 Screening and Randomization SOA	Added Fitzpatrick Skin Type Assessment as a baseline assessment (performed only at screening). Added a skin check to the training visit. Updated some notes for clarity.	Subgroup analysis based upon Fitzpatrick skin Types will be feasible with addition of this assessment.
1.3.2 Intervention Period, Follow up and Unplanned Safety Assessment SOA	Edited to reflect that the Week 6 or ET visit will be a home visit. Added a skin check to the Week 6/ET Visit and the Unplanned Safety Assessment. Updated some notes for clarity. Added review of eDiary.	CCI [redacted] Agreement will be evaluated between the efficacy assessments made in person by the HVP at home visits and the corresponding assessments completed by a Central Reader using standardized static digital images. These supportive analyses will contribute to validation of the imaging device technology.
Section 5.1 Inclusion Criteria, Section 5.2 Exclusion Criteria	Updated Inclusion Criteria #2 to more clearly define known and newly diagnosed SD. Updated Exclusion Criteria #1 regarding laboratory testing. Added Exclusion Criteria #16 to identify laboratory values which are considered exclusionary.	Due to lack of clarity in terminology, “inadequate response” has been replaced by TSS- and ISGA-based in-person assessment. Subject safety is further supported by exclusionary laboratory values confirmed at screening.
Section 6.1.1 Administration	Updated administration information to include definition of FTU dosing.	Crisaborole prescribing information for the approved indication of atopic dermatitis regarding fingertip unit has been added to optimize dosing instructions.
Section 6.3	Updated to reflect that study intervention will be dispensed per the schedule of activities and not at the study visits.	For clarification as study intervention will be shipped directly to the participants and not dispensed at visits.
Section 6.5.1 Medication Prohibited Prior to Randomization	Removed “Use of crisaborole ointment, 2% anywhere on the body”.	Use of crisaborole is exclusionary (Exclusion Criteria #10).

Section # and Name	Description of Change	Brief Rationale
Section 8, Section 8.1 Efficacy Assessments	Updated to reflect The Week 6/ET visit is a home visit.	Week 6 visit / ET visit in-person efficacy assessments are the basis for the primary analyses.
Section 8.2.5 Clinical Laboratory Safety Assessment	Removed the following bullet: • 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 eCRF	Removed text as there is no way to record local laboratory results in the CRF.
Section 8.1.1 Rater Qualifications	Updated Section 8.1.1 Rater Qualifications to include the HVP.	HVP in-person assessments are the basis for the primary efficacy analyses.
Section 8.1.2 Assessments of Lower Extremities	Added Section 8.1.2 Assessments of Lower Extremities, to clarify between in person assessment of lower extremities and static digital imaging of lower extremities for the Central Reader. Changed Section 8.1.2 Static Digital Imaging of the Lower Extremities for Investigator Assessments to Section 8.1.2.2 Static Digital Imaging of the Lower Extremities for Central Reader Assessments. Updated text to state that the static digital images will be used for the Central Reader Assessments only. Updated Management of Incidental Findings to clarify that the Investigator is responsible for the management of incidental findings.	CCI [redacted] Agreement will be evaluated between the efficacy assessments made in person by the HVP at home visits and the corresponding assessments completed by a Central Reader using standardized static digital images. These supportive analyses will contribute to validation of the imaging device technology.
Section 8.1.3 Standardized SD Lesion Images: Acquisition, Save and Transfer	Updated section to reflect static digital images are to be used to complete efficacy assessments by the Central Reader only.	Remote digital image-based central read assessments will be performed by expert dermatologists only.
Section 8.1.4 Clinician	Updated to reflect Week 6/ET is a home visit.	Week 6 visit/ET visit in-person efficacy assessments are the basis for the primary analyses.

Section # and Name	Description of Change	Brief Rationale
Reported Outcomes	Updated to reflect static digital images are to be used to complete efficacy assessments by the Central Reader only.	Remote digital image-based central read assessments will be performed by expert dermatologists only.
Section 8.2.2 Physical Examination	Added application site examination	Stasis Dermatitis targeted skin assessment or check has been added to emphasize safety assessments at the application sites.
Section 8.25 Clinical Laboratory Assessments, Appendix 2	Clarified that laboratory tests will be performed locally for any unplanned safety assessments.	Since post baseline laboratory tests may extend beyond those required for eligibility, we can expedite through local laboratory testing.
Section 8.2.7 Fitzpatrick Skin Type Assessment	Added a description of this assessment.	Stasis Dermatitis targeted skin assessment or check has been added to emphasize safety assessments at the application sites.
Section 8.3.6 Cardiovascular and Death Events	Removed this section.	This is not required template language and is not relevant to this protocol.
Section 9.2 Sample Size Determination, Section 9.4.1 Efficacy Analyses	Clarified that the primary endpoint will be based on the HVP Week 6 home visit assessment. Clarified that the supporting analyses will be based on the Central Reader assessments of the static digital images.	CCI [redacted] he Central Reader assessments will be used for supportive analyses. Agreement will be evaluated between the efficacy assessments made in person by the HVP at home visits and the corresponding assessments completed by a Central Reader using standardized static digital images. These supportive analyses will contribute to validation of the imaging device technology.
Section 9.3 Populations for Analyses	Populations for analyses table has been updated for clarity.	Updated to align with new templates/SAP.
Appendix 6: Virtual Randomized Clinical Trial Information	Updated %BSA to lesional % BSA. Clarified information regarding static digital imaging.	For consistency throughout the protocol. To accurately reflect current procedures.
Appendix 8: Abbreviations	Added abbreviation for ANOVA, ANCOVA, fingertip unit, and quality control.	Added abbreviations relevant to this amendment.

Amendment 2 (19 July 2021)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.3	Clarification on investigator's review of efficacy assessment scoring (Protocol Administrative Change Letter [PACL], 26 January 2021)	The investigator reviews HVP scoring, but does not review scores from the central readers
Section 1.3 and 8	Clarification that the telemedicine interaction occurs first at randomization.	There is no telemedicine requirement at pre-randomization or on Day 1.
Section 1.3, 8.2.4, and 10.6	Clarification of the ECG procedure (PACL 26 January 2021)	The ECG may be completed by a single lead or multiple lead device.
Section 3, 4.1, 9.1.1.1, 9.1.1.2, 9.4.2 and 9.4.3	Estimand 1 was changed as a while-on-treatment for the primary endpoint and other non-longitudinal endpoints analysis. Estimand 3 was changed as a hypothetical estimand for longitudinal continuous endpoints analysis.	The primary estimand is not based on completion of visits in the treatment phase other than the early termination visit when participant terminates early.
Section 5.3	Clarification of allowance of COVID-19 vaccination (PACL 26 January 2021)	COVID-19 vaccination should be allowed for participants on study.
8.1.1, and 10.6	Clarification of the rater approval process (PACL 24 August 2020). Removal of sentence that references the Rater Assessment Manual. Clarification that ratings are performed by HVP.	There is no Rater Assessment Manual. Approval of raters is from the sponsor or designee rather than from the CIG.
Section 8.1.2.3	Clarification of investigator role in review of photographic images of SD lesions	Photographic Images of each participant will be reviewed during study treatment for incidental findings as a safety assessment.
Sections 1.1, 4.1, and 9.2	Significance level was changed to one-side 5%. Sample size change to approximately 70 in total and approximately 35 per treatment arm.	To reduce sample size, this is a Phase 2 proof of concept study, 5% one-sided significance level is acceptable for decision making.
Sections 9.3, 9.5	An IA may be performed during study conduct.	An IA may be conducted.
Section 9.4.2	Detail of supportive/sensitive analyses was removed	Detail will be given in the SAP

Section # and Name	Description of Change	Brief Rationale
Section 7.1	Clarification of stopping rules around QTcF and clarification that study medication discontinuation is at the investigator's discretion if skin ulcer (s) occur outside the treatment area.	QTcF stopping rules were updated to clarify when discontinuation should be considered by the investigator. There is no requirement to discontinue study medication if skin ulcer (s) occur outside the treatment area.
Section 9.5, and 10.1.5.1	Description of role of IRC for IA data review was added	Per SOP, an IRC is necessary for review of IA data and to provide recommendations per instructions in the IRC Charter.
Section 4.3	Updated the age group for which crisaborole is approved for use.	Crisaborole has been approved for use in ages 3 months and older.
Section 10.6	Removed references to participant data entry in a web-based portal.	There is no web-based portal for participant entry of demographic information, date of birth, medical history, or concurrent medications.
Section 1.1 and 3	Removed HVP from HVP in-person assessment.	Including HVP with in-person assessment is redundant since all in-person assessments are completed by the HVP
Section 8.1	Removed description of the agreement between the in-person and centrally read assessments of SD.	This assessment is not relevant to this section of the protocol.
Section 6.3	Clarification added to specify that participants and study sites will not be unblinded in case a futility threshold is met during an IA.	A futility threshold would be a result of IA efficacy results and therefore, there is no rationale for unblinding.
Section 7	Clarification added to specify that participants may be discontinued from the screening phase and participants in the treatment or follow-up phase may continue in the study in case a futility threshold is met during an IA.	Participants are not required to terminate treatment if they are on treatment at the time a futility threshold is met.
Section 6.5.1 and 6.5.2	Clarification that oral antibiotic use for SD requires washout and is prohibited during the treatment phase. Clarification that immunosuppressant/immunomodulatory biologics are prohibited prior to and during study treatment.	Concomitant treatment with oral antibiotic is prohibited for use to treat SD, but it is not prohibited for other indications. Biologics other than those that are immunosuppressant/immunomodulatory are not prohibited.

Section # and Name	Description of Change	Brief Rationale
Section 8	Removal of sentence that defines the site as the CIG (PACL 24 August 2020)	The site is not defined as the CIG.
Sections 8.3.1.2, 8.3.6, 8.3.6.1, 8.3.7, 8.3.8, 8.4, 9.1.2, 9.4.1, 10.3.2, and 10.3.3	Changes made to align with updated protocol template.	New template language required.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Double-Blind, Vehicle-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, and Local Tolerability of Crisaborole Ointment, 2%, in Adult Participants with Stasis Dermatitis without Active Skin Ulceration

Short Title: Study Evaluating the Efficacy and Safety of Crisaborole Ointment, 2% in Adult Participants with Stasis Dermatitis without Active Skin Ulceration

Rationale: Crisaborole is a phosphodiesterase-4 (PDE-4) inhibitor approved for treatment of mild to moderate atopic dermatitis (AD) and is being developed as a topical treatment for patients with stasis dermatitis (SD) without active skin ulceration.

