TITLE PAGE

Teres Bio

Protocol Title:		A Multicenter, Randomized, Double-blind, Vehicle-Controlled, Phase 2a Study of TER-101 2.75% Topical Ointment to Assess Efficacy and Safety in Subjects with Mild to Moderate Atopic Dermatitis	
Protocol Number:		TER101-AD-201	
Compound:		TER-101 2.75% (w/w) Topical Ointment (TER-101 Ointment)	
Study Phase:		Phase 2a	
Short Title:		A Phase 2a Study of TER-101 Topical Ointment in Subjects with Mild to Moderate Atopic Dermatitis	
Sponsor	**Sponsor Name:**	Teres Bio, Inc.	
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Protocol Approver	**Name:**	[redacted]	
	Function:	Chief Medical Officer, Teres Bio	
Regulatory Agency Identifier Number(s)		IND 128134	
Protocol Date:		**Document Version**	**Date**
		Amendment 1 (v 1.1)	02 Feb 2021

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SPONSOR SIGNATORY:

A Multicenter, Randomized, Double-blind, Vehicle-Controlled, Phase 2a Study of TER-101 2.75% Topical Ointment to Assess Efficacy and Safety in Subjects with Mild to Moderate Atopic Dermatitis

I, the undersigned, have approved the amended version of the clinical trial protocol with the date of 2 Feb 2021.

Name and Title	Signature and Date
[redacted] Chief Medical Officer, Teres Bio	04-Feb-2021 | 06:19 PST DocuSigned by M Joyce Rico, MD [redacted] I approve this document 04-Feb-2021 | 06:19 PST 4D759E5F4FAB46C48CC7F968DF7F925A

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1.1 Synopsis

Protocol Title: A Multicenter, Randomized, Double-blind, Vehicle-Controlled, Phase 2a Study of TER-101 2.75% Topical Ointment to Assess Efficacy and Safety in Subjects with Mild to Moderate Atopic Dermatitis

Short Title: A Phase 2a Study of TER-101 Topical Ointment in Subjects with Mild to Moderate Atopic Dermatitis

Rationale:

TER-101 is a cytosolic phospholipase A2 alpha ($cPLA_{2\alpha}$) inhibitor currently in development for the treatment of inflammatory skin diseases, including atopic dermatitis (AD). This Phase 2a study will assess efficacy, safety, and tolerability of TER-101 (2.75% weight for weight [w/w]) ointment (TER-101 Ointment) with its vehicle (TER-101 Placebo Ointment) twice daily for 28 days in adult and adolescent subjects with mild to moderate AD.

Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
Primary	
• To assess the efficacy of TER-101 (2.75% w/w) ointment vs. vehicle in subjects aged 12 – 65 with mild to moderate AD	Primary Efficacy Endpoints • Percent change in EASI from baseline at Day 29 Secondary Efficacy Endpoints • Percent change in EASI from baseline over time • Percent change in individual components of EASI (erythema, induration/papulation, excoriation, lichenification) and by region (head, trunk, UE, LE) from baseline over time • EASI-75, EASI-50 responder analysis over time • Absolute change in EASI from baseline over time • Change in IGA from baseline over time • Change from baseline WI-NRS at Days 15, 29 (WI-NRS captured on e-diary daily) • Responder analysis: Reduction of ≥ 3 in subjects with baseline WI-NRS ≥ 4 • Change in TBSA affected from baseline over time
Secondary	
• To assess the safety and tolerability of TER-101 (2.75% w/w) ointment vs. vehicle in subjects with AD	• Safety: TEAEs, SAEs, VS, ECGs, laboratories • Tolerability: Scored by investigator at baseline and post-baseline visits on 4-point scale (0 = none; 3 = severe) to include subscores for erythema, burning/stinging, pruritus.
• To assess systemic exposure to TER-101 (2.75% w/w) ointment after BID treatment for 28 days	PK: systemic plasma trough levels of TER-101 on Days 15, 29

BID = twice daily; EASI = Eczema Area and Severity Index; EASI-50/75 = 50 or 75% reduction in EASI score from baseline; ECG = electrocardiogram; IGA = Investigator Global Assessment; LE = lower extremities; PK = pharmacokinetics; SAE = serious adverse event; TBSA = Total Body Surface Area; TEAE = treatment emergent adverse event; UE = upper extremities; VS = vital signs; WI-NRS = Worst Itch Numeric Rating Scale; w/w =. weight for weight.

Overall Design:

This is a Phase 2a, randomized, double-blind, vehicle-controlled study assessing efficacy, safety, and tolerability of TER-101 (2.75% w/w) ointment versus its ointment vehicle applied topically twice daily during a 28 day treatment period in adolescent and adult subjects (age 12 – 65) subjects with mild to moderate AD. Subjects will be randomized 1:1 to receive either TER-101 (2.75% w/w) ointment or vehicle. Efficacy assessments will include changes in Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), Worst Itch Numeric Rating Scale (WI-NRS), and Total Body Surface Area (TBSA) affected. Safety and tolerability assessments will include reported adverse events (AEs), laboratories, physical examinations, electrocardiograms (ECGs), and vital signs as well as a separate tolerability assessment of treated

areas. Systemic exposure will be determined by measuring trough TER-101 levels on Day 15 and Day 29/End of Trial (EOT). Photographs of representative areas of AD will be obtained at baseline, Day 15, and Day 29/EOT.

Disclosure Statement:

This is a study with 2 treatments that are subject- and investigator-blinded.

Number of Investigators and Study Sites:

Approximately 12 clinical research sites in the United States are expected to participate in this study.

Number of Subjects:

The study will enroll and randomize a total of approximately 60 subjects aged 12 - 65.

Diagnosis and Main Criteria for Inclusion:

Adolescent and adult subjects (age 12 – 65) with mild to moderate AD at baseline.

Major Inclusion Criteria

- Diagnosis of AD according to the Hanifin and Rajka criteria [Appendix 5, Section 10.5].
- AD disease duration of at least 6 months, with no change in treatment or severity for at least 4 weeks prior to screening.
- Overall IGA score of 2 (mild) or 3 (moderate) at baseline on a 5-point IGA scale.
- TBSA affected of between 2 and 30% at baseline.
- EASI $\geq$ 5 at baseline.

Major Exclusion Criteria

- AD with clinical evidence of superinfection.
- Other dermatological conditions that require concomitant treatment, potentially cause diagnostic confusion with AD, or interfere with the study assessments. This may include excessive facial hair, tattoos.
- Known hypersensitivity to study drug or excipients, including polyethylene glycol (PEG) 400, PEG 4000, or propylene glycol.
- Treatment of AD with the following therapies within the washout periods specified prior to baseline:
  - Topical corticosteroids including over the counter (OTC) corticosteroids – 1 week.
  - Topical calcineurin inhibitors, phosphodiesterase 4 (PDE4) inhibitors, topical antihistamines – 2 weeks.
  - Systemic or topical antibiotics – 2 weeks.

  - Initiation of systemic antihistamines or tricyclic antidepressants (TCAs) – 2 weeks
    - Subject on a stable dose of antihistamines or TCAs at screening may be enrolled
  - Systemic immunosuppressants (systemic corticosteroids, cyclosporine, mycophenolate, methotrexate, azathioprine, etc) – 4 weeks.
    - Nasal, ophthalmic, or inhaled corticosteroids for indications such as rhinitis, allergic conjunctivitis, or asthma/chronic obstructive pulmonary disease are permitted.
  - Biologics (dupilumab, other) – 12 weeks.
  - Investigational biologic agents – 12 weeks or 5 half-lives of the drug, whichever is longer.
  - Investigational nonbiologic agents – 4 weeks or 5 half-lives of the drug, whichever is longer.
  - Use of complementary and alternative medications and supplements including St. John's wort, cannabidiol (CBD) (oral or topical) – 2 weeks.
  - Systemic treatment with potent inhibitors or inducers of CYP3A4 – 2 weeks.
- Receipt of artificial or natural light therapy such as phototherapy (ultraviolet B [UVB], psoralens + ultraviolet A [PUVA]), regular use of a tanning booth/parlor, lasers, red light or blue light, or tanning within 4 weeks of baseline.
- Women of childbearing potential (WOCBP) who are pregnant or intending to become pregnant during the course of the study, lactating, or unwilling or unable to use an acceptable method of contraception as defined in Section 10.8 for the duration of the study.
- Males with female partners of childbearing potential who are not using or willing to use an acceptable method of contraception as defined in Section 10.8. Male subjects should refrain from sperm donation for 90 days after study completion.
- Receiving hormonal therapy (eg, estrogen, testosterone) for gender reassignment.
- Current or recent history (within 12 weeks of the Screening Visit) of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, or neurological disease per investigator opinion.
- Has clinically relevant abnormalities on the screening ECG, including long QT (eg, corrected QT [QTc] ≥ 480 msec).
- Is immunocompromised.
- Has recently (within 4 weeks of the Screening Visit) received live vaccine(s). Enrolled subjects should not receive live vaccines during the study and for 30 days after study discontinuation.
- Known history of hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) OR a recent (within 4 weeks of the Screening Visit) known infection with SARS-CoV-2 (coronavirus disease 2019 [COVID-19]).
- History of malignancy in the previous 5 years except for adequately treated nonmelanoma skin cancers or cervical carcinoma in situ.
- Recent (within 12 months of screening) history of substance abuse or unwilling to follow protocol restrictions on alcohol consumption (Section 5.3.2).

Treatment Groups and Duration:

At baseline, eligible subjects will be randomized to TER-101 (2.75% w/w) ointment or vehicle to be applied topically twice daily for 28 days to all affected areas. The study will include up to a 35-day screening period prior to enrollment/Baseline Visit and a 28-day active treatment period. Subjects will apply the first dose of medication at the baseline visit (Day 1) and will apply dispensed clinical trial ointment to the areas identified at baseline throughout the 28-day treatment period.

AD assessments will consist of the EASI, IGA, TBSA affected and a daily recording of the WI-NRS. EASI, IGA, and TBSA are strongly recommended to be performed by the same qualified evaluator throughout the study and particularly for baseline and Day 29/EOT visits.

