A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Protocol Number	**EVO101-AD001**
Protocol Final Date	**20 April 2022**
Amendment 1 Date	**10 June 2022**
Amendment 2 Date	**06 January 2023**
Amendment 3 Date	**11 May 2023**
Study Drug	**EVO101 Topical Cream, 0.1%**
IND Number	**155054**
Sponsor	**Evommune, Inc.** **1841 Page Mill Road** **Palo Alto, CA 94304** **USA**

PROTOCOL AMENDMENT 3.0 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 3.0, are summarized in the following table.

Section(s)	Modification	Rationale
Synopsis	Comparisons between active and vehicle treated arms will be conducted using a one-sided test instead of a two-sided test.	For consistency between the protocol and Statistical Analysis Plan (SAP)
15.1, 15.4, 15.8	Comparisons between active and vehicle treated arms will be conducted using a one-sided test instead of a two-sided test.	For consistency between the protocol and SAP

PROTOCOL AMENDMENT 2.0 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 2.0, are summarized in the following table.

Section	Modification	Rationale
Title Page	Updated Sponsor Address	New headquarters established for Evommune (Sponsor)
6	Updated Schedule of Assessments	For consistency between Table 3 and Section 13.1.4.1
13.1.4.1	Provided additional direction on recording local skin responses as adverse events where appropriate	Clarification for study sites
15.2	Removed “and received study drug” from the intent-to-treat (ITT) population definition	For consistency between the protocol and Statistical Analysis Plan (SAP)
15.5.1	Removed “and received study drug” from the ITT population definition	For consistency between the protocol and SAP

PROTOCOL AMENDMENT 1.0 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 1.0, are summarized in the following table.

Section	Modification	Rationale
1.1	Updated description of inhibitory properties of EVO101, primarily as an inhibitor of interleukin 1 receptor-associated kinase 4; removed characterization as an inhibitor of tropomyosin receptor kinase A (TrkA)	For a more accurate characterization of the primary pharmacology of EVO101
1.2.1	Removed subsection (formerly 1.2.1.2) that described TrkA	For consistency with the primary pharmacology of EVO101
1.2.1.3	Updated summary of genotoxicity assessment and included results of the Comet test in rats	To provide the most current safety information for EVO101
1.2.1.4.1	Made minor corrections to the summary of results from Study EVO101-HV001	To align with final data summarized in the clinical study report
Procedures in Case of Emergency	Updated Table 1: Emergency Contact Information	New general contact number for the CRO will be used for this study
13.1.4.1	Clarified that all local skin responses should be recorded as adverse events	FDA request

SPONSOR SIGNATURE PAGE

A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Protocol Number: **EVO101-AD001**

Protocol Final Date: **20 April 2022**

Amendment 1 Date: **10 June 2022**

Amendment 2 Date: **06 January 2023**

Amendment 3 Date: **11 May 2023**

The signature below constitutes approval of this protocol. I certify that I have the authority to approve this protocol on behalf of the Sponsor, Evommune, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations and with the International Council for Harmonisation Good Clinical Practice (ICH GCP), regulations of the United States (US) Food and Drug Administration (FDA), or according to the regulations of the country where the study is being conducted and the ethical principles that have their origin in the Declaration of Helsinki.

Authorized by:

[redacted]

[redacted]

05/15/2023

Date

INVESTIGATOR SIGNATURE PAGE

A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Protocol Number: **EVO101-AD001**

Protocol Final Date: **20 April 2022**

Amendment 1 Date: **10 June 2022**

Amendment 2 Date: **06 January 2023**

Amendment 3 Date: **11 May 2023**

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in the protocol, according to current Good Clinical Practice and local laws and regulations, including those of the United States (US) Food and Drug Administration (FDA) and according to the regulations of the country where the study is being conducted.

I will ensure that all sub-Investigators and other staff members associated with this study have read and understand all aspects of this protocol.

I have read and understand all study related information provided to me.