This is a proof-of-concept study that will evaluate crisaborole therapy twice daily (BID) for the treatment of SD without active skin ulceration.

Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of crisaborole ointment, 2%, BID versus vehicle at Week 6 in participants with stasis dermatitis without active skin ulceration.	• Percent change from baseline in Total Sign Score (TSS) at Week 6/EOT (in-person assessment).
Secondary Efficacy	
• To evaluate the efficacy of crisaborole ointment, 2%, BID versus vehicle over time in participants with SD without active skin ulceration.	• Achievement of an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2grade improvement from baseline at all time points (analyze both in-person assessment and Central Readers digital images assessment); • Achievement of an ISGA score of Clear (0) or Almost Clear (1) at all time points (analyze both in-person assessment and Central Readers digital images assessment);

Objectives	Endpoints
	• Percent change from baseline in TSS at all time points except (Central Readers digital images assessment); • Percent change from baseline in lesional % Body Surface Area (%BSA) at all time points (analyze both in-person assessment and Central Readers digital images assessment).
Secondary Safety	
• To evaluate the safety and local tolerability of crisaborole ointment, 2%, BID versus vehicle in participants with SD without active skin ulceration.	• Incidence and severity of treatment emergent adverse events, including local tolerability events.
Estimands	
Only discontinuation of study intervention will be considered as an intercurrent event. The primary estimand of this study is a while-on-treatment estimand, which estimates the treatment effect of crisaborole compared with vehicle at Week 6 or EOT. It includes the following 5 attributes: • Population: Participants ≥45 years of age with SD without active skin ulceration; • Variable: non-longitudinal endpoints at Week 6/EOT; • Treatment condition: crisaborole 2% BID or vehicle; • Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6/EOT will be included; • Population-level summary: difference in LSM for continuous endpoints and difference in proportion of participants with response for binary endpoints at Week 6/EOT between crisaborole ointment, 2%, BID versus vehicle. See Section 9.1.1 for additional information on estimands.	

Overall Design:
This is a Phase 2a, randomized, double-blind, vehicle-controlled, parallel-group, proof-of-concept study enrolling approximately 70 eligible participants randomized into the double-blind treatment period in a 1:1 ratio to receive BID crisaborole ointment 2% or vehicle for 43 days.

The total duration of participation in the study is up to 14 weeks, including up to 4 weeks for screening, a 6-week double-blind treatment period, and follow-up period of 4 weeks after treatment completion.

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

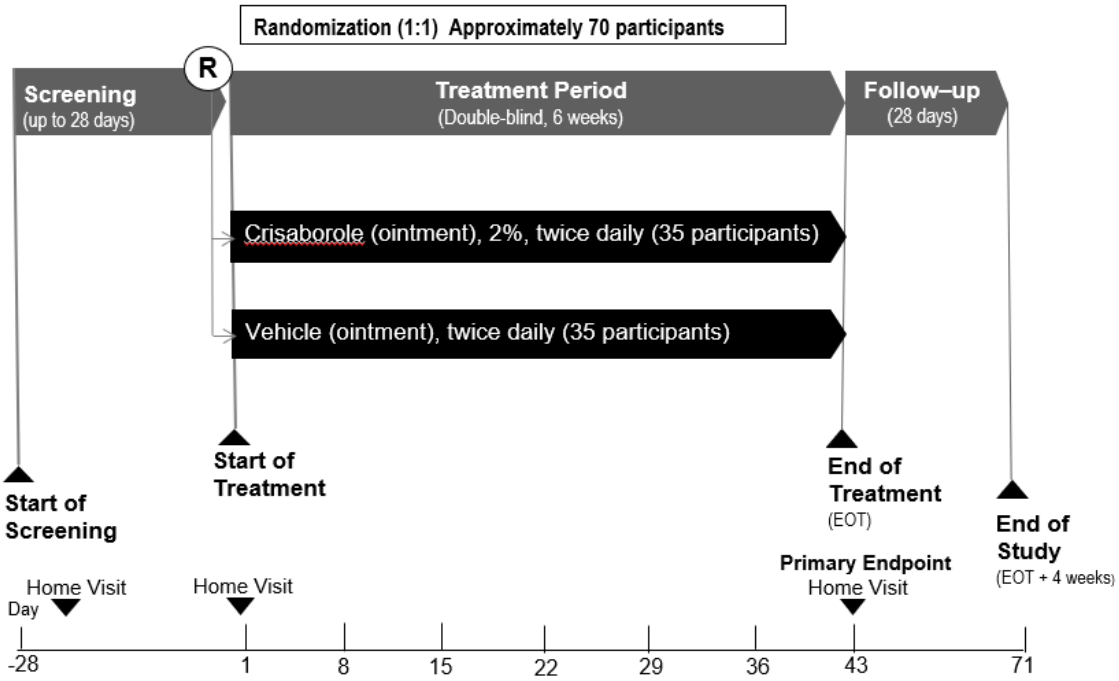
Number of Participants:
Approximately 70 participants will be randomized.

Intervention Groups and Duration:
Group 1 (N=35): Crisaborole ointment, 2% (w/w) BID for 43 days

Group 2 (N=35): Vehicle BID for 43 days

Data Monitoring Committee:
An IRC will be utilized if an IA is performed

1.2. Schema



1.3. Schedule of Activities (SoA)

1.3.1. Screening, Pre-randomization and Randomization

Procedure	Screening Period				Notes
	Screening Visit (Home Visit)	Pre-Randomization Period	Randomization (telemedicine)	Training Visit (Home Visit)	Telemedicine visits are defined as health care professional evaluations using synchronous audio and video telecommunications technology. Telephone interview only is permitted in the event of technical difficulties which preclude video component.
Day(s)	-28 to -15	-14 to -8	-7 to -2	-2 to +1	
Window (days)	±2	±2	±2	±2	
Enrollment					
Informed consent	X				Section 10.1.3
Demographics, medical history, SD history, SD prior treatments	X				At screening, the participant's primary care physician and subspecialist physician contact information may be collected. Disease history regarding specific comorbid conditions to be recorded on the eCRF. Section 8.2.1.
Inclusion and exclusion criteria	X	X	X		Investigator reviews all screening period information (eg HVP face to face assessments, HVP scoring, and eDiary) to confirm participant meets all study entry criteria. Section 8
Mini-Mental State Examination-2 (MMSE-2, Brief Version)	X				To be performed by HVP at screening visit. See Section 8.2.6.
Fitzpatrick Skin Type Assessment	X				To be performed by HVP at screening visit. See Section 8.2.7.
Randomization by IRT			X		Randomization will result in an order for direct shipment of the study intervention to the participant. See Section 6.3

Procedure	Screening Period				Notes
	Screening Visit (Home Visit)	**Pre-Randomization Period**	**Randomization (telemedicine)**	**Training Visit (Home Visit)**	Telemedicine visits are defined as health care professional evaluations using synchronous audio and video telecommunications technology. Telephone interview only is permitted in the event of technical difficulties which preclude video component.
Day(s)	-28 to -15	-14 to -8	-7 to -2	-2 to +1	
Window (days)	±2	±2	±2	±2	
Clinical Examination					
Vital Signs	X				To be performed by HVP at home visit. Section 8.2.3
ECG	X				To be performed by HVP at the screening visit. Section 8.2.4
Height and Weight	X				To be performed by HVP at the screening visit. Section 8.2.2
Complete physical examination	X				To be performed by HVP at the screening visit. The participant's family member, friend, or advocate may be present if requested by the participant. Section 8.2.2
Application site (skin) examination	X			X	To be performed by HVP at the screening visit (as part of the complete physical examination) and Training Visit. Section 8.2.2
Laboratory Procedures					
Clinical chemistry, Hemoglobin A1c, PT/INR, and hematology (central lab)	X				To be performed by HVP at the screening visit. Section 8.2.5, Section 10.2
FSH	X				To confirm postmenopausal status for female participants only. Section 10.4
Efficacy Evaluation					

Procedure	Screening Period				Notes
	Screening Visit (Home Visit)	Pre-Randomization Period	Randomization (telemedicine)	Training Visit (Home Visit)	Telemedicine visits are defined as health care professional evaluations using synchronous audio and video telecommunications technology. Telephone interview only is permitted in the event of technical difficulties which preclude video component.
Day(s)	-28 to -15	-14 to -8	-7 to -2	-2 to +1	
Window (days)	±2	±2	±2	±2	
Lower extremity digital imaging	X			X	The HVP will instruct the participant how to obtain static SD lesion images at the training visit. Section 8.1.2 and Section 8.1.3
Total Sign Score (TSS)	X			X	To be completed by the HVP prior to dose administration at the training visit. Section 8.1.4.1
Investigator's Static Global Assessment (ISGA)	X			X	To be completed by the HVP prior to dose administration at the training visit. Section 8.1.4.2
Lesional % of Body Surface Area (BSA)	X			X	To be completed by HVP prior to dose administration at the training visit. Section 8.1.4.3
Patient Reported Outcomes					
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]

Procedure	Screening Period				Notes
	Screening Visit (Home Visit)	Pre-Randomization Period	Randomization (telemedicine)	Training Visit (Home Visit)	Telemedicine visits are defined as health care professional evaluations using synchronous audio and video telecommunications technology. Telephone interview only is permitted in the event of technical difficulties which preclude video component.
Day(s)	-28 to -15	-14 to -8	-7 to -2	-2 to +1	
Window (days)	±2	±2	±2	±2	
CCI [redacted]	[redacted]				[redacted]
Safety Assessment					
Serious and non-serious AE reporting	X	X	X	X	Including AEs reported during referral clinic visits. Section 8.3
Study Intervention					
Prior and Concomitant medications / therapies recording on eCRFs	X	X	X	X	Section 6.5
eDiary • Device and compatibility assessment • eDiary completion training	X				Training and assessment provided by the HVP at the screening visit. Section 8.1.5
Home visit practitioner (HVP) demonstration • Study intervention handling and dosing instruction				X	Training visit by the HVP will occur following participant randomization and study intervention assignment. In the event that study intervention cannot be applied, HVP may use ointment without a pharmacologically active ingredient for demonstration. Section 6.1.1 and Section 6.2

