16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

Protocol Number: TER101-AD-201

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

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STATISTICAL ANALYSIS PLAN - TEXT

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Protocol: **TER101-AD-201**
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List of Abbreviations

Abbreviations/Acronyms

AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BID	twice daily
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CRF	case report form
CV	coefficient of variation
EASI	eczema area and severity index
ECG	electrocardiogram
ES	efficacy analysis set
GLMM	generalized linear mixed model
IGA	investigator global assessment
KM	Kaplan-Meier
LE	lower extremities
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics

Abbreviations/Acronyms

PKS	pharmacokinetics analysis set
PPES	per protocol efficacy analysis set
PT	preferred term
SAE	serious adverse event
Std Dev	standard deviation
SOC	system organ class
SS	safety analysis set
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TBSA	total body surface area
UE	upper extremities
VS	vital signs
WI-NRS	worst itch numeric rating scale
w/w	weight for weight

1 STUDY OBJECTIVES AND SAMPLE SIZE RATIONALE

1.1 STUDY OBJECTIVES

TER-101 is a cytosolic phospholipase A2 alpha (cPLA2α) inhibitor currently in development for the treatment of inflammatory skin diseases, including atopic dermatitis (AD). This Phase 2a study is to 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. Primary and Secondary Objectives are summarized below.

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 EASI 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.

1.2 SAMPLE SIZE

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.

1.3 UNBLINDING

After all subjects complete the end of treatment visit, the database will be locked and unblinded for statistical analysis of topline results while awaiting completion of 30-day post-treatment period for all subjects. Topline summaries will be provided to the sponsor's Chief Medical Officer for planning future drug development strategies, with no impact on this study's conduct. Subject level unblinded results will not be disclosed to study subjects, investigators, or TrialSpark project team members until 30 days after the last visit of the last subjects to collect reported adverse events (AEs).

2 STUDY DESIGN SUMMARY

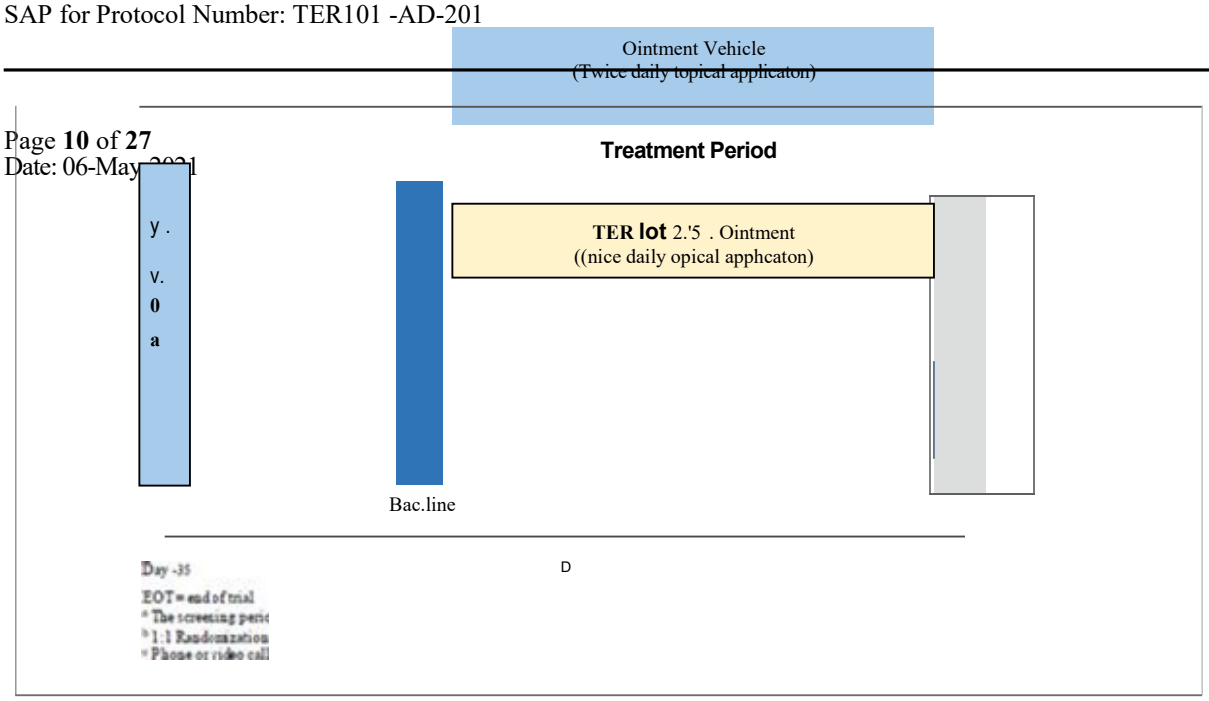
This is a Phase 2a, randomized, double-blind, vehicle-controlled study assessing efficacy, safety, and local tolerability of TER-101 (2.75% w/w) ointment vs. its ointment vehicle topically twice daily in adolescent and adult subjects (age 12 - 65) subjects with mild to moderate AD.