Safety assessments will include reported AEs/treatment emergent AEs (TEAEs), periodic vital signs, physical examinations, pregnancy tests, ECGs, and clinical laboratory evaluations.

Tolerability will be assessed at baseline (pre-dose), 15 minutes post-baseline dose, and Days 15 and 29 by the investigator and include assessments for erythema, stinging/burning, and pruritus.

If severe local application site AEs or scores of 3 on two or more tolerability subscores arise with BID dosing, treatment will be withheld to the affected area. When the local AE(s) has resolved or tolerability score returns to baseline, subjects may restart application to the affected area once daily. See Section 6.2 of protocol.

Pharmacokinetics: Trough levels on Days 15, 29.

Other Assessments:

Photography of representative lesions will be taken at baseline, Day 15, and Day 29. The same areas will be photographed throughout the study under the same conditions.

Statistical Methods:

The sample size is based on a clinical rather than statistical rationale. Approximately 60 subjects are planned to be enrolled and randomized, considering a potential 15% dropout rate, to yield approximately 50 subjects completing the study. Statistical analyses will be exploratory to assess the drug's activity and potential for further study.

All randomized subjects who receive at least 1 application of the study treatment will be included in the Safety Analysis Set (SS). All randomized subjects who receive at least 1 application of the study treatment and have 1 post-baseline efficacy assessment will be included in the Efficacy Analysis Set (ES). All subjects in ES without major protocol deviations will be included in the Per Protocol Efficacy Analysis Set (PPES).

The primary efficacy endpoint (percent change in EASI total score) will be analyzed using a mixed model for repeated measures (MMRM). The model will include fixed effects for study treatment (TER-101 [2.75% w/w] ointment or vehicle), visit (Day 15, Day 29), and treatment-

by-visit interaction with visit as the repeating factor, subject as a random effect, and baseline score as a covariate. The treatment p-value (TER-101 [2.75% w/w] ointment vs. vehicle), treatment difference, and 95% confidence limits from the model will be presented for the percent change in EASI from baseline at Day 29. Sensitivity analyses will include analysis of covariance (ANCOVA) at each timepoint. The impact of dropouts and missing data on results for the primary endpoint will be explored using the last value carried forward (LOCF) and multiple imputation methods, as appropriate.

Secondary efficacy endpoints that are continuous variables (percent change in EASI over time, and absolute change in EASI component scores, IGA, TBSA, and WI-NRS) will also be analyzed using the MMRM model as described above. The treatment difference in response rates (75% reduction in EASI score [EASI-75], 50% reduction in EASI scores [EASI-50]) at each visit will be evaluated using a logistic generalized linear mixed model (GLMM) for binary data, with fixed effects for treatment, visit, and treatment by visit interaction. The odds of response will be reported from the model together with the 95% confidence interval. (Note: If repeated measures models fail to converge, the response proportions will be analyzed using the generalized Cochran-Mantel-Haenszel test, stratified by baseline IGA.) The proportion of WI-NRS responders (defined by a reduction of ≥ 3 in subjects with baseline WI-NRS ≥ 4) will be analyzed using a chi-square test.

Time to onset of response (EASI 75, EASI-50) will be estimated using the Kaplan-Meier method, with treatment comparisons based on the logrank test. Subjects who do not achieve response criteria will be censored on the day of last assessment.

Given the exploratory nature of this study, p-values from all significance tests will be reported without adjustment for multiplicity.

Descriptive statistics will include line graphs of % change in EASI scores and bar charts of response rates at each time point, to describe the effect of treatment over time.

The number and percentage of subjects reporting TEAEs, coded using the Medical Dictionary for Regulatory Activities, will be summarized by treatment, by treatment related, by maximum severity, by leading to study treatment or study withdrawal, and by serious TEAEs.

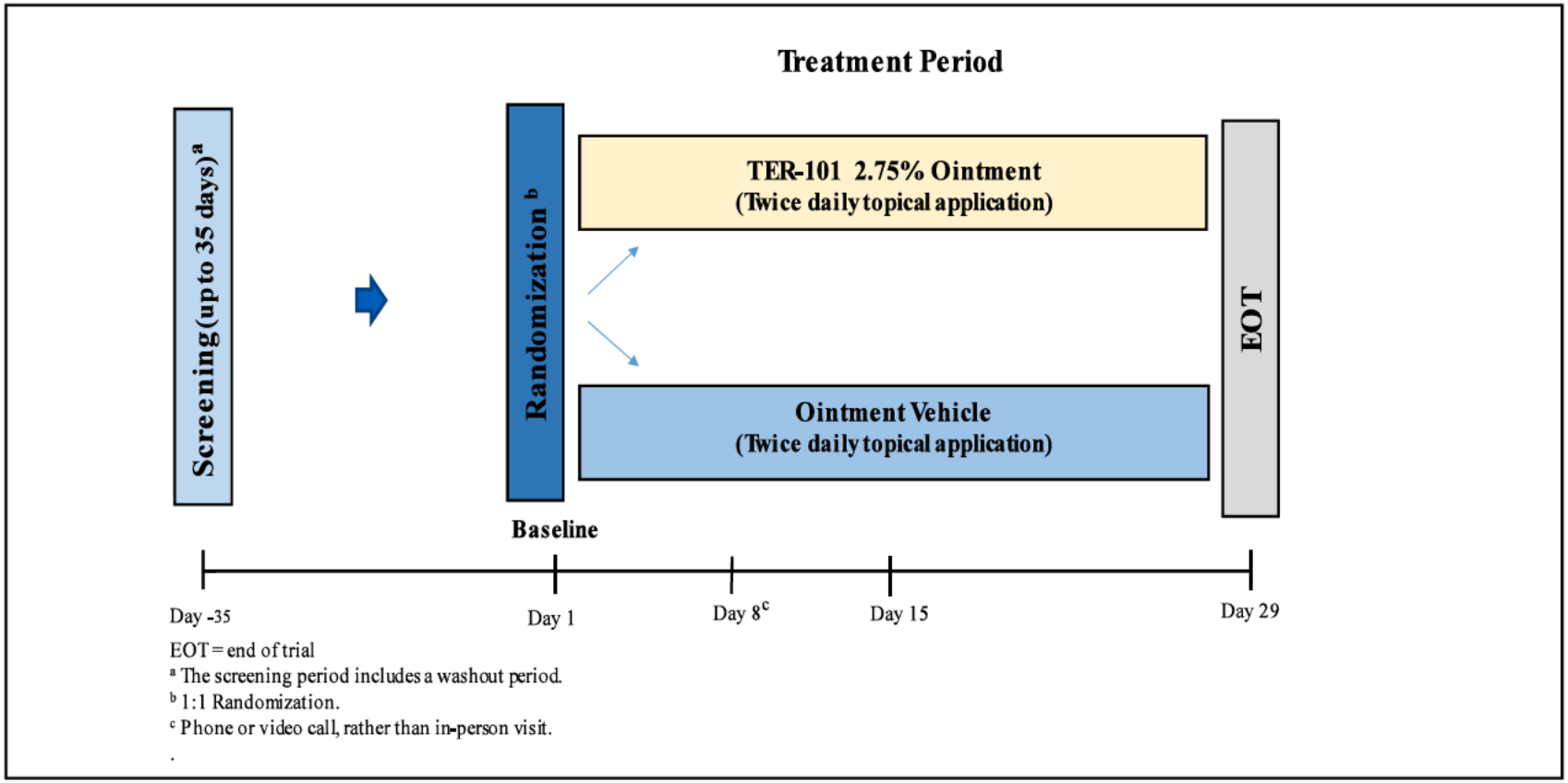
Changes from baseline in laboratory measurements, ECG assessments, and vital signs will be summarized using descriptive statistics.

Tolerability scores and pharmacokinetic (PK) parameters will be summarized by treatment and visit.

Data Monitoring Committee: None.

1.2 Schema

Figure 1 Study Schema



1.3 Schedule of Activities (SoA)

Table 1: Schedule of Activities

Period	Screening	Baseline	Treatment Period			
Visit	**1**	**2**	**3**	**4**	**5**	**Notes**
Visit Day and Window	**D-35 to D-1**	**Day 1**	**D8 ± 3 days (Phone)**	**D15 ± 3 days**	**D29/ETV[a] ± 3 days**	
Informed consent	X					Informed consent will be obtained from adult subjects and parent/guardian of subjects age 12 – 17; assent will be obtained from any subject age 12 – 17.
Demographics	X					
Medical history, including AD history	X	X				Complete medical and AD history will be collected at screening and interval medical history (or any change from Screening Visit) collected at baseline.
Physical examination	X	X			X	Clinically significant abnormal findings from the physical examinations after baseline will be reported as AEs.
Vital signs	X	X		X	X	Blood pressure, pulse rate, and temperature strongly recommended to be measured after the subject has rested for ≥ 5 minutes seated.
Body weight, height		X				
Clinical laboratory tests[b]	X	X			X	
ECG[c]	X				X	ECG strongly recommended to be performed after the subject has rested in a supine position for ≥ 10 minutes.
Blood for PK[d]				X	X	Date/time of last dose should be recorded for PK blood draws.
Urine pregnancy test (WOCBP)	X	X			X	Urine pregnancy tests may be performed more frequently as required by local regulations. The use of contraception will be discussed at each visit.
AD assessments	X	X		X	X	Includes IGA, EASI, and TBSA *(in this order)*.
Inclusion/exclusion criteria	X	X				Confirm subject meets all inclusion/exclusion criteria before randomization.
Emollient and cleanser review	X	X	X	X	X	Site should confirm the emollient and cleanser the subject plans to use during the study are acceptable.
Concomitant medications	X	X	X	X	X	

Period	Screening	Baseline	Treatment Period			
Visit	**1**	**2**	**3**	**4**	**5**	**Notes**
Visit Day and Window	**D-35 to D-1**	**Day 1**	**D8 ± 3 days (Phone)**	**D15 ± 3 days**	**D29/ETV[a] ± 3 days**	
AE recording	X	X	X	X	X	AEs will be monitored and recorded throughout the study, beginning at the time that informed consent has been obtained.
Photography		X		X	X	Baseline photographs will be obtained prior to study drug application. The same regions will be photographed through the study under same conditions.
Randomization		X				
Local tolerability		X		X	X	At baseline, tolerability will be assessed pre-dose and 15 minutes after the first dose and also at Days 15 and 29.
Study drug application		X				1st dose of study drug will be applied by site staff and the subjects instructed on application. All subsequent application will be at home through evening dose on Day 28.
Dispense study medication, Instructions for Use, e-diary		X		[X]		Study drug will be weighed at the Baseline Visit, prior to first dose. Additional study drug may be dispensed on Day 15 if needed.
Instruct on WI-NRS tool		X	X	X		
Review e-diary, WI-NRS for compliance			X	X	X	The e-diary will be reviewed at each visit.
Collect and weigh study drug.				X	X	Study drug (used and unused tubes) will be collected and weighed at in person visits on Day 15 and Day 29. Study drug will be returned to subject at Day 15 and not returned to subject at Day 29.