Procedure	Screening Period				Notes
	Screening Visit (Home Visit)	Pre-Randomization Period	Randomization (telemedicine)	Training Visit (Home Visit)	Telemedicine visits are defined as health care professional evaluations using synchronous audio and video telecommunications technology. Telephone interview only is permitted in the event of technical difficulties which preclude video component.
Day(s)	-28 to -15	-14 to -8	-7 to -2	-2 to +1	
Window (days)	±2	±2	±2	±2	
Study intervention dispensing			X		Section 6.2

1.3.2. Intervention Period, Follow-Up and Unplanned Safety Assessment

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8.
Window (days)		±2	±2	±2	±2	±2	±2	+7		End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
Clinical Examination										
Vital Signs							X		X	To be performed by HVP at any unplanned safety assessment visits. Section 8.2.3

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied. Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8. End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		
Window (days)		±2	±2	±2	±2	±2	±2	+7		
ECG									(X)	May be performed by HVP at any unplanned safety assessment visits. Section 8.2.4
Complete physical examination							(X)		(X)	May be performed by HVP at any unplanned safety assessment visits. The participant's family member, friend, or advocate may be present if requested by the participant. Section 8.2.2
Application Site Skin Examination							X		X	To be performed by HVP at Week 6 (or early termination) visit and at unplanned safety assessments (s). Section 8.2.2.
Laboratory Procedures										
Clinical chemistry, Hemoglobin A1c, PT/INR, and hematology (central lab)							(X)		(X)	Local labs may be requested at any unplanned safety assessment visits. Section 8.2.5 Section 10.2
Efficacy Evaluation										

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied. Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8. End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		
Window (days)		±2	±2	±2	±2	±2	±2	+7		
Lower extremity digital imaging	X	X	X	X	X	X	X		(X)	Section 8.1.2 and Section 8.1.3
Total Sign Score (TSS)	X	X	X	X	X	X	X		X	Completed by HVP at all home visits. Completed by Central Reader for all weekly static digital images. Section 8.1.4.1
Investigator's Static Global Assessment (ISGA)	X	X	X	X	X	X	X		X	Completed by HVP at all home visits. Completed by Central Reader for all weekly static digital images. Section 8.1.4.2
Lesional % of Body Surface Area (BSA)	X	X	X	X	X	X	X		X	Completed by HVP at all home visits. Completed by Central Reader for all weekly static digital images. Section 8.1.4.3
Patient Reported Outcomes										

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8.
Window (days)		±2	±2	±2	±2	±2	±2	+7		End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
[redacted]	CCI									[redacted]
[redacted]										[redacted]
[redacted]										[redacted]
[redacted]										[redacted]
[redacted]										[redacted]
[redacted]										[redacted]
Safety Assessment										

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied. Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8. End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		
Window (days)		±2	±2	±2	±2	±2	±2	+7		
Serious and non-serious AE reporting	X	X	X	X	X	X	X	X	X	Including AEs reported during referral clinic visits Section 8.3
Study Intervention										
Prior and Concomitant medications / therapies recording on eCRFs	X	X	X	X	X	X	X	X	X	Section 6.5
Study intervention dispensing			X							At Day 15, participants confirmed to be continuing in the study will have a second study intervention supply processed in the IRT system and shipped for use beginning Day 22. Section 6.3
Self-administration of ointment	→	→	→	→	→	→	→			Participants will begin applying study intervention the morning after it is received.

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8.
Window (days)		±2	±2	±2	±2	±2	±2	+7		End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
eDiary completion for: • study intervention compliance • compression therapies	→	→	→	→	→	→	→			Section 6.5
Review eDiary data	X	X	X	X	X	X	X		X	RTC to document weekly review of eDiary data entries during the Intervention Period
Study intervention return				X			X			Study intervention should be returned by the participant within 7 days of the visit. Section 6.3
Study intervention accountability	X	X	X	X	X	X	X		X	At each scheduled assessment, tubes (used and unused) can be reviewed by the RTC or CIG. Section 6.2

Procedure	Intervention Period (telemedicine) Visits and Week 6/EOT or Early Termination (home) Visit							End of Study (follow-up) (telemedicine)	Unplanned Safety Assessment (home visit or telemedicine visit)	Notes
Day(s)	1	8	15	22	29	36	43	71		Day 1 is the first day of intervention applied. Randomization, Day 8, 15, 22, 29, 36, and Follow-up (Day 71) are scheduled telemedicine contacts. The contact may be conducted solely by phone in the event of technical problems. Interviews may be extended over 2 days to accommodate unforeseen circumstances. Section 8. End of treatment (home) visit to be performed by HVP at Week 6 (Day 43) or at early termination.
Week(s)	0	1	2	3	4	5	6	At least 28 days after the last dose		
Window (days)		±2	±2	±2	±2	±2	±2	+7		

AE = adverse event; BSA = body surface area; CIG = central investigator group; CCI [redacted] ECG = electrocardiogram; CCI [redacted] FSH = follicle stimulating hormone; HVP = home visit practitioner; ISGA = Investigator's Static Global Assessment; eCRF = electronic case report form; INR = international normalized ratio; IRT = interactive response technology; MMSE-2, Brief Version = Mini Mental State Examination; CCI [redacted] PT = prothrombin time; RTC = remote trial coordinator; SD = stasis dermatitis; TSS = Total Sign Score; (X) = performed at the Investigator's or HVP's discretion.

2. INTRODUCTION

Stasis dermatitis (SD) affects a significant proportion of the older population. A slight female preponderance has been reported in SD most likely due to pregnancy-related stress on the lower-extremity venous system, with many women experiencing earlier and more severe derangement of lower-extremity venous valvular function. Studies have estimated an approximately 6-7% prevalence of the condition in patients older than 50 years, which translates into approximately 15-20 million patients older than 50 years with stasis dermatitis in the United States. This finding makes SD twice as prevalent as psoriasis and only slightly less prevalent than seborrheic dermatitis. The risk of developing SD steadily increases with each passing decade; when considering only adults older than 70 years, the prevalence of SD in developed countries may exceed 20%.[1,3]

2.1. Study Rationale

2.2. Background

SD occurs in the setting of lymphedema and impaired venous drainage affecting the lower extremities.[11-14] Concurrent medical conditions which may predispose patients to develop SD include, but are not limited to, varicose veins, prior lower extremity vein graft harvest, morbid obesity, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), chronic liver disease with ascites, chronic kidney disease (CKD) with or without nephrotic syndrome, diabetes mellitus, pulmonary embolism and inferior vena cava (IVC) filter placement, IVC thrombosis, iliac vein thrombosis, and proximal deep vein thrombosis (DVT) of the lower extremities. Tissue hypoxia in edematous skin of the lower extremities due to one or more of these conditions produces erythematous/ discolored skin, skin scaling and dryness, pruritus, and painful extremities. As lymphedema and venous insufficiency (VI) and venous hypertension (VHTN) progress, increasing hydrostatic pressures in vascular watershed (hypoxic) areas in the region of the ankle are observed. Venous reflux (or reversal of venous blood flow) promotes peripheral edema and the SD immunohistochemical changes become prominent particularly in the region of the medial malleolus. Generally, edema and spongiosis originating from the feet and ankles progress proximally toward the knees. Inadequately treated inflammation associated with SD may become secondarily infected resulting in additional limitation of activities of daily living and reduced quality of life.

Histologically, SD is characterized by the onset of papillary structure alteration, spongiosis and proliferation of small blood vessels in the papillary dermis. This morphologically altered skin is littered with extravasated erythrocytes and serum macromolecules which act as chemoattractant for mononuclear leukocytes. As lymphocytes and other mononuclear cells progressively infiltrate the lower extremity interstitial spaces (“leukocyte trapping”), MMPs and TIMP-1 and -2 are also found in abundance as tissue remodeling and inflammation persist. Inflammatory cells continually influence the remodeling of the extracellular matrix directly by MMPs and both directly and indirectly by released cytokines (eg, TNFα and TGFβ1).[6-8,15-17] Mast cells (associated with tissue remodeling) and marked TGFβ1 presence (associated with up-regulation of MMPs and down-regulation of TIMPs) herald the onset of extracellular matrix deposition and intense tissue fibrosis.[18,19]

SD may be seen unilaterally (occurs due to unilateral DVT or unilateral venous valvular dysfunction) or bilaterally. Regardless of SD etiology and laterality, signs and symptoms may include edema, aching and heaviness of the legs, erythema, hyperpigmentation, papulation, pruritus, scaling, erosions and denudation, scaling and lichenified skin, pitting edema, and fluid weeping from the lower extremities.[4,18,20-26]

2.3. Benefit/Risk Assessment

Crisaborole ointment is approved for the treatment of AD in pediatric and adult patients. Its safety profile is well-characterized and positive benefit/risk assessment has been established in the treatment of AD. The potential benefits of crisaborole ointment, 2%, for treatment of SD have not been established. It is not known if SD may improve, worsen, or remain unchanged during the treatment period.

Because crisaborole impacts inflammatory pathways relevant to SD, it is anticipated that study intervention may ameliorate lower extremity SD signs and symptoms. Considering anticipated benefits and potential risks of the investigational product(s), as well as the low risk associated with protocol-specified study procedures, the potential benefits to study participation outweigh potential risks of short-term exposure to topical crisaborole ointment.

Participants will likely have one or more ongoing, chronic conditions which had predisposed to the development of SD. Management of these conditions will be provided by health care providers (HCP) already caring for the participant. Principal Investigators and Sub-Investigators will be required to record any interactions between the participant and non-study HCP throughout the study period in the electronic database and if any adverse events (AEs) include assessments of relatedness, causality, and severity (as appropriate) within the electronic database.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of crisaborole ointment, 2% may be found in the Investigator's Brochure, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of crisaborole ointment, 2%, BID versus vehicle at Week 6 in participants with stasis dermatitis without active skin ulceration.	• Percent change from baseline in Total Sign Score (TSS) at Week 6/EOT (in-person assessment).
Secondary Efficacy	
• To evaluate the efficacy of crisaborole ointment, 2%, BID versus vehicle over time in	• Achievement of an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2-grade

Objectives	Endpoints
participants with SD without active skin ulceration.	improvement from baseline at all time points (analyze both in-person assessment and Central Readers digital images assessment); • Achievement of an ISGA score of Clear (0) or Almost Clear (1) at all time points (analyze both in-person assessment and Central Readers digital images assessment); • Percent change from baseline in TSS at all time points (Central Readers digital images assessment); • Percent change from baseline in lesional % Body Surface Area (%BSA) at all time points (analyze both in-person assessment and Central Readers digital images assessment).
Secondary Safety	
• To evaluate the safety and local tolerability of crisaborole ointment, 2%, BID versus vehicle in participants with SD without active skin ulceration.	• Incidence and severity of treatment emergent adverse events, including local tolerability events.
CCI [redacted]	[redacted]

CCI	[redacted]

Estimands

Only discontinuation of study intervention will be considered as an intercurrent event.