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.

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.

2.1 VISITS

Study schema is as below:


Ointment Vehicle
(Twice daily topical applicaton)
Treatment Period
y .
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TER lot 2.'5 . Ointment
((nice daily opical apphcaton)
Bac.line
D
Day -35
EOT = end of trial

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 (phone) ±3 days**	**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 assessment	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 (phone) ±3 days**	**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.

2.2 SUBJECTS

2.2.1 Number of Subjects

Approximately 60 adolescent and adult subjects (age 12 – 65) with mild to moderate AD will be enrolled across approximately 12 clinical research sites in the United States.

2.2.2 Diagnosis and Main Criteria for Inclusion

Adolescent or adult subjects aged 12 – 65 years are eligible for the study if they have a diagnosis of AD with disease duration of at least 6 months and no change in treatment or severity for at least 4 weeks prior to screening.

At baseline, subjects must have an overall IGA score of 2 (mild) or 3 (moderate) on a 5-point Investigator Global Assessment (IGA) scale, Eczema Area and Severity Index (EASI) score ≥ 5, and total body surface area (TBSA) affected of between 2 and 30%.

2.2.3 Study Population Characteristics

Subjects with a clinical diagnosis of AD who meet all the inclusion criteria and none of the exclusion criteria will be eligible to enroll in the study. Detailed inclusion and exclusion criteria are provided in the protocol (see protocol sections 5.1 and 5.2).

2.2.4 Replacement Subjects

No replacement of subjects is allowed for the study.

2.3 TREATMENT AND RANDOMIZATION

2.3.1 Study Medications, Treatment, and Mode of Administration

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% body surface area (BSA). Additional instructions on application will be provide in the ‘Instructions for Use’ provided to each subject at randomization.

2.3.2 Randomization

Qualified subjects will be randomly assigned (1:1) to two treatment groups: TER-101 2.75% ointment or vehicle ointment. Blinded study drug will be dispensed on Day 1 (Baseline Visit).

2.3.3 Administration of Treatment

The study medications are for external, topical use on the AD areas twice daily for 28 days.

2.3.4 Duration of Treatment

The duration of the study participation is anticipated to be up to 64 days, including up to 35 days for screening/prior treatment washout and 28 days of study drug treatment. Subjects may be followed for up to an additional 30 days for resolution of AEs after end of treatment.

2.4 ASSESSMENTS

2.4.1 Evaluators

The investigator, a designated and appropriately trained staff member (e.g., sub investigator) or the subject will perform the study assessments according to the defined schedules.

2.4.2 Evaluations – Efficacy

2.4.2.1 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

Half-point scores of 1.5 and 2.5 can also be reported. 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 electronic case report form (eCRF) page. The EASI score will be calculated by the sponsor/designee. The formulation of the score is as shown below:

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)

2.4.2.2 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.

2.4.2.3 Worst 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.

2.4.2.4 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.

2.4.3 Evaluations – Safety

2.4.3.1 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 individual components of burning/stinging, pruritus, and erythema based on the average for scores 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

2.4.3.2 Adverse Events

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

2.4.3.3 Laboratory Sampling

- All study-required laboratory assessments as detailed in the following table 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).
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Tests listed below will be those analyzed descriptively and/or listed.

Hematology	**Chemistry**	**Urinalysis**
Platelet Count Red blood cell (RBC) Count Hematocrit Hemoglobin RBC Indices: MCV MCH White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Blood urea nitrogen (BUN) Bicarbonate Calcium Chloride Creatinine Glucose (random) Potassium Sodium Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Total bilirubin Total protein Albumin	Specific gravity pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick 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.		

MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume.
[a]Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

2.4.3.4 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 baseline. Physical examinations will only be performed at the indicated visits per study schedule of activities. 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 medical history.

2.4.3.5 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).

2.4.3.6 Electrocardiogram

At screening and Day 29/end of treatment (EOT), a single 12-lead electrocardiogram (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.