AE=adverse event; BID = twice daily; D = Day; e-diary = electronic diary; EASI = Eczema Area and Severity Index; ECG= electrocardiogram; IGA = Investigator Global Assessment; PK = pharmacokinetics; TBSA = Total Body Surface Area; WI-NRS = Worst Itch Numeric Rating Scale.

[a]ETV: Early Termination Visit. All assessments scheduled for Day 29 will be conducted in event subject early terminates from study.

[b]Clinical labs: Complete blood count with differential, chemistry will be conducted at screening, baseline, Day 29. Urinalysis will be conducted at screening only. If the clinical laboratories were obtained within 14 days of baseline (Day 1), the screening labs will be used as the baseline labs and do not need to be repeated.

[c]The screening ECG will be used as the baseline ECG.

[d]PK blood draws should be done at least 4 hours after last study drug application. The date, time of last application will be recorded on electronic case report form page. Avoid drawing PK samples through study drug application site.

2 INTRODUCTION

2.1 Study Rationale

TER-101 1% topical ointment was tested in a previous Phase 1/2a randomized, double-blind, vehicle-controlled, sequential group study assessing safety, tolerability, pharmacokinetics (PK), and efficacy of twice daily topical application of TER-101 1% on body surface areas (BSAs) up to 50% for up to 2 weeks in healthy volunteers (n=8) and subjects with atopic dermatitis (AD) (n=28).

The application of TER-101 (1% w/w) ointment was well tolerated by both healthy volunteers and subjects with moderate to severe AD. Absorption of TER-101 (1% w/w) ointment into the bloodstream was evident in subjects with AD, but absorption was low; while in healthy volunteers, absorption was sporadic and limited. There was no evidence of toxicity or safety concerns. In this small study, statistical evidence to conclude that there was a difference between TER-101 (1% w/w) ointment and ointment vehicle for improvement in disease severity and itching was insufficient.

This Phase 2a study will compare the higher concentration TER-101 (2.75% weight for weight [w/w]) ointment to its vehicle over a longer treatment period (ie, 4 weeks) than the prior Phase 1/2a study and will be performed in subjects aged 12 – 65 with mild or moderate AD. The proposed TER-101 2.75% dose and patient population is supported by nonclinical studies.

2.2 Background

2.2.1 Disease Background

AD is a chronic, relapsing, inflammatory skin disease characterized by impaired epidermal barrier function, inflammatory infiltration, extensive pruritus, and a clinical course defined by symptomatic flares and remissions (Yang et al, 2020). Features include poorly defined erythema with edema, vesiculation, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage (Williams, 1994; Eichenfield, 2004). These signs and symptoms result in a severely reduced quality of life. In particular, pruritus (itching) that continues throughout the day and worsens at night causes sleep loss and impacts everyday activities and psychosocial wellbeing (Kini, 2011). AD is commonly associated with other atopic and inflammatory disorders, such as asthma and allergic rhinitis (Eichenfield et al, 2014).

The disease occurs in all races and geographic locations, with the highest incidence in urban areas and developed countries (Shaw et al, 2003; Beikert et al, 2013; Bantz, 2014). Up to approximately 20% of children and up to 10.2% of adults are affected by AD (Abuabara, 2013; Bantz, 2014). The majority of adult patients have a chronic, recurrent disease (Pugliarello, 2011).

Topical corticosteroids (TCs) have been the mainstay of treatment for AD for several decades (Eichenfield, 2014). Well known side effects of TC treatment include skin thinning, striae, and

possible hypothalamic pituitary adrenal (HPA) axis suppression (Sidbury and Poorsattar, 2006; Thomas et al, 2011). An alternative to TCs are topical calcineurin inhibitors (TCIs) which include a boxed warning regarding the potential of increased long-term malignancy risk due to systemic immunosuppression. (Prucha et al, 2013). A phosphodiesterase 4 (PDE4) inhibitor approved for the treatment of AD, crisaborole ointment, is also limited by skin irritation or discomfort on application (Paller et al, 2016).

Given limitations of currently available topical treatments, there is an unmet need for new agents that are safe and effective for the long-term management of AD.

More detailed information on AD may be found in the Investigator Brochure (IB).

2.2.2 Teres Bio, Inc. Investigational Product Background: TER-101 2.75%

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) is an inflammatory mediator that is implicated in the pathogenesis of AD. Selective inhibitors of $cPLA_2\alpha$ with distinct chemical structures have demonstrated significant anti-inflammatory activity in a wide variety of skin inflammation models (Burke, 2001; Williams 2006).

$cPLA_2\alpha$ releases arachidonic acid from phospholipid membranes and is the rate -limiting enzyme in the biosynthesis of chemical lipid mediators, including various prostaglandins, leukotrienes, thromboxane A_2, and platelet activating factor.

In AD, the levels of eicosanoids such as leukotriene B_4 and prostaglandin E_2 are elevated in skin lesions, as compared with nonlesional skin in patients (Fogh et al, 1989). Prostaglandin E_2 has been shown to induce vasodilation and itch in patients with AD (Neisius et al, 2002). In addition, leukotriene B_4 and cysteinyl leukotrienes are involved in keratinocyte hyperproliferation, an important process in AD (Sadik et al, 2013; Honda et al, 2019). The available scientific evidence supports the rationale that inhibition of $cPLA_2\alpha$ would provide therapeutic benefits in the treatment of AD.

TER-101 is a highly potent and selective inhibitor of $cPLA_2\alpha$ that prevents the biosynthesis of these pro-inflammatory mediators. Teres Bio is studying TER-101 in a topical ointment formulation for the treatment of patients with AD.

A detailed description of the chemistry, pharmacology, and previous human studies of TER-101 is provided in the IB.

2.3 Benefit/Risk Assessment

TER-101 was safe and well tolerated when administered as a topical ointment (1.0% w/w) twice daily for up to 2 weeks to healthy volunteer subjects (n=8) and patients (n=28) with moderate to severe AD. The most common treatment emergent adverse events (TEAEs) in TER-101 treated subjects were local application site events including pruritus, dry skin, and dermatitis. The majority of reported TEAEs in healthy volunteers or subjects with AD were mild to moderate in

severity. Three of 10 subjects with moderate to severe AD randomized to the vehicle arm withdrew due to TEAEs related to lack of efficacy. No healthy volunteers or subjects with AD treated with TER-101 withdrew from the study. There were no clinically significant safety concerns identified in vital signs, physical examinations, electrocardiograms (ECGs), or clinical laboratory assessments.

In this small study, there was no statistically significant difference in the primary efficacy analysis (percentage change from baseline in Eczema Area and Severity Index [EASI] score at Week 2) or in a sensitivity analysis using multiple imputation, between the TER-101 and placebo groups. In the sensitivity analysis using last observation carried forward, there was evidence of a trend towards a larger decrease in EASI scores and other efficacy assessments in the TER-101 compared with the placebo group. This result was also supported by the worst-case imputation sensitivity analysis. Three patients in the TER-101 group were assessed as EASI-75 (75% reduction in EASI score from baseline) responders. No patients in the placebo group met this definition. A trend towards greater improvement in the TER-101 group was also evident in the Patient Global Impression of Change assessment.

Teres Bio anticipates the most likely TEAE in the Phase 2 upcoming study will be local application site TEAEs including pruritus, dry skin, stinging/burning, pain, or dermatitis including atopic dermatitis. The protocol includes rules for treatment cessation in the event that subjects develop severe local TEAEs or high scores on the tolerability assessments. Once local AEs have abated, treatment may be re-initiated once daily. Teres Bio believes that the accrued clinical safety and preliminary efficacy data support a favorable benefit-risk profile for the proposed protocol and that appropriate monitoring and stopping rules have been included in the planned study design.

Sexually active males and females must use appropriate contraception as indicated. It is unknown whether TER-101 is excreted in human breast milk; hence TER-101 should not be administered to lactating females.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with TER-101 2.75% ointment are justified by the anticipated benefits that may be afforded to subjects with mild to moderate AD.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of TER-101 may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
• To assess the efficacy of TER-101 (2.75% w/w) ointment vs. vehicle in subjects aged 12 - 65 with mild to moderate AD	Primary Efficacy Endpoints • Percent change in EASI from baseline at Day 29 Secondary Efficacy Endpoints • Percent change in EASI from baseline over time • Percent change in individual components of EASI (erythema, induration/papulation, excoriation, lichenification) and by region (head, trunk, UE, LE) from baseline over time • EASI-75, EASI-50 responder analysis over time • Absolute change in EASI from baseline over time • Change in IGA from baseline over time • Change from baseline WI-NRS at Days 15, 29 (WI-NRS captured on e-diary daily) • Responder analysis: Reduction of ≥ 3 in subjects with baseline WI-NRS ≥ 4 • Change in TBSA affected from baseline over time
Secondary	
• To assess the safety and tolerability of TER-101 (2.75% w/w) ointment vs. vehicle in subjects with AD	• Safety: TEAEs, SAEs, VS, ECGs, laboratories • Tolerability: Scored by investigator at baseline and post-baseline visits on 4-point scale (0 = none; 3 = severe) to include subscores for erythema, burning/stinging, pruritus.
• To assess systemic exposure to TER-101 (2.75% w/w) ointment after BID treatment for 28 days	PK: systemic plasma trough levels of TER-101 on Days 15, 29

BID = twice daily; EASI = Eczema Area and Severity Index; EASI-50/75 = 50 or 75% reduction in EASI score from baseline; ECG = electrocardiogram; IGA = Investigator Global Assessment; LE = lower extremities; PK = pharmacokinetics; SAE = serious adverse event; TBSA = Total Body Surface Area; TEAE = treatment emergent adverse event; UE = upper extremities; VS = vital signs; WI-NRS = Worst Itch Numeric Rating Scale; w/w = weight for weight.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, randomized, double-blind, vehicle-controlled study assessing efficacy and safety, and local tolerability of TER-101 (2.75% w/w) ointment vs. its ointment vehicle topically twice daily in adolescent and adult subjects (age 12 - 65) subjects with mild to moderate AD.