The objectives and conduct of this protocol as well as the results deriving from this study will be treated confidentially and will not be made available to third parties without prior authorization by Evommune. All rights of publication of the results reside with Evommune unless other agreements were made in a separate contract.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (print)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number/email
Responsible Physician	[redacted]	[redacted]
24-hour emergency contact	[redacted]	[redacted]

SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company: Evommune, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product: EVO101 Topical Cream, 0.1%</td></tr>
<tr><td>Protocol Number:
EVO101-AD001</td><td>Phase: 2a</td><td>Country: USA</td></tr>
<tr><td colspan="3">Title of Study: A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS</td></tr>
<tr><td colspan="3">Objectives:
Primary: Assess the safety, tolerability, and preliminary efficacy of EVO101 Topical Cream, 0.1%, applied twice daily in adults with atopic dermatitis (AD).
Secondary: The secondary objective of this study will be to assess the pharmacokinetics of EVO101 Topical Cream 0.1%, applied twice daily in adults with AD.
Study Design: Randomized, Double-Blind, Parallel Group, Vehicle Controlled</td></tr>
<tr><td colspan="3">Number of subjects (planned): 118</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion: Adults with mild to moderate AD</td></tr>
<tr><td colspan="3">Investigational product, dosage, and mode of administration: EVO101 Topical Cream, 0.1% twice a day (BID)</td></tr>
<tr><td colspan="3">Duration of treatment: 8 weeks</td></tr>
<tr><td colspan="3">Reference therapy, dosage, and mode of administration: EVO101 Topical Cream, Vehicle BID</td></tr>
<tr><td colspan="3">Criteria for evaluation:
Efficacy: Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI), Body Surface Area (BSA), Pruritus-Numerical Rating Scale (NRS)
Safety: Adverse Event (AEs), Local Skin Response (LSRs), Physical Exam, Serum Chemistry, Hematology and Urinalysis, ECG
Pharmacokinetics: Plasma drug concentrations</td></tr>
<tr><td colspan="3">Statistical methods:
Sample size justification:
The assumed true standard deviation of the percentage change from Baseline to Week 8 in the EASI score is 50%. Based on the use of a one-sided test at the alpha=0.05 level of significance, a total sample size of 118 subjects (59 subjects/treatment arm) will provide greater than 90% power to detect a mean between-group difference of 30 percentage points.
Primary efficacy analysis:
The primary efficacy analysis will be conducted in the intent-to-treat population (all randomized subject) using an analysis of variance (ANOVA) model with the percentage change from Baseline to Week 8 in EASI as the dependent variable and treatment group and the randomization stratification variable as factors. The two arms will be compared using a one-sided test at the alpha=0.05 level of significance.
Secondary efficacy analyses:
All secondary endpoints defined as the percentage change from Baseline will be analyzed using the same type of ANOVA model as specified for the primary analysis. All change from Baseline</td></tr>
</table>

secondary endpoints will be analyzed using analysis of covariance (ANCOVA) models with treatment group and the randomization stratification variable as factors and with the baseline value of the corresponding endpoint as a covariate. Secondary endpoints that are defined as proportion variables will be analyzed using Pearson's chi-square test or (if more than 25% of expected cell frequencies are less than 5) Fisher's exact test. All secondary analyses will be conducted using one-sided tests at the alpha=0.05 level of significance, with no adjustments for multiplicity.

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LIST OF ABBREVIATIONS

The abbreviations listed below are a non-exhaustive list of those commonly used in Evommune, Inc., study documents. Not all acronyms listed below are used within this document.