2.4.4 Evaluations – PK

Plasma levels of TER-101 on Days 15, 29 will be analyzed and reported in a separate PK report, if topline results indicate a signal for clinical activity or before the samples exceed their stability, whichever comes first.

3 STATISTICAL METHODOLOGY

This plan describes methods planned for the analysis and display of efficacy and safety endpoints.

3.1 GENERAL STATISTICAL CONSIDERATIONS

Descriptive statistics (mean, standard deviation [Std Dev], median, minimum, and maximum) will be used for continuous variables; number and percentage of subjects will be used for discrete variables. In general, the last measurement prior to the first dose of study treatment will be used as the baseline value with exception of WI-NRS, where the score recorded on Day 1 describing the worst itch score 24 hours prior will be used as the baseline. Nominal visits will be used for by-visit summaries and analyses for safety evaluations (i.e., laboratory sampling, physical examinations, vital signs, and electrocardiogram). For efficacy evaluations of EASI, IGA, and TBSA, analysis visits will be used for by-visit summaries. Analysis visits are defined as below:

Analysis Visit*	Target Day	Range
Day 8	Day 8	Day 2 – Day 11
Day 15	Day 15	Day 12 – Day 21
Day 29	Day 29	≥Day 22

* If there are multiple observations in the range, then the record collected closest to the target day will be selected; if there are multiple observations that have equal distance from the target day, the latter one will be used.

All treatment group comparisons will be made at the 0.05 level using a two-sided hypothesis test, unless otherwise specified. Given the exploratory nature of this study, p-values from all significance tests will be reported without adjustment for multiplicity.

Summaries will be presented by each treatment group, ie, TER-101 2.75% ointment, Vehicle ointment.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

3.2 ANALYSIS POPULATION AND DISPOSITION OF SUBJECTS

3.2.1 Data Sets Analyzed

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. The treatment group as assigned (randomized to) will be used for analyses.
Per protocol efficacy analysis set (PPES)	All subjects in ES without major protocol deviations that impact the interpretation of the results. The treatment group for the first application will be used for analyses.
Safety analysis set (SS)	All randomized subjects who receive at least 1 application of the study treatment. If any TER-101 was applied, then the subject will be summarized under TER-101 treatment group.
PK analysis set (PKS)	All subjects in SS with at least 1 blood draw to measure TER-101.

3.2.2 Protocol Deviations

Protocol deviations (eg, due to violations of inclusion or exclusion criteria, lack of study treatment compliance, or use of nonpermitted medication) will be identified and documented before database lock and unblinding. Number and percentage of subjects with deviations will be summarized by deviation categories. Major protocol deviations leading to exclusion of efficacy data from the analysis set PPES as described above will be listed.

3.2.3 Disposition of Subjects

The numbers of subjects screened (ie, signed informed consent), randomized, treated, and discontinued from treatment (by reason) or completed treatment, discontinued from study (by reason) or completed study will be summarized for each treatment group separately. Any mis-randomization or mis-treatment will also be described.

3.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the SS. Gender, race, and ethnicity will be summarized with number and percentage presented for each category. Age,

height, weight, body mass index (BMI) will be described with summary statistics (n, mean, Std Dev, median, minimum, and maximum).

3.4 MEDICAL HISTORY

All medical history and current ongoing medical history will be summarized separately by system organ class using the SS.

3.5 PRIOR/CONCOMITANT MEDICATIONS

The number and percentage of prior medications, and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) and preferred term (PT) separately using SS.

Medications taken any time prior to the first study treatment and stopped prior to the first study treatment are counted as prior medications. Those taken any time on or after the first application of study treatment or ongoing medication started prior to the first application of study treatment are counted as concomitant.

Subject will be counted only once within each classification. The same subject may contribute to two or more PTs within the same ATC classification.

3.6 EFFICACY ANALYSIS

All efficacy analyses and summaries will be performed on the ES by randomized treatment group. Additional analyses based on PPES will be specifically mentioned.

3.6.1 EASI Analyses

For each visit (baseline, Day 15, Day 29), the following analyses will be performed. All analyses will be based on the ES.

- Descriptive statistics (n, mean, Std Dev, median, minimum, and maximum) will be provided for the per-subject EASI total score (continuous), change from baseline, and percent change from baseline in EASI total score.
- Descriptive statistics (n, %) will be provided for the number and percentage of subjects who achieve EASI-50 (i.e., ?50% reduction from baseline) and EAST-75 (i.e., ?75%).