Subjects will be randomized 1:1 to receive either TER-101 (2.75% w/w) ointment or vehicle. Both the subject and the investigator will be blinded to the treatment assignments.

Approximately 60 adolescent and adult subjects (age 12 – 65) are planned to be enrolled across approximately 12 clinical research sites in the United States. Institutional Review Board (IRB) approval will be obtained for each clinical research site prior to recruiting any subjects at the site.

The study will include up to a 35-day screening period prior to enrollment/baseline visit and a 28-day active treatment period. Subjects will apply assigned treatment to all areas affected by AD at baseline twice daily throughout the treatment period. If the subject develops new areas of AD, those areas will also be treated. Treatment areas will exclude the scalp, nose, mouth and eyes. Subjects may use bland emollients on non-affected body sites once daily. Rescue medications are not permitted.

Efficacy assessments will include the EASI, Investigator Global Assessment (IGA), Worst Itch Numeric Rating Scale (WI-NRS), and Total Body Surface Area (TBSA) affected. Safety and tolerability assessments will include reported adverse events (AEs), clinical laboratories, physical examinations, ECGs, and vital signs as well as a separate tolerability assessment for treated areas. Systemic exposure will be determined by measuring trough TER-101 levels on Day 15 and Day 29/End of Trial (EOT). Photographs of representative areas of AD will be obtained at baseline, Day 15, and Day 29/EOT. The study procedures and visit timelines are described in the Schedule of Activities (SoA; Table 1). An overview of the study design is presented in Figure 1.

If there are no safety concerns identified in the study, but additional subjects are needed to reach 50 subjects completing the study for efficacy, then additional subjects may be enrolled and randomized.

4.1.1 Screening (Day -35 to Day -1)

Informed consent will be obtained from adult subjects and parent/guardian; assent will be obtained from any subject age 12-17. Inclusion and exclusion criteria will be reviewed for subject eligibility. Demographics, complete medical history, complete AD history, prior and concomitant medications, physical examination, and overall baseline AD severity assessment, including overall EASI, IGA, and TBSA affected, will be conducted. A urine pregnancy test will be obtained for women of childbearing potential (WOCBP). Safety assessments, including AE recordings, vital signs, clinical laboratory tests, and ECG will be conducted. During the screening period, subjects may be required to undergo a washout period. During the screening period, the site will confirm whether the bland emollient therapy and cleanser the subject plans to use during the study are acceptable for use. Subjects will be instructed on appropriate use of bland emollient cream therapy and cleanser during the screening and treatment periods.

4.1.2 Baseline (Day 1)

An interval medical and medication history (or change from Screening Visit) will be obtained at the Baseline Visit. AEs occurring between screening and baseline will be obtained. Vital signs, physical examination, and clinical laboratory tests will be conducted. Clinical laboratory tests obtained within 14 days of the Baseline Visit do not need to be repeated. Interval AD history (or any change from Screening Visit) will be collected at Baseline Visit. A urine pregnancy test will be obtained for females of childbearing potential. The IGA, EASI, and TBSA will be obtained for overall baseline AD severity assessments. Standardized photographs of up to 4 affected areas will be obtained. Subjects who meet the inclusion/exclusion criteria will be randomized to either active or vehicle arm at the Baseline Visit.

Subjects will be instructed on use of electronic diary (e-diary) and WI-NRS tool. Subjects will record their worst itch in the previous 24-hour period daily, with the first assessment at the Baseline Visit. The first dose of study drug will be applied by site staff and the subjects instructed on application. Local tolerability will be assessed pre-dose and 15 minutes after investigational product application. The study medication will be dispensed, along with an e-diary to monitor compliance.

4.1.3 Treatment Period (Day 1 to Day 29)

Subjects will continue to administer study agent twice daily, morning and evening, from Day 1 to Day 28 to all areas identified at the Baseline Visit and record each application in the e-diary. Study drug will be applied as a thin film to all involved areas twice daily, with at least 8 hours between applications. New areas that develop during the trial will be treated with study drug. Study drug will not be applied to the scalp, mouth, inside the nose, or eyes.

Subjects will be contacted by phone or video on Day 8 to assess for AEs, adherence with study agent application and prohibited medication use, and WI-NRS and e-diary completion. Compliance with study agent application will be emphasized.

Subjects will be present for in person visits on Day 15 and Day 29 when efficacy will be assessed using IGA, EASI, and TBSA. Safety assessments, including AEs, vital signs, urine pregnancy test, clinical laboratory tests, ECG, and local tolerability assessments will be conducted as per the SoA. The scores for WI-NRS will be reviewed. Adherence to study agent application will be confirmed by collecting and reviewing the e-diary at each visit and obtaining weight of the medication tubes at in person visits on Day 15 and Day 29/EOT. Standardized photographs of the same areas photographed at baseline will be obtained as per the SoA. If necessary, study procedures and visits may be modified in response to needs related to eg, coronavirus disease 2019 (COVID-19) (see Section 8 and SoA [Table 1]).

Regardless if the lesions are decreased in area or resolved prior to the scheduled end of treatment (Day 29), the subject should continue to apply study drug twice daily for the entire treatment

period. New lesions that arise post-baseline will also be treated. Subjects will be instructed to bring all investigational product (used and unused tubes) to study visits on Day 15 and Day 29.

4.2 Justification for Dose

At the previous dose tested in a Phase 1/2a trial, there was no evidence of toxicity or safety concerns with TER-101 (1% w/w) ointment. In this small study, there was no statistical difference between TER-101 (1% w/w) ointment and vehicle treated subjects on the primary efficacy endpoints; there was a trend to efficacy in TER-101 treated subjects. This Phase 2a study will compare the higher concentration TER-101 2.75% ointment with its vehicle over a longer treatment period (ie, 4 weeks) in a population with milder disease and lower TBSA affected (mild or moderate AD, up to 30% BSA) compared to the prior Phase 1/2a study (moderate or severe AD, up to 50% BSA). The proposed twice daily TER-101 2.75% w/w dose in subjects aged 12 - 65 is supported by previous nonclinical and clinical studies. The nonclinical studies were initiated in juvenile rats (age 6 - 7 weeks) and minipigs (age 5 - 6 months).

4.3 End of Study

4.3.1 End of Study Definition

End of Study (Individual Subject)

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit or last scheduled procedure shown in the SoA (Table 1).

5 STUDY POPULATION

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 10.1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Eligibility criteria will be evaluated during screening.

5.1 Inclusion Criteria

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

1. Adolescent or adult subject aged 12 – 65 years.
2. Able to understand and give documented informed consent if an adult/parent/guardian and able to understand and provide assent if a minor (age 12-17).
3. Diagnosis of AD according to the Hanifin and Rajka criteria [Appendix 5, Section 10.5].
4. AD disease duration of at least 6 months, with no change in treatment or severity for at least 4 weeks prior to screening.
5. Overall IGA score of 2 (mild) or 3 (moderate) at baseline on a 5-point IGA scale.

6. TBSA affected of between 2 and 30% at baseline.
7. EASI ≥ 5 at baseline.

5.2 Exclusion Criteria

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

1. AD with clinical evidence of superinfection.
2. Other dermatological conditions that require concomitant treatment, potentially cause diagnostic confusion with AD, or interfere with the study assessments. This may include excessive facial hair, tattoos.
3. Known hypersensitivity to study drug or excipients including polyethylene glycol (PEG) 400, PEG 4000, or propylene glycol.
4. Treatment of AD with the following medications/treatment within the washout periods specified prior to baseline:
    a. Topical corticosteroids including over the counter (OTC) corticosteroids – 1 week
    b. Topical calcineurin inhibitors, PDE4 inhibitors, topical antihistamines – 2 weeks
    c. Systemic or topical antibiotics – 2 weeks
    d. Initiation of systemic antihistamines or tricyclic antidepressants (TCAs) – 2 weeks
        i. Subject on a stable dose of antihistamines or TCAs at screening may be enrolled
    e. Systemic immunosuppressants (systemic corticosteroids, cyclosporine, mycophenolate, methotrexate, azathioprine, etc) – 4 weeks
        i. Nasal, ophthalmic, or inhaled corticosteroids for indications such as rhinitis, allergic conjunctivitis, or asthma/chronic obstructive pulmonary disease are permitted.
    f. Biologics (dupilumab, other) – 12 weeks
    g. Investigational biological agents – 12 weeks or 5 half-lives of the drug, whichever is longer
    h. Investigational nonbiological agents – 4 weeks or 5 half-lives of the drug, whichever is longer
    i. Use of complementary and alternative medications including St. John's wort, cannabidiol (CBD) (oral or topical) – 2 weeks
    j. Systemic treatment with potent inhibitors or inducers of CYP3A4 – 2 weeks.
5. Receipt of artificial or natural light therapy such as phototherapy (ultraviolet B [UVB], psoralens + ultraviolet A [PUVA]), regular use of a tanning booth/parlor, lasers, red light or blue light, or tanning within 4 weeks of baseline.
6. WOCBP who are pregnant or intending to become pregnant during the course of the study, lactating, or unwilling or unable to use an acceptable method of contraception as defined in Section 10.8 for the duration of the study.