The primary estimand of this study is a while-on-treatment estimand, which estimates the treatment effect of crisaborole compared with vehicle at Week 6/EOT. It includes the following 5 attributes:

- Population: Participants ≥45 years of age with SD without active skin ulceration;
- Variable: non-longitudinal endpoints at Week 6/EOT;
- Treatment condition: crisaborole 2% BID or vehicle;
- Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6/EOT will be included;
- Population-level summary: difference in LSM for continuous endpoints and difference in proportion of participants with response for binary endpoints at Week 6/EOT between crisaborole ointment, 2%, BID versus vehicle.

See Section 9.1.1 for additional information on estimands.

4. STUDY DESIGN

4.1. Overall Design

Study C3291038 is a Phase 2a, randomized, double-blind, vehicle-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, and local tolerability of 6 weeks of treatment with crisaborole in adult participants with SD without active skin ulceration. Approximately 70 eligible participants will be randomized into the double-blind treatment period in a 1:1 ratio to receive crisaborole ointment, 2%, or vehicle twice daily for 6 weeks.

The study will recruit male and female participants aged ≥ 45 years with a clinical diagnosis of SD. Participants who meet all inclusion but none of the exclusion criteria presented in Section 5 will be eligible to participate in the study. If a participant meets any of the exclusion criteria, the participant will be excluded.

The total duration of participation in the study will be up to 14 weeks, including up to 4 weeks for screening, a 6-week double-blind treatment period, and a follow-up period of 4 weeks after treatment completion.

Study enrollment and management will be de-centralized, where participants do not visit an investigator or a clinic for clinical assessment. The participants will participate in the study at home. The sponsor (or designee) will provide home visits by qualified home visit practitioners (HVP), remote contact by telemedicine, and clinical database electronic case report forms (eCRFs), eDiary, and other electronic data entries from 3rd party vendors for study data collection.

Participants who withdraw from further study intervention treatment (but do not withdraw consent for further data gathering) should continue to complete all scheduled assessments at the EOT visit and complete the follow-up phase of the study.

4.2. Scientific Rationale for Study Design

SD prevalence is up to 2% in the 5th decade of life, 6-7% in the 6th decade of life, and more than 20% beyond age 70 years.[1,2] Eligible participants must be 45 years or older. Potentially eligible study participants will have one or more concurrent medical conditions which predispose[20,21] to lymphedema or VI and VHTN resulting in SD lesions: morbid obesity, COPD, coronary artery disease/CHF, DVT with or without IVC filter placement, diabetes mellitus, and varicose veins of the lower extremities.

Extrapolating from AD clinical trial efficacy data for BID crisaborole applications, efficacy by Week 6 in participants with SD may be expected. It is relevant to note that active skin ulceration may be observed in close proximity to SD-affected skin. Because active skin ulcers may require more than 3 months of debridement and wound repair treatments, participants with SD and active skin ulcers will be excluded from study participation.[12,13,18]

4.3. Justification for Dose

The crisaborole dose strength and regimens selected for this study have been demonstrated to be safe, well tolerated, and efficacious in participants with mild to moderate AD in previous clinical trials (see the Investigator's Brochure [IB]). Crisaborole ointment, 2%, BID is proposed as an appropriate dose strength and regimen based on the favorable benefit: risk profile established in mild to moderate AD for patients age 3 months and older. The 2% dose strength is the maximum feasible for the ointment formulation.

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 End of Study (follow-up) visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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 the following criteria apply:

Age

1. Participant must be ≥45 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have SD:

   - A known diagnosis of SD based upon HCP medical records for at least 3 months prior to screening with inadequate response to current treatment. Inadequate response is defined by ISGA ≥2 (range 0-4) and TSS ≥3 (range 0-12) at the screening visit;

     OR

   - Newly diagnosed by the Investigator based upon the following:

     a. Participant confirmation of symptoms present on lower extremities for at least 3 months prior to screening;

     b. HVP complete physical examination findings;

     c. Telemedicine assessment by the Investigator;

     d. Inadequate response to current treatment. Inadequate response is defined by ISGA ≥2 (range 0-4) and TSS ≥3 (range 0-12) at the screening visit.

   - Active unilateral or bilateral SD lesions on the lower extremities (from knee to ankle and dorsum of foot) and the involved areas total ⩾1% BSA (1 handprint of the participant) at the screening visit.

Sex

3. Male or Female

Informed Consent

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

Other

5. Participant's mental and physical status allows them to be able to mostly perform their activities of daily living with minimal assistance including the ability to:
    a. Apply ointment to the lower part of their legs;
    b. Comply with compression therapy, if worn prior to screening;
    c. Comply with study procedures, including home visits, digital imaging and image capture;
    d. Comply with use of an internet-enabled device, (eg smartphone, tablet, laptop or desktop computer) to complete patient-reported outcome assessments (PROs), and the dosing diary.

5.2. Exclusion Criteria

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

Medical Conditions

1. Has any clinically significant active or potentially recurrent non-SD dermatological conditions and known genetic dermatological conditions that overlap SD or clinically significant physical examination finding that in the investigator/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).
   In the clinical judgment of the Investigator, prior medical testing may be needed to determine whether a chronic medical condition is medically stable.
2. Has any unstable concurrent medical condition(s) associated with lymphedema or VI and VHTN such as: morbid obesity, COPD, coronary artery disease/CHF, status/post lower extremity vein graft harvest(s), DVT of the lower extremities, status/post IVC filter placement, diabetes mellitus, or varicose veins of the lower extremities. For the purposes of this study, any of the following are exclusionary:

    - Unstable concurrent medical condition defined as a change in treatment of the concurrent medical condition(s) within 28 days prior to screening

    - Unstable concurrent medical condition defined as a hospitalization for management of any concurrent medical condition(s) within 2 months prior to screening.

- New York Heart Association (NYHA) Class III or higher (see Appendix 7) or hospitalization for CHF exacerbation within 2 months prior to screening.

- COPD Global Initiative for Obstructive Lung Disease (GOLD) Group C or higher (see Appendix 7) or hospitalization for COPD exacerbations within 2 months prior to screening.

- CKD with an estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2 (by CKD-EPI formula) at screening or history of dialysis or kidney transplant.

- Chronic liver disease with ascites (Child-Pugh Category >9 [see Appendix 7]) or aspartate aminotransferase (AST), or alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) (See Appendix 5), or history of paracentesis for management of ascites.

3. Active venous stasis ulceration on either lower extremity.
4. Has current infection or suspected infection of any SD lesions or infection of the lower extremities in the 2 months prior to screening.
5. Has a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the study interventions.
6. History of or active suicidal ideation or behavior, or chronic psychiatric 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.
7. Has a history of cancer or has undergone treatment for any type of cancer within 5 years (except squamous cell carcinoma, basal cell carcinoma, or carcinoma in situ of the skin, curatively treated with cryosurgery or surgical excision only).
8. Has received a solid organ (eg kidney, liver, heart, or lung) transplant.

Prior/Concomitant Therapy

9. Has received any of the prohibited medications/therapies that may alter the course of SD without the required minimum washout period or anticipated concomitant use of any of the prohibited medications/therapy (See Section 6.5.1).
10. Had previous treatment or is currently being treated with crisaborole, or other topical or systemic PDE-4 inhibitor.
11. Participants on biological drugs (eg dupilumab, etanercept, ustekinumab, secukinumab, adalimumab, infliximab) (See Section 6.5.1).
12. Has a concurrent medical condition which requires use of systemic immunosuppressive agent(s) (See Section 6.5.1 for prohibited medications).

Other Exclusions

13. Has any planned surgical or medical procedure that would interfere with study participation or influence study results.
14. Women of child-bearing potential (WOCBP) are not eligible for this study (See Appendix 4).
15. Mini-Mental State Examination-2 (MMSE-2, Brief Version) score of <13 (range 0 to 16).
16. Has any of the following laboratory abnormalities confirmed at screening: Hemoglobin value <9.0 g/dL; Platelet count <100,000/mm^3; INR > 3.5; Hemoglobin A1C ≥10.0%.

5.3. Lifestyle Considerations

1. Participants should continue to use medically prescribed compression therapies if in use prior to screening. Participants not using compression therapies prior to screening should not initiate use of compression therapies during study participation.
2. For participants using compression therapies:
    - The HVP will check that the participant is using the correct technique for compression therapy application, and if required the correct technique will be demonstrated with the participant and documented.
    - Compression therapies must be removed at least 1 hour prior to acquiring the static digital images of the lower extremities.
    - Compression therapies can be worn any time AFTER the morning study intervention application;
    - Compression therapies should not be worn following the afternoon/evening application of study intervention. Participants may apply a non-occlusive dressing (eg roll gauze) to prevent loss of ointment to clothes and bedclothes;
    - Participants should NOT wear compression therapies overnight.
3. Participants not using compression therapies may apply a non-occlusive dressing (eg roll gauze) to prevent loss of ointment to clothes and bedclothes.
4. Participants should continue frequently elevating the legs if done prior to screening.
5. Participants should avoid applying study intervention within 4 hours prior to static image collection.
6. Participants must avoid swimming, showering/bathing, or other prolonged contact with water within 4 hours after the study intervention application.
7. Participants must avoid sunbathing or tanning bed use that may interfere with assessment of their SD disease activity.
8. Routine preventative immunizations, including Emergency Use Authorized vaccinations for COVID-19 as per guidance from the local health authority are

permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the study.
9. Use of sunscreen is permitted, but only on areas without SD involvement.
10. When applying study intervention, the participant will not be required to wear gloves. However, they must be instructed to wash their hands with mild soap and water before and after each application.
11. Caregivers should avoid accidental exposure by either avoiding applying the study intervention or wearing gloves during its application.

5.3.1. Meals and Dietary Restrictions

Participants should refrain from consumption of foods to which they have known allergy or intolerance. Dietary restrictions for concurrent medical conditions prior to screening should continue to be followed during the study.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants should refrain from excessive caffeine, alcohol, and tobacco consumption that may exacerbate concurrent medical conditions or impair the participant's ability to comply with study procedures.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. 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. Participants should be assigned a new participant number for rescreening.