Descriptive statistics (n, mean, Std Dev, median, minimum, and maximum) will be provided for the per-subject EASI by region (head, trunk, upper extremity [UE], lower extremity [LE]), change from baseline, and percent change from baseline values. Treatment group comparisons

in 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 nested within the investigational site as a random effect, and baseline score as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then the replacement of variance-covariance matrix will be explored in the order of Toeplitz, first-order autoregressive, compound symmetric. 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. Similarly, the treatment difference (TER-101 2.75% vs. vehicle) and 95% confidence limits will be presented for Day 15 as well. Line graphs of least squares mean in percent change from baseline of EASI scores will be presented for Day 15 and Day 29. These treatment group comparisons will be repeated for the PPES.

The following sensitivity analyses will be conducted for the percent change from baseline in EASI total score at Day 29 to explore the impact of dropouts and missing data at Day 29.

- Last value carried forward (LOCF): for timepoint Day 29, if missing, the last available post baseline EASI total score will be carried forward to the timepoint. After this imputation, an analysis of covariance (ANCOVA) will be used for analyzing the treatment effect at Day 29. The treatment group will be the fixed effect and baseline score will be the covariate. The treatment difference, 95% confidence limits, and p-value will be presented.
- Return to baseline: missing Day 29 value will be imputed based on the baseline value for the patient, with variance adjustment of the Day 29 EASI total score. That is, the missing data will be imputed with values from Normal distribution N (***baseline***$_i$, $\_$,^{2}); i = ith subject, where ***ó***,^{2} is the variance estimate of treatment k at Day 29. Five hundred (500) imputation will be implemented. ANCOVA model will be used for each imputation. The results from all imputed datasets will be combined using Rubin's combination rule (PROC MIANALYZE).

In addition, the percent change from baseline in EASI scores and the absolute change from baseline in EASI total score by each region will 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 (EASI-75, EASI-50) at each visit will be evaluated using a logistic generalized linear mixed model (GLMM) for binary data. The model will include fixed effect for treatment, visit and treatment-by-visit interaction, with subject nested within the investigational site as a random effect. 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.] Bar charts of the response rates at Day 15 and Day 29 will be presented by treatment groups for each response rate (EASI-75, EASI-50).

3.6.2 IGA Analyses

Descriptive statistics (n, mean, Std Dev, median, minimum, and maximum) will be provided for the IGA scale, and its change from baseline at Day 15 and Day 29. Number and percentage of subjects for each scale value (0-4) will also be provided for each visit.

The change from baseline IGA values will be analyzed using generalized linear model for repeated ordinal data method. The multinomial distribution will be used with link function of cumulative logit. 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 subject nested within the investigational site as a random effect, and baseline IGA scale 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. All analyses will be based on ES.

3.6.3 WI-NRS Analyses

Descriptive statistics (n, mean, Std Dev, median, minimum, and maximum) will be provided for the 11-point WI-NRS scale at baseline, Day 15 and Day 28 visits, and its change from baseline at Day 15 and Day 28. A line plot over time of the change from baseline (daily, and weekly average [see intervals specified below]) will be generated. Mean (±Std Dev) will be displayed at each time point. Change from baseline WI-NRS scale will also be analyzed using the MMRM model for Day 15 and Day 28 assessments. The model will include fixed effect for study treatment (TER-101 2.75%, vehicle), visit day (Day 15, Day 28), and treatment-by-visit interaction, with visit as the repeating factor, subject within the investigational site as a random effect, and baseline WI-NRS scale 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.

The proportion of WI-NRS responders (defined by a reduction of ? 3 in subjects with baseline WI-NRS ? 4) will be analyzed using a logistic regression. The odds ratio, and 95% confidence limits from the model, will be presented. The chi-square test p-value will also be provided. In addition, the number and percentage of subjects who respond during each weekly interval (defined by the maximum reduction between Day 2-Day 8, Day 9-Day 15, Day 16-Day 22, Day 23-Day 28) will be summarized and presented in a bar chart.

All analyses will be based on ES.

3.6.4 TBSA Analyses

The TBSA involved with AD at baseline, Day 15, and Day 29 will be summarized descriptively (n, mean, Std Dev, median, minimum, and maximum). The change from baseline values will also be analyzed using MMRM method. 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 TBSA 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. All analyses will be based on ES.

3.7 SAFETY ANALYSIS

The safety and tolerability of the investigational product will be determined by local tolerability assessment, reported AEs, laboratory tests, physical examinations, vital signs, and ECGs. The Safety analysis set with actual treatment received (as opposed to randomized treatment) will be used for all safety summaries, unless otherwise specified.