7. Males with female partners of childbearing potential who are not using or willing to use an acceptable method of contraception as defined in Section 10.8. Male subjects should refrain from sperm donation for 90 days after study completion.
8. Receiving hormonal therapy (eg: estrogen, testosterone) for gender reassignment.
9. Current or recent history (within 12 weeks of the Screening Visit) of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, or neurological disease per investigator opinion.
10. Has clinically significant abnormalities on the screening ECG, including long QT (e.g corrected QT interval (QTc) $\geq$ than 480 msec.
11. Is immunocompromised.
12. Has recently (within 4 weeks of screening) received live vaccine(s). Enrolled subjects should not receive live vaccines during the study and for 30 days after study discontinuation.
13. Known history of hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) OR a recent known infection (within 4 weeks of screening) with SARS-CoV-2 (COVID-19).
14. History of malignancy in the previous 5 years except for adequately treated nonmelanoma skin cancers or cervical carcinoma in situ.
15. Recent (within 12 months of screening) history of substance abuse or unwilling to follow protocol restrictions on alcohol consumption (Section 5.3.2).
16. Subject who the investigator believes should not be enrolled for any reason not listed above.

5.3 Lifestyle Considerations

Enrolled subjects should practice good skin hygiene during the screening and treatment periods by limiting bathing/showers (preferably once daily with tepid water and of short duration) and by using mild cleansers and non-sensitizing emollients. Dietary and activity-related restrictions are not required for this study other than limiting alcohol usage. In general subjects should be instructed that if they experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

5.3.1 Use of Cleanser, Moisturizer, and Sunscreen During the Study

Subjects may use their own mild cleanser up to twice daily and bland emollient cream therapy once daily. Site staff should review and confirm the cleanser and emollient are acceptable for use (eg, not mediated) at Screening. Bleach baths are not permitted during the study.

Subjects may apply the approved bland emollient cream therapy to non-involved skin once daily at least 15 minutes after application of investigational product. Emollients should not be used in the 24 hours prior to the Baseline Visit, Day 15, or Day 29.

Sun exposure of treatment areas should be avoided. If the location of the treatment sites makes avoidance of sun exposure not feasible, protective clothing and application of an approved

sunscreen with a sun protection factor (SPF) of at least 15 should be used and should be applied at least 15 minutes after application of study interventions.

Throughout the duration of the study, subjects may use their preferred shampoo and may apply makeup to the face. Cosmetics should be applied at least 15 minutes after study drug application. Makeup should not be used in the 24 hours prior to the Baseline Visit and Day 29 Visit.

5.3.2 Meals and Dietary Restrictions

There are no meal and dietary restrictions for this study other than limiting alcohol usage as follows: no more than 21 drinks/week for males or 14 drinks/week for females (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor).

5.3.3 Activity

Subjects will be instructed not to bathe, swim, or expose treated areas to water and not to engage in vigorous activity for at least 4 hours after investigational product application.

5.4 Screen Failures

Screen failures are defined as subjects 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 subjects 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, medical history, prior therapies, and any serious AE (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with approval of the study medical monitor. Rescreened subjects should be assigned the same subject number as for the initial screening. Informed consent is required before subjects can be rescreened. See Section 10.1.3 for Informed Consent Process details.

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 subject according to the study protocol.

Section 6.3 summarizes instructions for preparation, handling, storage and accountability of study interventions. Refer to the IB for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

6.1 Study Intervention(s) Administered

Intervention Name	TER-101 2.75%	TER-101 Vehicle
Type	Drug	Drug
Dose Formulation	Topical ointment	Topical ointment
Unit Dose Strength(s)	2.75% (w/w)	Not Applicable
Dosing Regimen	Apply a thin film to affected areas twice daily for 28 days	Apply a thin file to affected areas twice daily for 28 days
Route of Administration	Topical application	Topical application
Use	Experimental	Placebo comparator; not distinguishable in appearance from the TER-101 2.75% active ointment
Sourcing	Provided locally by the sponsor/designee	Provided locally by the sponsor/designee
Packaging and Labeling	TER-101 2.75% active ointment will be provided in laminate tubes with a 15 g fill.	TER-101 2.75% ointment vehicle will be provided in laminate tubes with a 15 g fill.
Former Names	ZPL-5212372, PLA-950, WAY-278950, PF-05212372	Not Applicable

6.1.1 Study Treatment Application

TER-101 (2.75% w/w) ointment and ointment vehicle will be applied topically twice a day for 28 days, with at least 8 hours between applications. Subjects will apply sufficient study drug to provide a thin covering. A pea-sized amount (approximately 250 mg) should cover approximately 2% BSA. Additional instructions on application will be provide in the 'Instructions for Use' provided to each subject at randomization.

6.1.2 Excluded Treatments, and/or Procedures During Study Period

Excluded treatments include those that are noted in the exclusion criteria (Section 5.2) or noted in the washout criteria (Section 10.9). Subjects should not receive live vaccines during the study or for 30 days after the last dose of investigational product.

6.2 Dose Modification

If a subject develops severe local application site adverse effects or a total skin tolerability score > 7, treatment will be held at that treatment site until the local AE resolves or skin tolerability score returns to baseline. The subject may then reinitiate application of study drug once daily to that site. Any interruptions in study treatment will be recorded, as well as the discontinuation date, restart date, and reason for discontinuation. The reason for discontinuation will also be recorded as an AE (See Section 8.3 for additional information on AEs and SAEs). If the subject continues to experience signs and symptoms of treatment-related AEs, and the discomfort is

intolerable and continues despite decreased frequency of study treatment application, then the study treatment may be discontinued completely, at which time the subject will be discontinued from the treatment period (Day 1 to Day 29). See Section 7 for additional information on discontinuation of study intervention.

6.3 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Subjects should be instructed to store the drug at room temperature and not to leave the study drug in a vehicle. Study drug may be transported with temperature excursions beyond storage conditions. Further instructions on storage will be provided to the subject in the 'Instructions for Use' provided at the Baseline visit.
3. Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Randomization

Study Using Precoded Randomization Provided to Site

On Day 1 (Baseline Visit), subjects will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the subject's assignment to receive study interventions, either TER-101 2.75% ointment or ointment vehicle according to the randomization schedule generated prior to the study by the Statistics Department at sponsor's designee. Each subject will be dispensed blinded study interventions, labeled with his/her unique randomization number, throughout the study.

6.4.2 Blinding

Application of the TER-101 2.75% ointment and ointment vehicle will be randomized and blinded to both the subject and the investigator.

Blind break

In case of an emergency, where knowledge of the treatment assignment could influence the subject's care, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject 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 subject's treatment assignment unless this could delay emergency treatment of the subject. The procedure for breaking the blind will be detailed in the clinical trial study manual. If a subject's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

If more than 2 of the first 6 subjects enrolled develop an AE including application site reactions requiring cessation of treatment, then the sponsor's Chief Medical Officer (CMO)/designee may be unblinded as to treatment assignment. The determination to unblind will be made by the CMO/designee and will take into account the number of subjects with such reactions and their severity. The CMO/designee will determine whether to: (a) continue enrollment; (b) modify the regimen to once daily; or (c) terminate the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been performed accurately.

6.5 Study Intervention Compliance

When subjects self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by subject e-diaries and during the site visits and documented in the source documents and electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

If subject is demonstrating nonadherence with study drug application (see Section 8.3.5), adherence/compliance should be reinforced with the subject. If continued nonadherence is demonstrated at the next assessment, then the subject should be considered for discontinuation from the study as per Section 7.1 after discussion with the medical monitor.

A record of the number and weight of the medication tubes dispensed to and applied by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the eCRF.

6.6 Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

In addition, therapies utilized for AD in the 6 months prior to screening should also be captured in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. Please see Section 10.9 for excluded therapies for AD.

Acetaminophen, at doses of ≤ 2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered case-by-case by the investigator in consultation with the medical monitor.

6.6.1 Rescue Medication

Use of rescue medication is not permitted in this study. Any subject requiring rescue therapy per investigator opinion should undergo the early termination visit consisting of the Day 29 assessments and be withdrawn from the study prior to receiving rescue therapy.

6.7 Intervention After the End of the Study

The Sponsor will not provide any additional treatments to subjects after they complete or discontinue the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study drug treatment. If a subject discontinues study treatment due to reasons such as tolerability, other AEs, or other reasons, every attempt should be made for the subject to complete an early termination visit consisting of the Day 29 assessments. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Reasons for removal from study intervention include any of the following:

- AEs.
- Pregnancy (see Section 10.8 and Section 8.4.5).
- Disease-state criteria (eg, progressive disease that requires discontinuation of the study intervention)
- Protocol deviation
  - Noncompliance with study protocol

  - Requires treatment not allowed in the protocol for disease flare/rescue.
  - If the subject meets an exclusion criterion (either newly developed or not previously recognized) that poses a safety risk and precludes further study participation
- Sponsor decision.
- Subject request to discontinue study intervention or withdraws from the study (See Section 7.2). If subject request to withdraw is due to an AE or lack of efficacy, then AE or disease-state criteria, respectively, should be the reported reason for discontinuation.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Discontinuation/Withdrawal from the Study

A subject 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 termination visit should be conducted, as shown in the SoA (Table 1). If a subject discontinues or withdraws from the study due to reasons such as tolerability, other AEs, or other reasons, every attempt should be made for the subject to complete an early termination visit consisting of the Day 29 assessments. See SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The subject will be permanently discontinued both from the study intervention and from the study at that time.