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.

6.1. Study Intervention(s) Administered

ARM Name	Crisaborole Ointment, 2% BID	Vehicle (ointment) BID
Intervention Name	Crisaborole	Vehicle of Crisaborole
Type	Small molecule	Other
Dosage Form	Ointment	Ointment
Dose Strength	2% wt/wt (20 mg/g)	Not applicable
Dosage	BID	BID

Route of Administration	Topical	Topical
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in 60 gram tubes in cartons in a blind 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 a blind label fashion. Each tube and carton will be labeled as required per country requirement.
Aliases	PF-06930164 or AN2728	Crisaborole Vehicle

For crisaborole ointment ingredients see the IB. Vehicle contains the same excipients as crisaborole, 2% ointment.

6.1.1. Administration

- Study intervention (also known as study ointment) will be applied to the lower extremities only.
- An even layer of ointment, targeting 3 mg / cm^2, should be applied to the lower extremities (knees to feet) twice a day at approximately the same times each day.
- One fingertip unit (FTU) is defined as the amount of topical product that is squeezed out from a standard tube onto a fingertip (end of the finger to the first crease in the finger). One FTU is sufficient to cover an area of skin the size of 2 handprints (2% BSA) of the participant. A handprint refers to a flat hand with fingers in a closed position. Approximately 5 FTUs would be required to treat the skin from knee to ankle and dorsum of foot of 1 leg.
- Further details are supplied in the investigational product (IP) manual.
- Study intervention should be applied to the lower extremities (knees to feet) for the entire duration (6 weeks) of the study, even when SD lesions have resolved or nearly resolved.
- If bilateral lower extremity SD lesions are present prior to Day 1, then both lower extremities should be treated for the entire 6-week treatment period;
- If unilateral lower extremity SD lesions are present prior to Day 1, then only the SD-affected lower extremity should be treated for the entire 6-week treatment period. If bilateral lower extremity SD lesions are present after Day 1, then both lower extremities should be treated to the end of the study (Week 6) from the time of the onset.

- The two dosing applications should be at least 8 hours apart within each day. Avoid applying study intervention within 4 hours prior to static image collection.

- The study intervention handling and dosing instruction and other relevant information for participants will be provided by the HVP, who will provide instructions and demonstration of study intervention application to participant. In the event that study intervention cannot be applied, HVP may use ointment without a pharmacologically active ingredient for demonstration.

6.2. Preparation/Handling/Storage/Accountability

- The study intervention will be packaged and labeled with double blind labels. Each label will be printed with a random and unique container identification (ID) number that is linked to a serialized randomization list.

- An interactive response technology (IRT) system will be used for the randomization of participants into treatment groups and for study intervention assignment.

- The study intervention assignment/dispensing events will be converted to an order for direct shipment of the study intervention to the participant.

- Study intervention shipped at randomization will be sufficient to treat SD lesions through Day 21. Participants will receive one further study intervention supply shipment sufficient to treat SD lesions from Day 22 through Day 43.

- Participants will receive instructions on how to report receipt, store, use and return the study intervention. At each scheduled assessment, tubes can be reviewed by the RTC or CIG.

- A pharmacy service provider will be appointed by the sponsor to support storage and shipment of study intervention, documentation of study intervention assignment, collection and return of study intervention, and completion of study intervention accountability.

- See the investigational product manual for more detailed information.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using IRT	All participants will be centrally assigned to randomized study intervention using an Interactive Response (IRT) Technology System. Before the study is initiated the log in information & directions for use of the IRT will be provided to the Investigator and appropriately trained designees. Study intervention will be dispensed as summarized in Schedule of Activities.

	Returned study intervention should not be re-dispensed to the participants.

Blind Break (IRT)	The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator or sponsor has the sole responsibility for determining if unblinding of a participant's 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 a participant's treatment assignment unless this could delay emergency treatment of the participant. 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, as applicable. An IA may be performed during the conduct of the study. Participants or study sites will not be unblinded as a result of a meeting a futility threshold.

6.4. Study Intervention Compliance

- Participant compliance with study intervention will be assessed by Investigator (or designee) review of eDiary responses.

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

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine or non-medication therapies that the participant is receiving at the time of enrollment or receives during the study must be recorded at all study visits/contacts.

All concomitant medications taken during the study must be recorded in study records with indication, reference to any associated adverse event, dose, and start and stop dates of administration.

The Pfizer Medical Monitor should be consulted if there are any questions regarding concomitant or prior therapy for SD prior to determining participant eligibility.

6.5.1. Medications Prohibited Prior to Randomization

Classes of medications and non-medication therapies that may alter the course of SD and for which washout is required prior to randomization 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 Randomization

- Biological drugs (e.g., dupilumab, etanercept, ustekinumab, secukinumab, adalimumab, infliximab) used primarily for immunosuppressant or immunomodulation to treat a pre-existing chronic inflammatory disease.

Medications/Therapies Prohibited 28 Days Prior to Randomization

- Use of systemic (oral, parenteral) corticosteroids.

  Note: Participants on stable use (regular regimen) of intranasal/inhaled/ophthalmic corticosteroids for at least 14 days of intranasal/inhaled/ophthalmic corticosteroids with ≥14 days of consistent use prior to randomization are permitted to continue use of intranasal/inhaled/ophthalmic corticosteroids but must not alter or stop their regimen during the study.

- Use of systemic immunosuppressive agents, including but not limited to methotrexate, cyclosporine, tacrolimus, Janus kinase (JAK) inhibitors (eg tofacitinib), azathioprine, 6 mercaptopurine, cyclophosphamide, chlorambucil, rituximab, antilymphocyte globulin, hydroxychloroquine, or mycophenolate mofetil (MMF).

Medications Prohibited 14 Days Prior to Randomization

- Use of oral or parenteral antibiotics for SD.

- Use of topical corticosteroids (TCS) or topical calcineurin inhibitor (TCI) anywhere on the body.

- Use of topical antihistamines anywhere on the body.

Medications Prohibited 7 Days Prior to Randomization

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

- Escalating, decreasing, or as-needed (PRN) use of topical or systemic antihistamines.

Note: Participants on stable dose of oral antihistamines (sedating or non-sedating) for at least 7 days of consistent use prior to randomization are permitted to continue use of oral antihistamines with minimum alteration of dose/regimen during the study.

Medications Prohibited 1 Day Prior to Randomization

- Use of non-medicated emollients (NOTE: can be used on other regions of body, except on lower extremities).

6.5.2. Medications/Therapies Prohibited During the Study

Classes of medications and non-medication therapies that may alter the SD disease course are prohibited during the study from Day 1 through to the end-of-treatment.

- Biological drugs (eg, dupilumab, etanercept, ustekinumab, secukinumab, adalimumab, infliximab) used primarily for immunosuppressant or immunomodulation to treat a pre-existing chronic inflammatory disease.
- 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, cyclosporine, tacrolimus, JAK inhibitors (eg tofacitinib), azathioprine, 6-mercaptopurine, cyclophosphamide, chlorambucil, rituximab, antilymphocyte globulin hydroxychloroquine, or MMF.
- Use of systemic (sedating or non-sedating) antihistamines, unless on stable regimen (see note in Section 6.5.1).
- Use of any other PDE-4 inhibitor (topical, oral, or parenteral).
- Use of oral or parenteral antibiotics for treatment of infection of SD lesion(s).

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

- Use of topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products on the lower extremities.
- Use of bland (non-medicated) emollients, moisturizers or sunscreen on SD lesions.
- Participation in another drug or device research study.

6.5.3. Medications/Therapies Allowed During the Study

Classes of medications/therapies that are allowed during the study are recorded as concomitant medications/therapies on eCRF. 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 eCRF. The permitted medications/therapies are summarized below:

- Stable regimen of non-medicated emollient(s) is permitted during the study to manage dry skin outside of the SD-treated areas.Stable regimen of intranasal/inhaled/ophthalmic corticosteroids;
- Stable regimen of oral (sedating or non-sedating) antihistamine;
- Short courses (≤14 days) of oral or parenteral antibiotics if clinically indicated in the judgment of the investigator for the treatment of new onset infections (dermal or non-dermal) not involving SD treatment sites.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), eg, Ibuprofen;
- Concomitant medications for other chronic medical conditions are permitted during the study unless specifically prohibited by the protocol.
- For management of peripheral edema and antecedent co-morbidities, permitted concomitant medications and treatments include the following if regimen has been stable for at least 2 weeks prior to screening:
- Use of compression therapies;
- Oral diuretic(s) for management of peripheral edema and/or ascites;
- Inotropic or chronotropic medications for congestive heart failure;
- Oral or subcutaneous anticoagulants (eg warfarin, rivaroxaban, dabigatran, apixaban, enoxaparin) for prior DVT,
- Use of a continuous positive airway pressure (CPAP) device;
- Use of appetite suppressants;
- Dietary regimen for weight loss;
- Oral corticosteroids (no more than prednisone (or equivalent) 15 mg daily) for treatment of chronic non-dermatologic medical condition (eg, COPD, rheumatoid arthritis, nephrotic syndrome, vasculitides, cardiomyopathy).

6.5.4. Rescue Medicine

No rescue medications (eg, corticosteroids, calcineurin inhibitors, or other PDE4 inhibitors) are permitted for SD during treatment with study intervention.

In the event of worsening SD, the Investigator may determine that an unplanned safety visit (telemedicine assessment or face-to-face assessment (by HVP or a local HCP) is indicated.

6.6. Dose Modification

Dose Modification is not permitted in this study. Study intervention must be applied BID at the targeted application rate (approximately 3 mg/cm^2).

6.7. Intervention after the End of the Study

There is no intervention required by the protocol following the end of study. Participants should resume their usual medical care.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At the discretion of the Investigator, study intervention may be temporarily or permanently discontinued. In the event of a participant being hospitalized for management of a chronic medical condition, study intervention must be permanently withdrawn.

If an IA (described in Section 9.4) is performed and the IRC recommends ending the study because of futility, participants in the screening phase may be discontinued from the study based on sponsor decision. If a futility threshold is crossed based on the IA results, participants may be withdrawn from study treatment, complete an early termination visit, and complete the study follow-up phase.

Participants may be discontinued due to study termination (as described in Section 10.1.9).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should continue to complete all scheduled assessments at the EOT visit and complete the follow-up phase of the study.