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AD	atopic dermatitis
AUC_{0-24}	area under the plasma concentration-time curve over the last 24-h dosing interval
BID	twice a day
BSA	body surface area
C	Celsius
CFR	code of federal regulations
CNS	central nervous system
eCRF	electronic case report form
CRO	clinical research organization
C_{max}	maximum plasma concentration
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DNCB	dinitrochlorobenzene
DP	drug product
DRF	dose range-finding
DS	drug substance
EASI	eczema area and severity index
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	good clinical practices
GLP	good laboratory practices
HED	human equivalent dose
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	International ethics committee
IGA	investigator global assessment
IL	interleukins

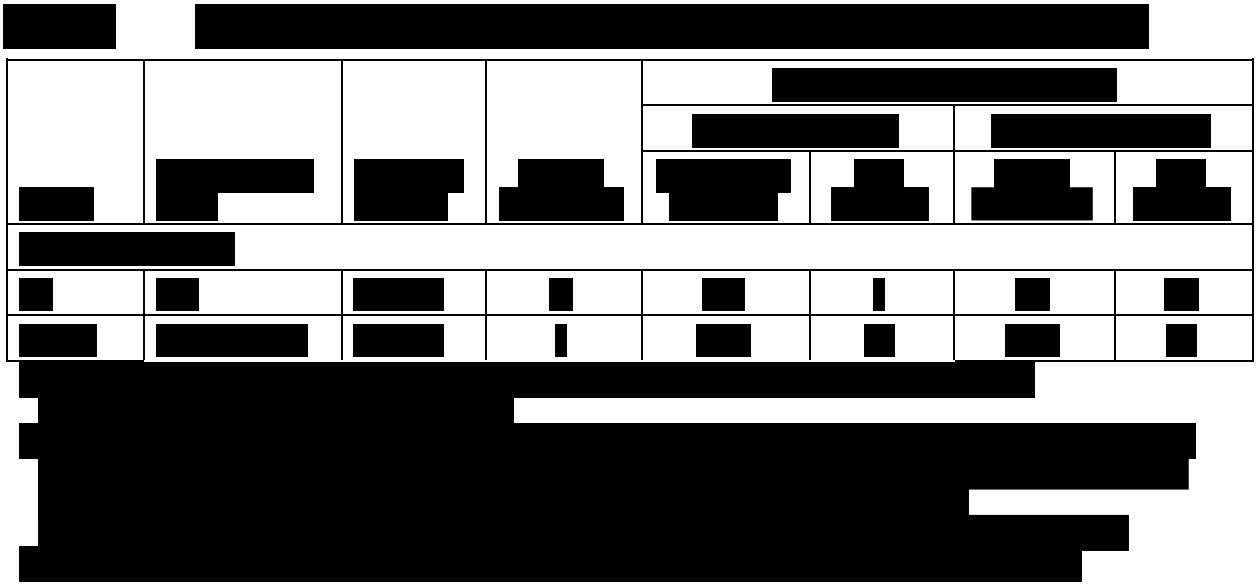
Abbreviation or Specialist Term	Explanation
IND	Investigational New Drug
IR	infrared (spectrophotometry)
IRAK4	interleukin 1 receptor associated kinase 4
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web-based randomization system
kg	kilogram
LSR	local skin response
MedDRA	medical dictionary for regulatory activities
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MyD88	myeloid differentiation primary response gene 88
NF-kB	nuclear factor-kappa B
ng	nanograms
NGF	nerve growth factor
NOAEL	no-observed-adverse-event-level
NRS	numerical rating scale
PK	pharmacokinetics
ppm	parts per million
PI	principal investigator
RBC	red blood cell
SAE	serious adverse event(s)
SD	standard deviation
Th	T helper type
TLR	toll-like receptor
TEAE	treatment emergent adverse event
TRPV1	Transient Receptor Membrane Potential cation channel subfamily V member 1
US	United States
VEGF	vascular endothelial growth factor

1. INTRODUCTION

1.1. [redacted]

[redacted]

[redacted]



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1.3. Study Rationale

Study EVO101-AD001 is planned as a randomized, double-blinded, parallel group proof-of-concept trial in which safety, preliminary efficacy and pharmacokinetics will be assessed. Approximately 118 adult subjects with mild-to-moderate AD will be randomized and apply study drug or vehicle to their affected areas twice daily for 8 weeks. This dosing regimen has been selected because it was found to be well-tolerated in a previous study, EVO101-HV001, conducted in adult healthy volunteers.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study will be to assess the safety, tolerability, and preliminary efficacy of EVO101 Topical Cream, 0.1%, applied twice daily, in adults with AD.