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

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 phone or video calls and, if

necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject 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 in Section 10.1.9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Severe, clinically significant safety concerns should be discussed with the sponsor or designee immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the informed consent/assent forms may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- In person visits are the preferred approach to the study visits where in person evaluation is designated per the SoA; however, due to COVID-19, a virtual visit or home health visit may need to be performed. The Screening and Baseline Visits are not permitted to be conducted virtually. The medical monitor should be contacted to provide approval for a virtual visit(s) to be conducted instead of an in person (or home health visit, if arranged) visit. This permission should be documented and obtained prior to the visit(s). In case of a virtual visit, assessments should be completed over video, and the subject should submit photographs of areas of involvement to the site if possible. The conduct of a virtual or home health visit instead of in person visit should be captured in the eCRF.
- If necessary, arrangements may be made for subjects to return study drug by alternative methods, eg, mail, courier.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

A properly executed, written, informed consent will be obtained from each subject or subject's parent/guardian (for adolescents) and assent (for adolescents) prior to entering the study. Information will be given in both oral and written form and subjects must be given ample

opportunity to inquire about the details of the study. The inclusion and exclusion criteria will be reviewed to assess subject eligibility.

8.1.1.1 Demography

Subjects' demographic information including age, sex (gender assigned at birth), birthdate, race, and ethnicity will be collected at the Screening Visit.

8.1.1.2 Medical History

Subjects will be asked about their medical history at the Screening Visit and Baseline Visit (Day 1) to determine eligibility and safe participation in the study.

8.1.1.3 Atopic Dermatitis History

Subjects will be asked about their AD history at the Screening Visit and Baseline Visit, including approximate date of diagnosis and prior therapies for AD in the last 6 months. Subjects will be asked about current and recent prior medications. The medication name, dosing, frequency, route, start and stop dates, and indication will be recorded at the Screening Visit. Any changes in concomitant medications throughout the duration of the study will be noted.

8.1.2 Treatment Period

The treatment period begins on Day 1 when the first dose of TER-101 2.75% ointment or ointment vehicle is topically administered to a subject.

8.2 Efficacy Assessments

The below assessments will be used to assess overall AD disease severity. Planned time points for all overall baseline AD severity assessments are provided in the SoA (Table 1). Additional information on these instruments may be found at the Harmonizing Outcome Measures for Eczema website (http://www.homeforeczema.org/).

8.2.1 Investigator Global Assessment

The IGA is a 5-point scale that provides a global clinical assessment of overall AD severity based on an ordinal scale. The assessment is static, meaning that the evaluation is done without reference to any other time point.

0 = Clear: minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting.

1 = Almost clear: trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting.

2 = Mild: faint pink erythema with mild induration/papulation and no oozing/crusting.

3 = Moderate: pink-red erythema with moderate induration/papulation with or without oozing/crusting.

4 = Severe: deep or bright red erythema with severe induration/papulation and with oozing/crusting.

8.2.2 Eczema Area Severity Index

The EASI is a scoring system that measures 4 clinical signs, the extent of BSA involved, over 4 separate areas (head/neck, trunk, upper extremities, and lower extremities). Total EASI scores range from 0 to 72.

The 4 clinical signs are:

- Erythema
- Induration/papulation
- Excoriation
- Lichenification

And each feature is graded for each region on a 4-point severity scale of 0 to 3, as below, with:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

The investigator or qualified assessor will enter the value for erythema, induration/papulation, excoriation and lichenification and extent of BSA for each region on the eCRF page. The EASI score will be calculated by the sponsor/designee. See Appendix 6 (Section 10.6).

8.2.3 Total Body Surface Area

The TBSA involved with AD will be determined. The subject's palm and fingers with fingers together represent approximately 1% of the TBSA.

8.2.4 Itch Numeric Rating Scale

The WI-NRS asks subjects to report their worst itch (maximal intensity) during the last 24 hours on an 11-point NRS, ranging from 0 = "no itch at all" to 10 = "worst itch you can imagine". This will be recorded by the subjects daily in the e-diary.

8.2.5 Photographs

Standardized photographs of up to 4 representative areas will be obtained at Baseline, Day 15, and Day 29. The areas photographed at baseline will be photographed on Day 15, Day 29. Details regarding photography will be supplied in the Study Reference Manual.

8.3 Safety Assessments

Safety assessments will include the following:

- Monitoring and recording of all reported AEs.
- Physical examinations, including height and body weight measurements.
- Periodic measurement of vital signs.
- ECG.
- Assessment of local tolerability.
- Clinical laboratory tests.
- Urine pregnancy tests.

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.3.1 Physical Examination, Height, and Body Weight

A physical examination including a thorough skin examination will be conducted by the investigator at the Screening and Baseline Visits to ensure that the subject does not have conditions that would interfere with participation in the study.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal systems. Height and body weight will also be measured and recorded at Screening. Physical examinations will only be performed at the indicated visits per the SoA. For all other visits during the study, physical examinations will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical examinations after baseline will be reported as AEs; prior to baseline, they will be reported as interval history.

8.3.2 Vital Signs

At in person visits at screening, baseline, Day 15, and Day 29, vital signs will be collected.

- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure, pulse measurements, and temperature (to be taken before blood collection for laboratory tests) are strongly recommended to be preceded by at least 5 minutes of rest with the subject in a quiet setting without distractions (eg, television, cell phones).

8.3.3 Electrocardiogram

At screening and Day 29/EOT, a single 12-lead ECG with the subject in a supine position will be performed. The ECG is strongly recommended to be preceded by at least 10 minutes of rest with

the subject in a quiet setting without distractions (eg, television, cell phones) and before any blood sampling procedures.

8.3.4 Local Tolerability

At baseline and visits on Days 15 and 29, the investigator will assess erythema at the application sites. In addition, at baseline and visits on Days 15 and 29, subjects will be asked about any symptoms (pruritus, burning/stinging) following the last study drug application (see SoA, Table 1). Each feature will be scored from 0 to 3 as per the table in Section 10.7. Care should be made as much as possible to distinguish local tolerability findings from the underlying AD.

8.3.5 Adherence to Study Agent

Adherence with twice daily application of the study agents will be monitored using an e-diary in which the subject will record date and time of application. The e-diary will be dispensed at the Baseline Visit and collected and reviewed at each visit. Adherence will also be monitored by weighing the medication tubes at the Baseline Visit prior to dispensing the study medication to the subject, and at in person visits on Day 15 and Day 29. If the subject has missed more than 2 or more doses in a 7-day period due to reasons related to noncompliance, then study staff will re-emphasize the importance of medication adherence. If the subject continues to consistently miss doses, other than for treatment hold due to local application site or tolerability concerns as described in Section 6.2, then the sponsor should be notified, and the investigator and sponsor may consider discontinuing the subject for noncompliance, as per Section 7.1. Subjects should also be queried by site staff at in person visits that the investigational product is being applied correctly.

8.3.6 Clinical Safety Laboratory Assessments

- See Section 10.2 and the laboratory manual for the clinical laboratory tests to be performed and to the SoA (Table 1) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record in the AE section of the eCRF any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.4 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

AE(s) will be reported by the subject.

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 for following up on any AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study (see Section 7). Note that lack of efficacy of the investigational therapy should not be considered an AE.

AEs related to the skin should clearly be designated if related to underlying condition and if related to the application site in the eCRF.

8.4.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

AEs or SAEs occurring in the 30-day period following the last dose of investigational product should be reported, regardless of causality. SAEs occurring after this 30-day period should be reported only if considered related to investigational product or a study-related procedure.

SAEs will be collected from the signing of the informed consent form (ICF) until the end of treatment at the time points specified in the SoA (Table 1).

Medical occurrences that begin before the start of study intervention but after obtaining ICF will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section, unless related to a study specific procedure.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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, IRB, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate, according to local requirements.

8.4.5 Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study intervention and at all other timepoints specified in the SoA (Table 1).
- 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 Section 10.8.
- Pregnancy itself is not considered an AE, but if the study drug is suspected of causing contraceptive failure then contraceptive failure should be recorded as an AE.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Sexually active males and females must use appropriate contraception as indicated in Section 10.8. The use of contraception are strongly recommended to be discussed at each visit.

8.4.6 Adverse Events of Special Interest

There are no AEs of special interest for this study.

8.5 Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose; however, any skin to which study drug was applied should be thoroughly washed with cleanser and water to remove any drug remaining on the skin. Treatment of overdose should consist of general supportive measures.

In the event of a suspected overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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 subject.

8.6 Pharmacokinetics

Blood draws for PK evaluation should be done at least 4 hours after last study drug application in accordance with the SoA (Table 1). The date, time of last application should be recorded on eCRF page.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economic parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis(es)

Hypothesis tests will be undertaken to evaluate whether the drug's effect is superior to the vehicle control. Statistical analyses will be exploratory to assess the drug's activity and potential for further study.

Efficacy endpoints will be assessed by statistical comparison of TER-101 (2.75% w/w) ointment vs. vehicle; 2-sided p-values will be presented, together with the estimate of the treatment effect and 95% confidence limits.

9.2 Sample Size Determination

The sample size is based on a clinical rather than statistical rationale. Approximately 60 subjects are planned to be enrolled and randomized, considering a potential 15% drop-out rate, to yield approximately 50 subjects completing the study.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy analysis set (ES)	All randomized subjects who receive at least 1 application of the study treatment and have at least 1 post-baseline efficacy assessment.
Per protocol efficacy analysis set (PPES)	All subjects in ES without major protocol deviations.
Safety analysis set (SS)	All randomized subjects who receive at least 1 application of the study treatment.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including the primary endpoint.

Efficacy endpoints will be analyzed using the ES.

In addition, the primary efficacy endpoint will be analyzed using the PPES. Major protocol deviations leading to exclusion of efficacy data from the PPES (eg, due to inclusion or exclusion criteria violations, study treatment compliance and use of nonpermitted medication) will be identified and documented before database lock and unblinding.

Safety will be analyzed using the SS.

9.4.1 General Considerations

Disposition, analysis populations, demography, baseline characteristics, medical history, and concomitant medication data will be summarized overall and by treatment, where applicable.