Note that discontinuation of study intervention does not represent withdrawal from the study.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Appendix 5 or if the investigator believes that it is in best interest of the participant.

If signs and symptoms of hypersensitivity are attributable to the study intervention, including contact urticaria, it must be discontinued immediately, and appropriate therapy initiated.

If skin ulcer(s) develop in any of the SD treatment areas, then study intervention must be permanently discontinued. If skin ulcer (s) develop in any of the untreated areas (including an untreated leg in the case of unilateral disease), study medication may continue at the discretion of the investigator.

If an unscheduled ECG is necessary after randomization to evaluate an AE, discontinuation of study ointment should be considered if the QTcF interval on the unscheduled ECG is $\geq$ 481 msec or if there is an increase in the QTcF interval of $\geq$ 60 msec in comparison to the QTcF interval on the ECG completed during screening. This review of the electrocardiogram (ECG) at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the Schedule of Activities (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.

7.1.1. Temporary Discontinuation

Participants who experience medical conditions that require treatment (not prohibited concomitant medications) may have their study intervention temporarily discontinued for <6 days after consultation with the Pfizer medical monitor. Temporary discontinuation of study intervention should be recorded in the eCRF.

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 Schedule of Activities. See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study records and notify the sponsor accordingly.

- When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the CT SAE Report.

7.3. Lost to Follow up

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

The following actions must be taken if a participant fails to complete a required telemedicine 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 the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or 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

In addition to the 3 scheduled HVP home visits, assessments will be conducted by the Central Investigator Group (CIG) and Remote Trial Coordinator (RTC) through telemedicine (videoconferencing for the purposes of this study) interviews with the participant. The first telemedicine interview will occur at randomization (Section 1.3.1). A telephone only interview is permitted in the event of technical difficulties which preclude video component.

During the intervention period, telemedicine interviews with the participant will be conducted by the RTC; the CIG may attend if requested by the RTC or if the Investigator chooses to attend.

End of treatment (EOT) home visit (Week 6 or Early Termination) will be conducted by the HVP. In addition, telemedicine interviews may be conducted by the CIG with the participant (see Schedule of Activities) if adverse event(s) assessment is indicated in the judgment of the investigator.

Further specifications for study assessments and procedures include:

- The CIG and RTCs will perform all the rater assessments except for the scoring of TSS, ISGA, and lesional %BSA which will be performed by the HVP (in-person assessment at screening visit, training visit, Week 6 or early termination visit, and unplanned safety assessment) and by a Central Reader (at scheduled weekly digital image acquisition timepoints and at unplanned telemedicine visits [if any]). See Appendix 6 for information on VRCT.

- Study procedures and their timing are summarized in the Schedule of Activities. 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.

- Unplanned safety assessments may be conducted during the study using telemedicine interviewing to assess any ongoing or new onset safety events. The CIG will be present for any unplanned safety telemedicine interview. If an AE is suspected or determined to have occurred, then the CIG can recommend in person clinical evaluation by an HVP or referral to the participant's local HCP or subspecialist if warranted in the clinical judgement of the CIG. If a determination is made that the participant's medical condition warrants urgent evaluation, then the/ participant may be directed to urgent care or emergency department evaluation.

- Adherence to the study design requirements, including those specified in the Schedule of Activities, 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 ICF 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 Schedule of Activities.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 25 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

In-Person Assessments by HVP

Primary efficacy assessments of the TSS, ISGA, and lesional %BSA will be completed in person by the HVP at all home visits (Screening visit, Training visit, Week 6 or Early Termination visit, and Unplanned Safety assessments [if any]).

Remote Assessments by Central Reader

Efficacy assessments of the TSS, ISGA, and lesional %BSA will be completed by Central Readers remote review of static digital images acquired by participants trained to use the device and imaging accessories provided by the sponsor. Training will be provided to participants by the HVP to support standardized static digital image acquisition at protocol-specified timepoints outlined in the Schedule of Activities.

A Central Reader is an appropriately qualified and trained expert dermatologist. (Section 8.1.3)

8.1.1. Rater Qualifications

For specific rating assessments (TSS, ISGA, %BSA, and MMSE), only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be provided to the site. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training will be conducted, and written documentation will be provided by the sponsor or designee for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.1.2. Assessments of Stasis Dermatitis Lesions on the Lower Extremities

8.1.2.1. In-person Assessments by HVP

At each home visit, in-person physical examination and assessments will be performed only by a medically-qualified HVP with clinical experience conducting physical examination, including assessment of the skin. Prior to conducting home visits and completing in-person assessments of TSS, ISGA, and lesional %BSA, HVP rater training and standardization exercises and written and signed documentation will be provided by the CIG confirming each HVP's certification.

8.1.2.2. Static Digital Imaging Assessments by Central Reader

High-resolution, static, digital images of the participant's lower extremities (anterior, posterior, medial, and lateral aspects) will be obtained by the participant at times defined in the Schedule of Activities using only sponsor-provisioned digital imaging equipment and the study-specific Photo Studio. The provisioned digital imaging device and the Photo Studio and instructions for use are provided to each participant. CCI [redacted] At the training visit, the HVP will train the participant in the intended use of the digital imaging equipment and set-up of the Photo Studio. Participants will be instructed how to save and transfer the requisite static digital images for quality control (QC). Digital images will be subsequently provided to a blinded Central Reader for remote assessments of the TSS, ISGA, and lesional %BSA (see Section 8.1.3)

In-person and remote assessments of SD severity may be impacted by variation in time of study intervention application, frequency and duration of compression therapy use, the time and day of assessment, the presence of study ointment, and presence of debris on the skin of the lower extremities. Each participant will be instructed to:

- Cleanse the skin of the lower extremities using warm water and soap to remove any remaining study ointment and debris prior to digital images acquisition;
- Gently dry the skin of the lower extremities after cleansing and prior to digital images acquisition;
- Consistently apply study intervention at a similar time each morning and each evening;
- Avoid applying study intervention within 4 hours prior to static image collection.
- Acquire weekly static digital images on the same day of the week (±2 days) at approximately the same time of day each week.

8.1.2.3. Management of Incidental Findings by the Investigator

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

The investigator (dermatologist) must perform medical review of all available lower extremity static, digital images for incidental findings (eg skin ulcer formation, skin cancer, cellulitis) via the central imaging repository. . If an unexpected observation is identified, and this finding could, in the opinion of the investigator, have a significant health consequence, this finding may be shared by the investigator with the study participant. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-patient relationship. The investigator will be responsible for identifying and reporting any AEs from incidental findings as described in the Adverse Event Reporting section.

8.1.3. Standardized Static SD Lesion Images: Acquisition, Save and Transfer

At protocol-specified time points, the participant will acquire static digital images of the lower extremities using sponsor-provisioned digital imaging equipment. Images will automatically be saved and transferred to the central digital imaging repository. Following QC checks, images will be available for review by a Central Reader via a customized read portal. A Central Reader will assess TSS, ISGA, and lesional %BSA according to the Central Reader's Charter.

Participant Training by the Home Visit Practitioner

To promote consistent image acquisition, the participant must:

- Complete training for how to set up the digital imaging equipment and Photo Studio in the home;
- Successfully acquire, save, and transfer digital images for initial QC checks.

If it is determined that digital images are not of sufficient quality to remotely assess TSS, ISGA, and lesional %BSA, then the HVP can return to the participant's home to re-instruct the participant how to acquire requisite digital images.

8.1.4. Clinician Reported Outcomes

At all home visits, TSS, ISGA, and lesional %BSA assessments will be assessed in-person by the HVP. In addition, the TSS, ISGA, and lesional %BSA will be remotely assessed by an expert dermatologist Central Reader reviewing digital imaging of the lower extremities acquired by the participant. At unplanned safety assessments these TSS, ISGA, and lesional %BSA are performed only if relevant to the safety event.

8.1.4.1. Total Sign Score

The TSS is an assessment of the severity of SD skin lesions. Each of the 4 clinical signs (erythema, papulation/elevation [excluding papulation due to lipodermatosclerosis or varicose veins], superficial erosion/denudation, and scaling) across all the treatable SD lesions will be rated using the 4-point severity scale (ranging from 0 to 3 points). The four sub scores are summed to create the TSS, 13-point scale; ranging from 0 to 12 points, with a higher score representing a higher disease severity.

8.1.4.2. Investigator's Static Global Assessment (ISGA)

The ISGA is a 5-point scale (range 0-4), with a higher score representing a higher disease severity. ISGA is a global assessment of severity of all treatable SD lesions based on erythema, papulation/elevation, superficial erosion/denudation, and scaling. The assessment will be a static evaluation without regard to the score at a previous visit.

8.1.4.3. Stasis Dermatitis Lesional % BSA

Assessment of lesional %BSA skin areas of all treatable SD lesions will be performed by the handprint method, where the full palmar hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of BSA. For example, if all lesions added up are equivalent to 4 handprints, then the SD lesional %BSA is 4%.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities.

8.2.1. Medical History

Medical history includes diagnosis and disease duration, intolerance/allergy to any drug or food, and history of any significant alcohol, tobacco, controlled substance use.

Complete SD disease history includes SD diagnosis, the use of topical treatments, systemic treatments and other treatments for SD (eg compression stocking use) used within the last 3 months, including reason for SD treatment discontinuation.

Medication history includes all prescription or non-prescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.

8.2.2. Physical Examinations

- A **complete physical examination** by the HVP will include, at a minimum, assessments of general appearance, skin (includes SD areas and non-SD areas), head, ears, eyes, nose, throat, mouth, heart, lung, lymph nodes, extremities, abdomen, and neurological function. In addition, an assessment will be made of the condition of all SD-involved skin. Examination will not include anogenital region or female breasts.
    - Height and weight will be measured and recorded by the HVP during the home visit.
    - Complete physical examinations should be performed at any unplanned safety assessment.
- **Application site (skin) examination**, from knee to ankle and dorsum of foot, should be performed at all home visits.

8.2.3. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed. In the event of an adverse event, temperature, blood pressure and pulse rate will be assessed at any additional safety visits.

- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure 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

- An ECG will be obtained as outlined in the Schedule of Activities to electronically calculate the heart rate and measures PR, QRS, QT, QT_{cF} intervals. Refer to Section 7.1 for QT_{cF} withdrawal criteria and any additional QTc readings that may be necessary.