2.2. Secondary Objectives

The secondary objective of this study will be to assess the pharmacokinetics of EVO101 Topical Cream, 0.1%, applied twice daily, in adults with AD.

3. STUDY ENDPOINTS

3.1. Efficacy Endpoints

The primary efficacy endpoint for this trial will be:

- Mean percentage change from Baseline in EASI score at Week 8

Secondary efficacy endpoints for this study will be:

- IGA response (≥2 point change from baseline) at Week 8
- Change from Baseline in IGA at Week 8
- Mean change from Baseline in BSA affected at Week 8

Exploratory efficacy endpoints for this study will be:

- EASI-75 and EASI-90 from Baseline to Week 2, 4 and 8
- Mean change from Baseline in EASI at Weeks 2 and 4
- Proportion of subjects achieving an IGA score of 0 to 1 who have an improvement of ≥ 2 points from Baseline at Week 8
- Change from Baseline in IGA score at Weeks 2, 4 and 8
- Mean change from Baseline in the pruritus-NRS score at Weeks, 2, 4 and 8
- Mean and percentage change from Baseline in the pruritus-NRS score at Week 8
- Proportion of subjects achieving a 4-point improvement in the pruritus-NRS score from Baseline to Week 8
- Mean change from Baseline in BSA affected at Weeks, 2, 4 and 8

3.2. Pharmacokinetic Endpoints

Plasma levels of EVO101 at Baseline, Week 2 and 8.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The study is a randomized, double-blinded, vehicle controlled, parallel group study, designed to assess the safety, tolerability, and preliminary efficacy of EVO101 Topical Cream, 0.1%, in subjects with mild-to-moderate AD.

Approximately 118 adult subjects, ≥18 years of age will be enrolled into this trial. The duration of the study for each subject is expected to be approximately 12 weeks (up to 4 weeks screening, 8 weeks treatment).

Subjects will be in generally good health and have a clinical diagnosis of mild-to-moderate AD for at least one year, an IGA score of 2 or 3, an EASI of 5-20, and an affected BSA of 4-12%. Subjects must be willing to discontinue any therapies for AD and refrain from using any topical or systemic agents for AD, other than the investigational product, during the trial. Subjects will be randomized (1:1), at Baseline, to one of two treatment arms: EVO101 Topical Cream, 0.1%, or vehicle cream. The randomization will be stratified by baseline IGA score (IGA 2, IGA 3). At most 40% of randomized subjects can be in the IGA 2 stratum.

Subjects will be instructed to apply a thin layer of study drug to the affected areas, twice daily, during their trial participation.

Subjects will participate in the trial for 8 weeks in duration and be seen for in-clinic visits at Screening (up to 30 days prior to Baseline), Baseline, Week 2, Week 4 and Week 8 (Study Exit).

Efficacy will be assessed using the IGA for AD (scored from 0-4), EASI, percentage BSA affected, and pruritus (using an 11-point pruritus-NRS; assessing the worst itch in the last 24-hours, by the subject, daily).

Safety will be assessed through physical exam, serum chemistries, hematology, urinalysis, ECGs, AEs, and local skin reactions.

Pharmacokinetic samples will be collected at Baseline, Week 2 and Week 8.