Efficacy endpoints will be summarized by treatment and visit. For the efficacy endpoints that are collected longitudinally, a last observation analysis will be performed by carrying forward the last post-baseline assessment. These last observation carried forward (LOCF) analyses guarantee the maximum number of randomized patients who were assessed post-baseline will be included in the analyses. In addition, for continuous efficacy endpoints, mixed effect model repeated measures (MMRM) analyses will be performed to mitigate the impact of missing data, which will be assumed to be missing at random during the study. Continuous and score data will be summarized using descriptive statistics (eg, mean and standard deviation or standard error). Categorical and dichotomous data will be summarized using frequency tables (counts and percentages).

9.4.2 Primary Efficacy Endpoint

- Percent change in EASI from baseline at Day 29

9.4.3 Secondary Efficacy Endpoints

- Percent change in EASI from baseline over time
- Percent change in individual components of EASI (erythema, induration/papulation, excoriation, lichenification) and by region (head, trunk, upper extremity, lower extremity) from baseline over time
- EASI-75, EASI-50 responder analysis over time
- Absolute change in EASI from baseline over time
- Change in IGA from baseline over time
- Change from baseline WI-NRS at Days 15, 29 (WI-NRS captured on e-diary daily)
- Responder analysis: Reduction of ≥ 3 in subjects with baseline WI-NRS ≥ 4
- Change in TBSA affected from baseline over time

9.4.4 Safety Endpoints

- Safety: TEAEs, SAEs, change from baseline in vital signs, ECGs, and laboratory assessments
- Tolerability: Scored by investigator at baseline, post-baseline visits on 4-point scale (0 = none; 3 = severe) to include subscores for erythema, burning/stinging, pruritus.

9.4.5 PK Endpoints

- Summary of trough plasma TER-101 levels on Days 15, 29 in TER-101 treated subjects

9.4.6 Efficacy Analyses

The primary endpoint (percent change from baseline in EASI total score) will be analyzed using a mixed model for repeated measures (MMRM). The model will include fixed effect for study treatment (TER-101 2.75%, vehicle), visit day (Day 15, Day 29), and treatment-by-visit interaction, with visit as the repeating factor, subject as a random effect, and baseline score as a covariate. The treatment p-value (TER-101 2.75% vs. vehicle), treatment difference, and 95% confidence limits from the model will be presented for the percent change from baseline in EASI at Day 29. Sensitivity analyses will include analysis of covariance (ANCOVA) at each timepoint. The impact of dropouts and missing data on results for the primary endpoint will be explored using the last value carried forward (LOCF) and multiple imputation methods, as appropriate.

Secondary efficacy endpoints that are continuous variables (percent change from baseline in EASI component scores, absolute change from baseline in EASI, IGA, TBSA, and WI-NRS) will also be analyzed using the MMRM model, as described above. In each case, the treatment p-value (TER-101 2.75% vs. vehicle), treatment difference, and 95% confidence limits from the model, will be presented.

The effect of treatment on response rates (75% reduction in EAI Score [EASI-75], 50% reduction in EASI scores [EASI-50]) at each visit will be evaluated using a logistic generalized linear mixed model (GLMM) for binary data, with fixed effect for treatment, visit and treatment-by-visit interaction. The treatment p-value (TER-101 2.75% vs. vehicle), treatment odds ratio, and 95% confidence limits from the model, will be presented. [Note: In the event of model non-convergence, the response proportions will be analyzed using the Cochran-Mantel-Haenszel test, stratified by baseline IGA.] The proportion of WI-NRS responders (defined by a reduction of ≥ 3 in subjects with baseline WI-NRS ≥ 4) will be analyzed using a chi-square test.

Time to onset of response (EASI 75, EASI-50) will be estimated using the Kaplan-Meier method, with treatment comparisons based on the logrank test. Subjects who do not achieve response criteria will be censored on the day of last assessment.

Given the exploratory nature of this study, p-values from all significance tests will be reported without adjustment for multiplicity.

Descriptive statistics will include line graphs of % change from baseline in EASI scores and bar charts of response rates at each time point, to describe the effect of treatment over time.

9.4.7 Safety Analyses

The number and percentage of subjects reporting local tolerability symptoms will be summarized by treatment.

The number and percentage of subjects reporting TEAEs, coded using the Medical Dictionary for Regulatory Activities, will be summarized by treatment, by treatment related, and by maximum severity. TEAEs leading to discontinuation from study treatment or study and serious TEAEs will be summarized, with more details provided in a subject listing.

Changes from baseline in laboratory measurements, ECGs, and vital signs will be summarized by visit.

9.4.8 Other Analyses

No analysis by subgroups are planned.

9.5 Interim Analyses

No interim analyses are planned.

9.6 Data Monitoring Committee

A safety monitoring committee will not be established.

9.7 Handling of Missing Data

All possible efforts will be made to ensure that subjects complete study treatments and all the required assessments. However, in the rare case of subjects discontinuing from study treatment or discontinuing from the study, all attempts will be made to perform all efficacy and safety assessments at the time of discontinuing study treatment or study in order to minimize missing data.

The number of subjects with missing efficacy data at Day 15 and Day 29 visits will be presented as missing for TER-101 or vehicle, together with a summary of the reasons for the missing data. Missing efficacy data will be classified as missing at random (not informative) or missing not at random (informative eg, due to treatment-related discontinuation such as lack of efficacy or an AE), and documented prior to database lock and unblinding.

As missing efficacy data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies will be applied to provide a balanced assessment of treatment efficacy. The handling of missing data, including consideration of imputing values for missing data, for each efficacy endpoint and sensitivity analyses will be detailed in the SAP prior to the study database lock and unblinding.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent (ICF) and assent forms, Investigator Brochure (IB), and other relevant documents (eg, instructions for use, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB) by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events (SAEs) or other significant safety findings as required by IRB/procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and subinvestigators 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 and Assent Process

- An initial sample ICF and assent form will be provided for the investigator to prepare the informed consent and assent documents to be used at his or her site. Updates to the sample ICF/assent are to be communicated formally in writing from the sponsor Trial Manager to the investigator. The written ICF/assent form is to be prepared in the language(s) of the potential patient population.
- The investigator or his/her representative will explain the nature of the study to the subject and/or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative 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 or study center. Adolescent subjects will be required to sign a statement of assent.
- The medical record must include a statement that written informed consent (and assent, where applicable) was obtained before the subject was enrolled in the study and the date the written consent (and assent, where applicable) was obtained. The authorized person obtaining the informed consent must also sign the ICF and assent form, where applicable.
- Subjects or their legally authorized representatives must provide reconsent to the most current version of the ICF(s) during their participation in the study. Similarly, minors must also provide assent to the most current version of the assent form(s) during their participation in the study.
- The original signed ICF and assent form, as applicable, are to be retained in accordance with institutional policy, and a copy of the ICF(s) (and assent form[s] as applicable) must be provided to the subject or the subject's legally authorized representative.
- The investigator is also responsible for asking the subject or legally authorized representative if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator will then inform the primary care physician. If the subject/legally authorized representative agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

Subjects or their legally authorized representatives who are rescreened are required to sign a new ICF, and adolescents that are rescreened will be required to sign a new assent form.

10.1.4 Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

- The subject 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 subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject 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 members, and by inspectors from regulatory authorities.
- The investigator must ensure that the subject's confidentiality is maintained for documents submitted to sponsor.
- For SAEs reported to sponsor, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).
- Documents that are not submitted to sponsor (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.
- In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.
- The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study related records, including personal information.

10.1.5 Committees Structure

10.1.6 Dissemination of Clinical Study Data

The sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations. The sponsor will designate one or more of the participating investigators to be the signatory on the study report, along with the sponsor, and the sponsor will follow all applicable local regulations pertaining to study report signatories.

10.1.7 Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic case report forms (eCRFs) 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 eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies, and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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 a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the United States Food and Drug Administration (FDA) is notified 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. All subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, medical practice, or local regulations.
- In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from sponsor's Global Research and Development Compliance, and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct, and compliance with the protocol, ICH GCP, and applicable regulatory requirements.
- Retention of study documents will be governed by the Clinical Trial Agreement.
- All written information and other material to be used by subjects and investigative staff must use vocabulary, and language that are clearly understood.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the subject 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 Study Manual (eg, Site Trial Binder, other site communication).

10.1.9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

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, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

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

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the subject and must ensure appropriate subject therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally 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 will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11 Coronavirus Disease 2019 (COVID-19) and Other Public Health Emergencies

The FDA has issued guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity during the COVID-19 public health emergency.

It is recognized that the COVID-19 public health emergency may impact the conduct of clinical trials. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Protocol modifications may be required, and there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures.

Teres Bio, or its affiliated CROs, representatives, and clinical sites may need to make decisions regarding continuing trial recruitment, continuing use of the investigational product for subjects already participating in the trial, and the need to change subject monitoring during the trial. Teres Bio acknowledges that it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them. Teres Bio, following consultation with clinical investigators and IRBs, may determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. In addition, home health services may be utilized in this study per FDA guidance to enable patients to remain on study and have testing performed per the protocol.

It is generally Teres Bios' practice to implement protocol changes only after review and approval by the IRB, and in some cases, by FDA. Teres Bio or its affiliated CROs and clinical investigators will engage with IRBs as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Such changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (eg, to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the investigational new drug (IND), but will be reported afterwards.

These considerations are intended to remain in effect only for the duration of the public health emergency related to COVID-19.

10.2 Appendix 2: Clinical Laboratory Tests

- All study-required laboratory assessments as detailed in Table 2 and the laboratory manual will be performed by a local laboratory, and confirmation of review of the results must be entered into the electronic case report form (eCRF).
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2. Protocol-required Laboratory Assessments

Central Laboratory Hematology	Central Laboratory Clinical Chemistry	Central Laboratory Urinalysis
Complete blood count (CBC) with differential	Chemistry panel (includes liver function tests)	Dipstick urinalysis Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	Follicle stimulating hormone (as needed to confirm menopausal status for women of nonchildbearing potential only). Highly sensitive urine human chorionic gonadotropin (hCG) urine pregnancy test (as needed for women of childbearing potential).[a]	
All study-required laboratory assessments will be performed by a local laboratory.		

eCRF = electronic case report form.
[a]Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

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 Adverse Event

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a subject or clinical study subject, 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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiology scans, vital sign 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. • Any new condition 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/serious adverse event (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 an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject'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 subject'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 Serious Adverse Event

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).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. **Results in death**
b. **Immediately life threatening** The term 'life threatening' in the definition of 'serious' refers to an event in which the subject 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 subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. **Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. **Is a congenital anomaly/birth defect**
f. **Other medically important serious event:** 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- 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 electronic case report form (eCRF).
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to sponsor.
- 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.
- The investigator must assign the following AE attributes:
    - AE diagnosis or syndrome(s), if known (if not known, signs or symptoms).
    - Dates of onset and resolution (if resolved).
    - Intensity (or toxicity defined below).
    - Assessment of relatedness to investigational product, other protocol-required therapies; and
    - Action taken.