- If the QTcF interval on the screening ECG is $\geq$ 481 msec, the clinical significance of the ECG results should be considered relative to other physical exam findings and medical conditions that may exclude the participant from the study.

- ECG may be repeated at unplanned safety assessment at the discretion of the investigator.

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.

- During the pre-randomization period, the investigator must review the results of planned laboratory testing to confirm study eligibility and document this review (see Appendix 2). If any unplanned laboratory testing is performed after randomization, it should be completed at a local laboratory, then 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 28 days 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 Schedule of Activities.

8.2.6. Mini-Mental State Examination 2nd Edition (MMSE-2, Brief Version)

Prior to randomization, the Mini Mental-State Examination-2 (MMSE-2, Brief Version) will be administered to each participant. The original MMSE is one of the most widely used brief screening instruments for cognitive impairment. It has been used in a variety of settings, including screening individual patients, tracking progress over time, screening for large populations, and clinical trials.[32] The MMSE-2 Brief Version has been determined to be adequate for screening large populations and screening individuals in practice who have not been referred because of cognitive complaints.[32] Participants with a score of <13 (range 0 to 16) will be excluded from the study.

8.2.7. Fitzpatrick Skin Type Assessment

At the screening home visit, the Fitzpatrick skin-type is documented for each participant. Skin Type I-VI will be determined by the HVP at the screening visit.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

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 trials (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.

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 study intervention must be reported to Pfizer Safety.

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

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

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 study intervention 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 and female partners of male participants will be collected after the start of study intervention and until the Follow-up visit.

- 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 in female participants and female partners of male participants 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 an eCRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Adverse Events of Special Interest

Not Applicable

8.3.6.1. Lack of Efficacy

The term "lack of efficacy" is incongruous in the clinical trial setting with pre-approval products or marketed products used in a non-approved indication, because the effectiveness of the product has not been demonstrated. Lack of efficacy for a pre-approval product or for a marketed product used in a non-approved indication is reportable only if associated with an SAE.

8.3.7. Medical Device Deficiencies

Not Applicable

8.3.8. Medication Errors

Medication errors may result from the administration of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength, or to areas that have not been identified as treatable.

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 eCRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

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

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

Overdose following topical administration is unlikely. If too much study intervention has been applied, the excess can be wiped off.

In the event of an overdose, the investigator/designee should:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of crisaborole (whichever is longer).
3. Obtain a plasma sample for pharmacokinetic (PK) analysis within 5 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

Banked Biospecimens for Genetics will not be collected in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

Only discontinuation of study intervention will be considered as an intercurrent event.

9.1.1.1. Primary Estimand/Co-Primary Estimands

Estimand 1: The primary estimand of this study is a while-on-treatment estimand, which estimates the treatment effect of crisaborole compare with vehicle at Week 6 /EOT. It includes the following 5 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;
- Variable: non-longitudinal endpoints at Week 6/EOT;
- Treatment condition: crisaborole 2% BID or vehicle;

- Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6/EOT will be included;

- Population-level summary: difference in LSM for continuous endpoints and difference in proportion of participants with response for binary endpoints at Week 6/EOT between crisaborole ointment, 2%, BID and vehicle.

Estimand 1 will be used in analyzing the primary endpoint and it will also be used to analyze non-longitudinal continuous secondary endpoints %BSA in-person assessment CCI [redacted] and non-longitudinal binary endpoints ISGA success and ISGA clear/almost clear in-person assessment.

9.1.1.2. Secondary Estimands

Estimand 2: The second estimand of this study is a composite estimand, which estimates the treatment effect of crisaborole compared with vehicle at each time point. It includes the following 5 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;

- Variable: binary response endpoint per photography assessment, eg, response defined as a participant with an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline at each time point; a participant after an intercurrent event of discontinuation of study intervention will be considered a non-responder for the visit of interest;

- Treatment condition: crisaborole 2% BID or vehicle;

- Intercurrent event: there will be no intercurrent event since the discontinuation of study intervention is part of the variable definition;

- Population-level summary: difference in proportion of participants with response at each time point between crisaborole ointment, 2%, BID and vehicle.

Estimand 2 will be used in analyzing all applicable longitudinal secondary binary endpoints.Estimand 3: The third estimand of this study is a hypothetical estimand, which estimates the treatment effect of crisaborole compared with vehicle at each time point under the scenario of no discontinuation of study intervention. It includes the following 5 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;

- Variable: percent change from baseline in TSS at each time point;

- Treatment condition: crisaborole 2% BID or vehicle;

- Intercurrent event: all data after any intercurrent events will be excluded;

- Population-level summary: difference in mean percent change from baseline in TSS at each time point between crisaborole ointment, 2%, BID and vehicle.

Estimand 3 will be used in analyzing the longitudinal continuous endpoints.

9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment.

9.2. Sample Size Determination

The primary efficacy analysis is to compare the mean difference in percent change from baseline in TSS at Week 6 of crisaborole ointment, 2%, BID versus vehicle based on HVP home visit in person assessment. A sample size of 35 participants per treatment group will yield at least 80% power to detect a difference between crisaborole ointment, 2%, BID and vehicle at a one-sided significance level of 5%, assuming a mean difference of at least 22% and a common standard deviation of no more than 35% based upon clinical trial data of crisaborole in AD participants.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Participant Analysis Set	Description
Screened	All participants who sign the ICF.
Enrolled	All participants who sign the ICF and are not screen failure.
Randomly Assigned to Study Intervention	All participants who are randomized.
Full Analysis Set (FAS)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention. Participants will be analyzed according to the intervention they are randomized.
Safety Analysis Set (SAF)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Full Analysis Set-Interim Analysis (FAS-IA)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention and complete 6 weeks treatment or early discontinue study intervention at the IA cutoff date. Participants will be analyzed according to the intervention they are randomized.
Safety Analysis Set-Interim Analysis (SAF-IA)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention and complete 6 weeks treatment or early discontinue study intervention at the IA cutoff date. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed 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. General Considerations

In general, number, percent and 90% CI will be presented for binary endpoints. Descriptive summary statistics (n, Mean, Standard deviation, Median, Min., Max.) will be presented for continuous endpoints. In addition, graphics may be used to present the data.

Day 1 will be the date when a participant applies the first dose of study intervention. Baseline value will be the last non-missing assessment on or before Day 1 and prior to first dose of study intervention. CCI [redacted]

9.4.1.1. Analyses for Binary Endpoints

For binary endpoint at each time point, large sample approximation to the difference in binominal proportions will be used for testing (Normal Z-test) the superiority of crisaborole ointment, 2%, BID to vehicle and for forming 90% CI's and calculating p-values (one-sided).

9.4.1.2. Analyses for Continuous Endpoints

The non-longitudinal continuous data will be analyzed by ANOVA with treatment as the factor. ANCOVA will be used if relevant baseline value and/or other factors are included as covariates. Comparison of crisaborole ointment, 2%, BID to vehicle (providing LSM of the treatments, LSM of the treatment difference, one-sided p-value and 90% CI) will be generated.

The longitudinal continuous data will be analyzed using MMRM with fixed effects of treatment group, visit, and treatment-group by visit interaction, without imputation for missing values. If the endpoint is change from baseline, baseline will be included in the model as a covariate. A common unstructured variance-covariance matrix will be used, provided it converges. If this is a convergence issue, other type of covariance matrix such as first order autoregressive, compound symmetry will be used. Comparison of crisaborole ointment, 2%, BID to vehicle (providing LSM of the treatments, LSM of the treatment difference, one-sided p-value and 90% CI) at each time point during the first 6 weeks will be generated using this model.

9.4.1.3. Analyses for Categorical Endpoints

The frequency and percentage for each category will be presented for category endpoints.

9.4.2. Primary Endpoint/Estimand Analyses

Percent change from baseline in TSS at Week 6/EOT based on HVP in person assessments (primary analysis)will be analyzed using an ANOVA model that includes treatment group as a factor (see Section 9.4.1.2). . The primary analysis of the primary endpoint will be based on Estimand 1 using FAS.

Some supportive/sensitivity analyses and subgroup analyses may be performed for the primary endpoint. Detail will be given in the SAP.

9.4.3. Secondary Endpoints/Estimands Analysis

Percentage change from baseline in %BSA at Week 6/EOT based on in-person assessment will be analyzed using an ANOVA model that includes treatment group as a factor (see Section 9.4.1.2) based on Estimand 1 using FAS.

Achievement of an ISGA success and ISGA clear/almost clear at Week 6/EOT based on in-person assessment will be analyzed using the method described in Section 9.4.1.1 using Estimand 1 and FAS.

Percent change from baseline in TSS and %BSA based on Central Readers assessments will be analyzed using MMRM as described in Section 9.4.1.2. Missing data are assumed MAR. Under MAR assumption, MMRM will yield unbiased estimates and valid inferences for treatment effects assuming all participants maintain therapy.This analysis will be based on Estimand 3 using FAS.

Achievement of an ISGA success and ISGA clear/almost clear by time point based on Central Readers assessments will be analyzed using the method described in Section 9.4.1.1 Observations after the discontinuation of study intervention or missing values for any reason will be handled by setting the endpoint to nonresponsive. Note that this is a composite endpoint in the sense that a response requires the participant completes a visit of interest eg, Week 6, and achieves a response per the defined response criteria (otherwise it is considered a nonresponse). This method of handling missing response is known as missing response as non-response (MR-NR). The analysis will be based on Estimand 2 using FAS.

CCI [redacted]

9.4.5. Safety Analyses

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations. All safety analyses will be performed on the safety population as previously defined.

Endpoint	Statistical Analysis Methods
Secondary	Safety Population, Descriptive statistics.

9.5. Interim Analyses

An IA may be performed to assess efficacy and safety after approximately 50 participants complete 6 weeks treatment or early discontinue study intervention. If an IA is performed, IA results will be used for decisions regarding stopping for futility and planning for future studies. There is no efficacy claim and no sample size adjustment based on the IA results.

Participants may be discontinued from the study as a result of the IA, as described in Section 7.

This is an administrative interim analysis; no adjustment of p-values is planned for the analysis of the final study data.

Before the IA is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an IRC charter. In addition, the analysis details will be documented and approved in a SAP. The results of the IA will not be shared with the study team, sites, or participants during the conduct of the study, except in a situation where the IRC recommends early termination of the study.

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 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 (e.g., 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 (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, 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 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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The investigator must ensure that each study participant 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 is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented 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.