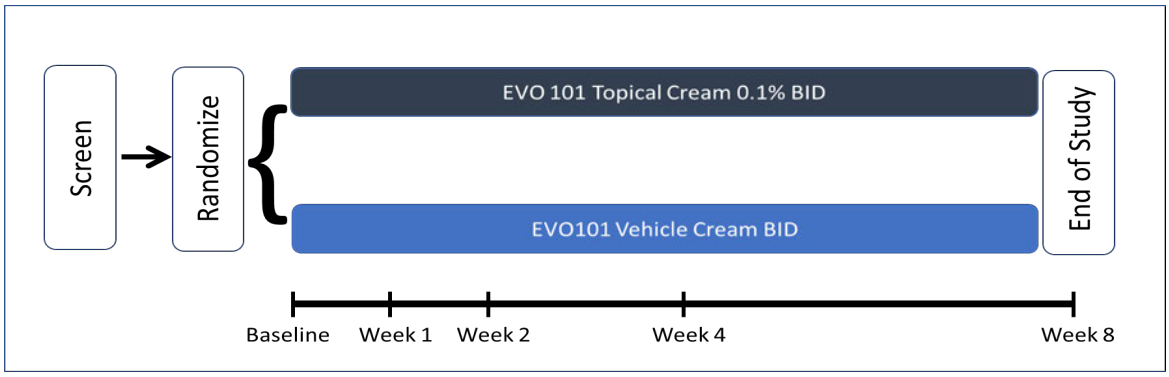
4.2. Study Population and Number of Subjects

Approximately 118 subjects with AD that are ≥18 years of age will be enrolled.

4.3. Duration of the Study

The duration of the study for each subject is expected to be approximately 12 weeks (up to 4 weeks screening, 8 weeks treatment).

5. STUDY DESIGN SCHEMATIC



6. SCHEDULE OF ASSESSMENTS

Table 3: Schedule of Assessments

Visit	Screening Day -30 to -1	Baseline Day 1	Week 2	Week 4	Week 8 Study Exit/ Early Withdrawal	Unscheduled Visit
Visit Window			+/- 1 day	+/- 2 days	+/- 4 days	
Informed Consent	X					
Demographics	X					
Medical History	X	X				
Inclusion/Exclusion Criteria	X	X				
Physical Exam	X	X			X	X[2]
Height and Weight	X					
Serum Chemistry, Hematology, Urinalysis	X				X	X[2]
Urine Pregnancy Test	X	X	X	X	X	X[2]
Vital Signs	X	X	X	X	X	X[2]
COVID-19 Test[4]	X					X[2]
12-lead ECG	X				X	X[2]
Adverse Events	X	X[1]	X	X	X	X[2]
Local Skin Reactions		X[1]	X	X	X	
Concomitant Medications	X	X	X	X	X	X[2]
IGA	X	X	X	X	X	
BSA	X	X	X	X	X	
EASI	X	X	X	X	X	
Pruritus-NRS (e-diary)	X[3]	X	X	X	X	
Pharmacokinetic Sample		X	X		X	
Dispense Study Drug		X	X	X		X[2]
Study Drug Compliance			X	X	X	

[1] LSRs collected pre-application and 15 minutes following application on Baseline/Day 1 (see Section 13.1.4.1 for details on LSR assessment).
[2] Perform these procedures only if clinically indicated
[3] Subjects are to rate pruritus severity daily, for 7 days prior to Baseline using e-diary.
[4] COVID test to be performed within Day -4 to -1 or at the Baseline visit.

7. SELECTION OF SUBJECTS

Subject selection criteria are outlined below. Any questions on the eligibility of a subject for this study must be referred to the Sponsor or their designee, prior to enrollment. No exceptions to inclusion or exclusion criteria will be made.

7.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

1. Signed informed consent.
2. Willing and able to comply with the study visit schedule, procedures, and questionnaires.
3. Male or non-pregnant, non-lactating, females, age ≥18 years.
4. Chronic AD (according to the American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year before the Screening visit.
5. Investigator's Global Assessment score of 2 to 3 at Screening and Baseline.
6. EASI of 5-20 at screening and baseline.
7. BSA of AD involvement, excluding the face and intertriginous areas, of 4% to 12% at Screening and Baseline.
8. Application of a stable dose of non-medicated topical moisturizer twice daily for ≥7 days prior to the Baseline visit and willing to maintain stable dosing during study participation
9. Completed electronic diary entries for pruritus for a minimum of 4 of 7 days preceding randomization at the Baseline visit.
10. Willing to use effective contraceptive method, if applicable, during study participation and for 30 days following the end of treatment.