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 subject, 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. The AEs must be characterized as related or unrelated. See Section 10.4 for a two-level definition of causality rating.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that 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 sponsor. However, the sponsor suggests that the investigator assesses causality for every event before the initial transmission of the SAE data to sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory 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 sponsor 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 subject dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any post mortem findings available including histopathology. • New or updated information will be recorded in the originally completed eCRF. • 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 via an Electronic Data Collection Tool
• The primary mechanism for initially reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool 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. • Further details related to SAE reporting including Contact Information will be found in the Study Manual.

10.4 Appendix 4: Definition of Causality Rating

Related	A clinical event, including laboratory test abnormality, which occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge)[a] should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals)

[a]Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).
[b]Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific subject in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur (negative rechallenge).

10.5 Appendix 5: Hanifin and Rajka Diagnostic Criteria for Atopic Dermatitis

Major criteria
Must have 3 or more of: 1. Pruritus 2. Typical morphology and distribution 3. Flexural lichenification or linearity in adults 4. Facial and extensor involvement in infants and children 5. Chronic or chronically relapsing dermatitis 6. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Minor criteria
Should have 3 or more of: 1. Xerosis 2. Ichthyosis, palmar hyperlinearity, or keratosis pilaris 3. Immediate (type 1) skin-test reactivity 4. Raised serum immunoglobulin E (IgE) 5. Early age of onset 6. Tendency toward cutaneous infections (especially *S. aureus* and herpes simplex) or impaired cell-mediated immunity 7. Tendency toward non-specific hand or foot dermatitis 8. Nipple eczema 9. Cheilitis 10. Recurrent conjunctivitis 11. Dennie-Morgan infraorbital fold 12. Keratoconus 13. Anterior subcapsular cataracts 14. Orbital darkening 15. Facial pallor or facial erythema 16. Pityriasis alba 17. Anterior neck folds 18. Itch when sweating 19. Intolerance to wool and lipid solvents 20. Perifollicular accentuation 21. Food intolerance 22. Course influenced by environmental or emotional factors 23. White dermographism or delayed blanch

10.6 Appendix 6: EASI Score

Eczema Area and Severity Index (EASI) case report form - age≥8 years

Area of Involvement: Each body region has potentially 100% involvement. Score 0 to 6 based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

Scoring table:

Body region	Erythema (0-3)		Edema/ Papulation (0-3)		Excoriation (0-3)		Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(	+	+	+	+	)		x	X 0.1	
Trunk	(	+	+	+	+	)		x	X 0.3	
Upper extremities	(	+	+	+	+	)		x	X 0.2	
Lower extremities	(	+	+	+	+	)		x	X 0.4	
The final EASI score is the sum of the 4 region scores:										_____ (0-72)

10.7 Appendix 7: Local Tolerability

The investigator will assess local tolerability by inspecting the application sites for application site erythema and query the subject as to symptoms of burning/stinging or pruritus associated with study drug application. The local tolerability assessment will be conducted at baseline pre-dose and approximately 15 minutes after the first dose, Day 15, and Day 29. The investigator should score the in individual components of burning/stinging, pruritus, and erythema based on the average for score of all application sites.

Grade	Burning/Stinging	Pruritus	Erythema
0 (none)	No stinging/burning	No pruritus	No detectable erythema, skin of normal color
1 (mild)	Slight warm, tingling sensation, not really bothersome	Occasional, slight itching/scratching	Skin pinkness present
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome	Constant or intermittent itching/scratching which is not disturbing sleep	Definite redness, easily recognized
3 (severe)	Hot, tingling/stinging sensation	Bothersome	Intense redness

10.8 Appendix 8: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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.

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

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

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 tubal ligation at least 1 year prior to Screening with no pregnancy since the procedure.
   - Documented bilateral oophorectomy.
3. Postmenopausal female.
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A documented high follicle stimulating hormone (FSH) level in the postmenopausal range, either historically or obtained at screening, may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Subjects

1. Male subjects with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol-defined time frame in Section 5.2:
   - Are abstinent from penile vaginal intercourse and agree to remain abstinent for duration of study and for 3 months after the final study treatment dose.
   - Agree to use a male condom and have their partner use a contraceptive method with a failure rate of < 1% per year described in the table below when having penile vaginal intercourse with a female.
2. In addition, male subjects must refrain from donating sperm for the duration of the study and for 3 months after the last dose of the study treatment.
3. Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female Subjects

WOCBP are eligible to participate if they practice abstinence or agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < % per year when used consistently and correctly*
Sexual Abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. Periodic abstinence, eg, rhythm or withdrawal methods, is not an acceptable form of contraception for this study.
Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[b]: • Oral. • Vaginal. • Transdermal.
Progesterone only hormone contraception associated with inhibition of ovulation[b]. • Oral. • Injectable. • Implantable.
Intrauterine device (IUD). Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized Partner A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

[a]Failure rates may differ from those reported when contraception is used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
[b]It is unknown whether hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Females must either practice abstinence from heterosexual contact or use one of the highly effective contraceptive options described. Females are not required to use two of the highly effective methods of contraception.

Pregnancy Testing

Urine pregnancy testing is required to be performed at the times shown in the SoA (Table 1) for all female subjects at screening at subsequent assessments in females who are considered WOCBP. Urine pregnancy tests may be performed more frequently as required by local regulations.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed informed consent form (ICF) from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form

and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow -up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event (SAE) and will be reported as such.
- Any post-study pregnancy-related serious adverse event (SAE) considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4 and Section 8.4.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.9 Appendix 9: Excluded Medications

Excluded medications are listed in the below table; these are excluded from use as per the indicated duration prior to Baseline and for the duration of the study.

Within 1 week prior to Baseline	Topical corticosteroids (TCS)
Within 2 weeks prior to Baseline	Topical agents including topical calcineurin inhibitors (TCIs), topical antibiotics, and crisaborole. Initiation of antihistamines or tricyclic antidepressants[a] Complementary and alternative medications including St. John's Wort, cannabidiol. Potent inducers or inhibitors of CYP3A4 (Appendix 10, Section 10.10).
Within 4 weeks prior to Baseline	Artificial or natural phototherapy (eg, narrowband or broadband ultraviolet B, excimer laser, ultraviolet A, or psoralen + ultraviolet A, a deliberate sun tanning, use of tanning booth). Systemic immunosuppressive therapy including, but not limited to, systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil.[b] Any nonbiological agent: 4 weeks or 5 half-lives, whichever is longer
Within 12 weeks prior to Baseline	Biologic agents including dupilumab. Any biological investigational product/agent: 12 weeks or 5 half-lives, whichever is longer

Note: Short courses (up to 14 days) of systemic antibiotics may be used post-baseline to treat infections such as impetigo or cellulitis but are not permitted to be used for the treatment of AD. Bleach baths are prohibited during the study.

[a]Antihistamines and tricyclic antidepressants may be used if the subject was on a steady dose prior to screening (Section 5.2) for the duration of the study.

[b]Systemic corticosteroids or immunosuppressive drugs for any purpose other than nasal, ophthalmic, or inhaled corticosteroids for indications such as rhinitis, allergic conjunctivitis, or asthma/chronic obstructive pulmonary disease.

10.10 Appendix 10: Drugs that Inhibit or Induce CYP3A4

Strong Inhibitor	Strong Inducers
Atazanavir	Apalutamide
Ceritinib	Carbamazepine
Clarithromycin	Enzalutamide
Cobicistat and cobicistat-containing coformulations	Fosphenytoin
Darunavir	Lumacaftor
Idelalisib	Lumacaftor-ivacaftor
Indinavir	Mitotane
Itraconazole	Phenobarbital
Ketoconazole	Phenytoin
Lopinavir	Primidone
Mifepristone	Rifampin (rifampicin)
Nefazodone	
Nelfinavir	
Ombitasvir-paritaprevir-ritonavir	
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	
Posaconazole	
Ritonavir and ritonavir-containing coformulations	
Saquinavir	
Telithromycin	
Tucatinib	
Voriconazole	

10.11 Appendix 11: Abbreviations

AD	Atopic dermatitis
AE	Adverse event
BSA	Body surface area
CFR	Code of Federal Regulation
CBD	Cannabidiol
CIOMS	Council for International Organizations of Medical Sciences
CMO	Chief Medical Officer
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CYP3A4	Cytochrome P450 3A4
$cPLA_2\alpha$	Cytosolic phospholipase A2α
e-diary	Electronic diary
EASI	Eczema Area and Severity Index
EASI-50/75	50 or 75% reduction in EASI score from baseline
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of trial
ES	Efficacy analysis set
ETV	Early termination visit
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLMM	Generalized linear mixed model
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IGA	Investigator Global Assessment
LOCF	Last observation carried forward

MMRM	Mixed model for repeated measure
NRS	Numeric rating scale
OTC	Over the counter
PDE4	Phosphodiesterase 4
PEG	Polyethylene glycol
PK	Pharmacokinetics
PPES	Per protocol efficacy analysis set
PUVA	Psoralens + ultraviolet A
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SS	Safety analysis set
TBSA	Total body surface area
TC	Topical corticosteroid
TCI	Topical calcineurin inhibitor
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
UVB	Ultraviolet B
WI-NRS	Worst-itch numeric rating scale
WOCBP	Woman of childbearing potential
w/w	Weight for weight

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