Participants who are rescreened are required to sign a new ICF.

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 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. Committees Structure

10.1.5.1. Data Monitoring Committee (DMC)

If an IA is performed, the IRC will be responsible for review of the IA and recommendation on any changes to study conduct based on the results of the IA according to the IRC

Charter. Safety data and efficacy results will be reviewed by the IRC during study conduct if an IA is performed. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries safety data, to regulatory authorities, investigators, as appropriate.

This study will not use an external DMC.

10.1.6. 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 United States (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 prespecified protocol or was terminated.

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (Clinical Study Report [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 eCRFs, 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.

10.1.7. 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 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 clinical 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.

10.1.8. 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 eCRF 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 clinical monitoring plan.

10.1.9. 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 contract research organization (CRO) 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.

10.1.10. 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.

10.1.11. 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 study portal.

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 study intervention 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 (CRU), 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 1 will be performed by the central laboratory.
- 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 at a local lab as determined necessary by the investigator or required by local regulations.

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Albumin	Bicarbonate or total carbon dioxide (CO_2)	Creatinine	Total Protein
	Alanine Aminotransferase (ALT)	Blood urea nitrogen (BUN)	Glucose (nonfasting)	Sodium
	Alkaline phosphatase	Calcium	Potassium	Hemoglobin A1c
	Aspartate Aminotransferase (AST)	Chloride	Total bilirubin	
Other	Prothrombin time (PT)/ international normalized ratio (INR), follicle stimulating hormone (FSH)[2]			

NOTES:

1 Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

2 For confirmation of postmenopausal status only.

Investigators must document their review of each laboratory safety report.

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, ECG, 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.

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, that 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.

A SAE is defined as any untoward medical occurrence that, at any dose:

- 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.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting 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 (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the study intervention 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 study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (And exposure during pregnancy [EDP] supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- 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 Pfizer Safety/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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).

Contraception Guidance:

Contraception is not required for participants in this study.

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 study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
  - 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 study intervention 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 study intervention, 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 (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

The threshold of laboratory abnormalities for a potential DILI case depends on the 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 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 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: Virtual Randomized Clinical Trial Information

The CIG and RTCs will perform all the rater assessments except for the scoring of TSS, ISGA, and lesional %BSA which are completed by the HVP.

All VRCT processes would follow GCP standards, CFR compliance, and relevant local laws (there may be differences in process from state to state). Study operational processes and documentation will comply with all applicable privacy requirements. All new technologies proposed will be validated to be in compliance with CFR Part 11.

Completion of the IRB-approved electronic Informed Consent Document, participant eligibility, participant randomization using the Sponsor's IRT system, study drug compliance, efficacy assessment completion, and monitoring of participant safety will be documented within the remote data capture electronic platform to facilitate ongoing Sponsor oversight and Regulatory Agency auditing of trial conduct.

C3291038 VRCT study data will be entered electronically or uploaded electronically by investigators, remote trial coordinators, HVPs, and other 3rd-party vendors (eg, central laboratory, central pharmacy). Once participants have completed training for the use of an electronic diary, the participant will complete ePROs using smart-devices during study participation.

Sponsor representatives will monitor adverse event data (including but not limited to severity, causality, onset and outcome), review clinical trial data to identify potential AEs and SAEs, and oversee input of electronic source documents for Pfizer's ARGUS database for every study participant.

Sponsor representatives (RTCs, HVPs, and CIG-based Investigators) will elicit and enter adverse event information monitor adverse event data (including but not limited to severity, causality, onset and outcome) at each encounter with participants. The principal investigator (PI) and sub-investigators (SubI) and Sponsor will review clinical trial data to identify potential SAEs and oversee input of electronic source documents for Pfizer's ARGUS database for every study participant.

Prior to database lock, all external data will be transferred to the electronic data capture (EDC)-based clinical trial database.

This study will utilize various methods of electronic data capture to provide source documentation. All electronic data will be integrated into an EDC-based clinical trial database. Electronic data from the trial will be obtained from the following sources:

1. Third-Party Vendor online portal. The vendor will manage the online portal, which is accessible through an application on the participant's smart device or through a web-based portal. The following study participants will use the portal to enter study data: PI, Sub-Is, HVPs, RTCs, and other designees.
2. Central Lab Laboratory vendor: participant blood samples will be sent to a central laboratory for analysis. Laboratory data will be transferred electronically to an

external vendor and the data are loaded in the EDC system. Data generated by laboratories will be stored in their diagnostic databases and serve as the source data.

3. Static Dermatologic Images of SD areas for % lesional BSA, TSS and ISGA assessment: after training by HVP, static digital images will be obtained by the trained participant using only provisioned digital imaging equipment. Participants will be trained on how to obtain the images by the HVP. Images will be sent from the mobile digital imaging equipment electronically to a central digital imaging repository and transferred to a central imaging vendor for central reading of digital images.
4. Third party vendors, such as a central imaging vendor, will manage a digital imaging repository, and provide blinded access to imaging for each Central Reader and the CIG.
5. ECG: An ECG will be obtained as outlined in the Schedule of Activities to electronically calculate the heart rate and measure PR, QRS, QT, QTcF intervals.

Interactive Response Technology Updates to any data will originate from the source data system and be resent to the other system(s), as per the initial transfer process.[4-8]

10.7. Appendix 7: NYHA Classification, CKD Guidelines, Child - Pugh Classification and GOLD Guidelines

NYHA Classification - Stages of Heart Failure

Class I - No symptoms and no limitation in ordinary physical activity, eg, shortness of breath when walking, climbing stairs etc.

Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20 - 100 m). Comfortable only at rest.

Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

National Kidney Foundation CKD Guidelines

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative has published clinical practice guidelines for staging CKD. These guidelines stage CKD using a classification system (G1 to G5) based upon glomerular filtration rate (GFR):

GFR Category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Child-Pugh Classification

The Child-Pugh Classification was developed to assess the prognosis of chronic liver disease and cirrhosis. There are 5 components of the Child-Pugh score:

Points	1	2	3
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Bilirubin (µmol/L)	<34	34–51	>51
Albumin (g/L)	>35	28–35	<28
Prothrombin (sec)*	<4	4–6	>6

*Difference between the patient and the control. Differences of 4 to 6 seconds correspond approximately to a prothrombin ratio of ~50 to 40% of normal.

The 5 components are summed to yield a Child-Pugh Classification-Class A (5-6 points), Class B (7-9 points), or Class C (10-15 points).

GOLD Guidelines

The GOLD guideline uses a combined COPD assessment approach to group patients according to symptoms and previous history of exacerbations. Symptoms are assessed using the Modified British Medical Research Council (mMRC) dyspnea scale or COPD assessment test (CAT) scale.

Modified British Medical Research Council (mMRC) Dyspnea Scale	
mMRC Grade	Symptomatology
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying (on level ground)
2	I walk slower than people of the same age on level ground because of breathless, or I have to stop for breath when walking at my own pace on level ground.
3	I stop for breath after walking about 100 meters or after a few minutes on level ground.
4	I am too breathless to leave the house OR I am breathless when dressing or undressing.

COPD Assessment Test (CAT)

The CAT contains 8 unidimensional sub-scores assessing health status impairment in COPD.[33] The summation of each sub-score (range, 0-5) provides a total score (range, 0-40):

Individual participant risk group assignment (Group A to D) is determined using the mMRC and CAT:

- **Group A: low risk** (0-1 exacerbation per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10).
- **Group B: low risk** (0-1 exacerbation per year, not requiring hospitalization) and more symptoms (mMRC≥ 2 or CAT≥10).
- **Group C: high risk** (≥2 exacerbations per year, or one or more requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10).
- **Group D: high risk** (≥2 exacerbations per year, or one or more requiring hospitalization) and more symptoms (mMRC≥2 or CAT≥10).

10.8. Appendix 8: Abbreviations

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariate
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CAT	COPD assessment test
CFR	code of federal regulations
CHF	chronic heart failure
CI	confidence interval
CIG	Central Investigator Group
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CO_2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease (2019)
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trials
CTTI	clinical trials transformation initiative
DILI	drug-induced liver injury
CCI	[redacted]
DMC	Data monitoring committee
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EC_{50}	half maximal effective concentration
EDP	exposure during pregnancy
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of Treatment
CCI	[redacted]
CCI	[redacted]

Abbreviation	Term
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FTU	fingertip unit
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	Gamma-glutamyl transferase
GOLD	Global Initiative for Obstructive Lung Disease
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
HVP	Home Visit Practitioner
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IC_{50}	half maximal inhibitory concentration
ID	identification
IEC	Independent Ethics Committee
IL	interleukin
IMP	Investigational medicinal product
IND	investigational new drug application
INF-γ	Interferon gamma
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	Internal Review Committee
IRT	interactive response technology
ISGA	Investigator's Static Global Assessment
IVC	Inferior vena cava
JAK	Janus kinase
LFT	liver function test
LSM	least squares mean
MAR	Missing Data Are Assumed
mMRC	British Medical Research Council
MMF	mycophenolate mofetil
MMP	matrix metalloproteinases
MMRM	mixed model for repeated measures
MMSE-2	Mini Mental State Examination
N/A	Not applicable
NIMP	Non-investigational medicinal product

Abbreviation	Term
NSAIDS	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
MR-NR	missing response as non-response
CCI	[redacted]
PCD	primary completion date
PDE-4	phosphodiesterase 4
CCI	[redacted]
[redacted]	[redacted]
PI	principal investigator
PK	Pharmacokinetic(s)
PRN	as needed
PRO	patient reported outcome
PACL	Protocol Administrative Change Letter
PT	prothrombin time
QC	quality control
QTcF	Fridericia's Correction Formula
RBC	red blood cell
RTC	Remote Trial Coordinator
SAE	serious adverse event
SAF	Safety Analysis Set
SD	stasis dermatitis
SoA	schedule of activities
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SRSD	single reference safety document
SubI	sub investigator
SUSAR	suspected unexpected serious adverse reactions
TBili	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TGFβ1	transforming growth factor β1
TIMP	tissue inhibitors of metalloproteinases
TNFα	tumor necrosis factor alpha
TSS	total sign score
% BSA	percent body surface area
ULN	upper limit of normal
US	United States
USA	United States of America
CCI	[redacted]
VHTN	venous hypertension
VI	venous insufficiency
VRCT	virtual randomized clinical trials
WBC	White blood cells

Abbreviation	Term
WOCBP	women of child-bearing potential

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