    For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 30 days after the last application of study drug.

    A woman of childbearing potential is defined as a postmenarcheal female, who has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause) and has not undergone surgical sterilization (removal of ovaries and/or uterus).

    The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Females must agree not to donate ova during the study and for 30 days after the end of study visit.

Male subjects must agree to use an effective barrier method of contraception during the study and for a minimum of 30 days following the last application of study drug if sexually active with a female of child-bearing potential. Males must agree not to donate sperm during the study and for 30 days after the end of study visit.

7.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Significant AD flare, in the opinion of the Investigator, within 4 weeks prior to Baseline.
2. Use of biologic therapy (e.g., dupilumab) within 12 weeks or 5 half-lives prior to Baseline.
3. Use of topical treatments such as corticosteroids, calcineurin inhibitors or phosphodiesterase-4 inhibitors within 2 weeks prior to the Baseline visit.
4. Use of systemic antibiotics within 2 weeks of Baseline.
5. Use of prescription moisturizers within 7 days of the Baseline visit.
6. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the Screening visit.
7. Presence of skin comorbidities or other condition that may interfere with study assessments.
8. Active participation in an experimental therapy study or who received experimental therapy within 30 days or 5 half-lives (whichever is longer) before Baseline.
9. Screening clinical chemistry or hematology laboratory value that is considered clinically significant, in the opinion of the Investigator.
10. Abnormal findings on screening ECG, deemed clinically significant by the Investigator.
11. Positive COVID-19 test within 3 days of Baseline visit or as part of the Baseline visit. Patients can be rescreened after recovering from COVID clinically, and a negative COVID PCR or antigen test must be done, after discussion with the sponsor's Medical Monitor.
12. COVID vaccination (last dose) within 2 weeks of start of Screening.
13. Systemic immunosuppressive or immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.) or phototherapy and photochemotherapy (PUVA) within 4 weeks prior to the Baseline visit.
14. Prior use of EVO101 Topical Cream.
15. Known hypersensitivity or severe reaction to the study drug or any of its excipients.
16. Subjects who are a poor medical risk because of other systemic diseases or active uncontrolled infections, or any other condition which, in the judgment of the Investigator, would put the subject at unacceptable risk for participation in the study.

8. STUDY DRUG

8.1. Description of Study Drug

Vehicle cream is identical in appearance and formulation but does not contain active drug.

8.2. Study Drug Packaging and Labelling

EVO101 Topical Cream, 0.1% and EVO101 Topical Cream, Vehicle, are provided in 30 g laminate tubes. Study drug labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill 21 CFR 312.6 requirements for labeling.

8.3. Study Drug Storage

Study drug is to be stored at ambient temperature (20–25°C) in a secure, locked facility accessible only to authorized study personnel.

8.4. Randomization and Blinding

The Sponsor, the clinical research organization (CRO), the Investigator, study site personnel and subjects will be blinded to treatment assignment.

The integrity of this clinical study must be maintained by observing the treatment blind. If an AE occurs which cannot be managed without knowing whether the subject is receiving active study drug or vehicle solution, the Interactive Web-based Randomization System (IWRS) system will be used to obtain treatment assignment information. The Medical Monitor must be notified whenever study medication is unblinded, preferably prior to unblinding a subject.

At the Baseline visit, qualified subjects will be randomized to treatment using an IWRS. The IWRS will assign a study drug kit number. The kit number will be recorded in the electronic case report form (eCRF).

Approximately 118 subjects will be randomized in a 1:1 ratio to active treatment or vehicle treatment. The randomization will be stratified by baseline IGA score (IGA 2, IGA 3). At most 40% of randomized subjects can be in the IGA 2 stratum.

8.5. Study Drug Administration and Application

At the Baseline visit, subjects should be provided with a two-week supply of study drug for Baseline and Week 2 visits, and a four-week supply of study drug for the Week 4 and Week 8 visits. Subjects will be instructed to enter application information in their diary.