3.7.1 Study Drug Exposure And Compliance

Duration of treatment (Last study treatment application date – First study treatment application date + 1) will be summarized descriptively for the SS. Study drug compliance will be assessed based on subject reports in the e-diary. The number of actual treatment applications as a percentage of the number of expected applications will be summarized. The usage of ointment (dispensed kit weight – returned kit weight) and average daily use (g) will also be summarized by treatment group.

3.7.2 Local Tolerability

For each visit (baseline [pre-dose, post-dose], Day 15, Day 29), the number and percentage of subjects with grades 0, 1, 2, 3 will be tabulated at timepoints specified for erythema and

symptoms of burning/stinging or pruritus associated with study drug application. In addition, severity grades will be summarized using a shift table based on the baseline pre-dose value at each visit. Severity grade shift from pre-medication at baseline to post-medication will be analyzed. The shift from pre-dose severity grade at baseline to the last post-dose severity grade will also be summarized by treatment groups for erythema, burning/stinging, and pruritus.

3.7.3 Adverse Events

All AEs will be coded and summarized using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.1). Treatment-emergent AEs (TEAEs) are defined as any new or worsening events reported at any time from the date of first dose of study medication until the end of study participation. All AEs will be presented in by-subject data listings, including the verbatim and coded terms, onset day (relative to start of treatment), severity, relationship to study medication, action taken, and outcome.

An overview of AEs for the SS will be provided, summarizing the frequency/incidence of the following:

- Incidence of all AEs;
- Count of TEAEs;
- Incidence of TEAEs;
- Count of Treatment-emergent SAEs (TESAEs);
- Incidence of TESAEs;
- Incidence of TEAE by maximum severity;
- Incidence of TESAE by maximum severity;
- Incidence of TEAEs that lead to discontinuation of study treatment;
- Incidence of TESAEs that lead to discontinuation of study treatment;
- Incidence of TEAEs that lead to interruption of study treatment;
- Incidence of TESAEs that lead to interruption of study treatment;
- Incidence of Treatment-related TEAEs;
- Incidence of Treatment-related TESAEs.

The number and percentage of subjects with AEs will also be summarized by System Organ Class (SOC) and Preferred Term (PT) for the following categories:

- Incidence of TEAEs;
- Incidence of TESAEs;
- Incidence of TEAEs by maximum severity;

- Incidence of TEAEs that lead to discontinuation from study treatment;
- Incidence of TEAEs that lead to interruption from study treatment;
- Incidence of Treatment-related TEAEs.

3.7.4 Laboratory Tests

For each laboratory test, summaries will be provided for baseline and Day 29. The absolute value and its change from baseline will be descriptively presented. Abnormal laboratory observations and urinalysis microscopic exams, if performed, will be listed.

3.7.5 Physical Examinations

Physical examination results will listed.

3.7.6 Vital Signs

Vital signs measurements include pulse rate, temperature, systolic blood pressure, and diastolic blood pressure. Measures at baseline and changes from baseline to post baseline visit (Day 15, Day 29) will be summarized using descriptive statistics.

3.7.7 Electrocardiogram

Electrocardiogram results will be descriptively summarized (n, mean, Std Dev, ..., etc.) for heart rate, PR, RR, QRS, QT interval, QTcB, and QTcF by visit. In addition, number and percentage of subjects with abnormal QTcB/QTcF (ie, >450 msec, >480 msec, >500 msec) or increase of QTcB/QTcF (>30 msec, >60 msec) from screening will be provided for each visit.

3.8 PK ANALYSES

Plasma concentration of the study drug will be summarized using descriptive statistics including number of subjects with plasma samples, number of assays with concentrations above lower limit of quantification (LLOQ), arithmetic mean, geometric mean, Std Dev, coefficient of variation (CV), minimum and maximum at each nominal visit (Day 15, Day 29). A concentration that falls below the LLOQ will be treated as zero in the summary. Analysis will be conducted on PKS.

3.9 INTERIM ANALYSES

There is no interim analysis planned for the study.

4 CHANGES TO PLANNED ANALYSES

Due to the small sample size of the study and the infrequent assessment of response over time, the Kaplan-Meier (KM) analysis of time to onset of response (EASI-75, EASI-50) will not be conducted.

Because the change from baseline in the IGA is expected to take on a limited set of values, it will be considered as ordinal data rather than a continuous variable, and thus will be analyzed using a generalized linear model for repeated ordinal data.

The change in individual components of EASI (erythema, edema/papulation, excoriation, lichenification) by visit will not be analyzed, only EASI by region will be analyzed due to limitation in defining EASI score for each sign/symptom.