Subjects will be instructed to apply a thin film of study drug to all affected body surface areas, including the face. Subjects will be instructed to use caution when applying study drug near the eyes or lips. Study drug should be applied to clean, dry skin.

Study site staff will use the Subject AD Mapping Image (Appendix 1) to identify and map all AD affected areas for each respective subject enrolled. A copy of the diagram will be given to each subject to use as a guide when applying study drug at home. Patients must apply study drug to the same affected areas throughout the study, even though their AD disease may improve or clear during the study. Subjects will be instructed to apply study drug to any new AD lesions, should they occur. The original diagram will be retained as a source document.

The first dose of the study drug will be applied at the study site for instructional purposes and will be recorded in the dosing diary as the first dose. Subjects will apply the study drug twice daily, in the morning and evening for a total of 8 weeks. Missed doses should be applied provided there is at least a 4-hour window until the next scheduled dose.

8.6. Study Drug Dispensing and Return

It is the responsibility of the Investigator to ensure that study drug is only used on study subjects enrolled in this study. Study drug must only be dispensed from official study sites by authorized personnel according to the protocol and local regulations.

Subjects should return their used and unused study drug at their next study site visit for study drug accountability purposes. Subjects may be re-dispensed unused study medication.

Subjects are to return all their study drug (used or unused) to the study site at the end of study participation. Study staff will record tubes dispensed and returned, by subject in any source documents and the eCRF.

Each subject is to be instructed on the importance of returning study drug to the study site at their final study visit. Subjects who fail to return their study drug will be directed to return it as soon as possible.

8.7. Study Drug Compliance

Treatment compliance will be assessed by the subject, daily, using an e-diary. A subject deviating significantly (less than 80% compliant) from the twice daily dosing regimen will be counseled or terminated from the trial, at the discretion of the Investigator. Study site staff will monitor subject compliance regularly.

8.8. Study Drug Accountability and Disposal

The Investigator or designee will be responsible for documenting drug accountability at the site. Study drug accountability records will document the receipt, dispensing and return of study drug and provide a complete account of all used and unused drug product.

Study drug accountability records will be reviewed by the Sponsor or designee. Following final accountability, instructions will be provided to the site regarding study drug return and destruction.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications, including over-the-counter drugs, vitamins, antacids, and skin care products, taken during screening and throughout the study will be recorded in the eCRF.

Medication entries should be specific to the generic name (if a combination drug, then marketed product name) and will include the dose, unit, and frequency of administration and/or treatment, route of administration, start date, discontinuation date, and indication.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations, and dietary supplements not explicitly prohibited in this study.

In order to ensure that appropriate concomitant therapy is administered, subjects will be instructed to consult with the Investigator prior to taking any medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician).

9.1. Permitted Treatments and Procedures

The use of concomitant medications for the treatment of an AE is permitted during this study.

Moisturizer Use:

- Non-medicated moisturizer must be used during trial participation, twice daily (may be applied at the time of study drug application), to all non-affected areas.
- Sunscreens may be used on all areas provided the application occurs at least 15 minutes following study drug application.
- Subjects are asked to avoid the use of moisturizers and sunscreens prior to the study visit but may use these products following study visits.

Concomitant medications for mild-to-moderate asthma, allergic rhinitis and allergies are permitted. Concomitant medications for the treatment of any other diseases except those prohibited concomitant medications listed in Section 10.2 are permitted. The medical monitor may be consulted if needed for questions on permitted and prohibited treatments and procedures.

9.2. Prohibited Treatments and Procedures

Subjects should not undergo any elective medical procedure without prior consultation with the Investigator. Elective out-patient procedures (e.g., minor outpatient surgery) that might require hospitalization or anesthesia must be deferred until after the study.

The following medications and treatments are prohibited during the study:

- Any prescription or over-the-counter product intended to treat AD.
- Use of tanning booth.
- Excessive sun exposure.

The medical monitor may be consulted if needed for questions on permitted and prohibited treatments and procedures.

10. STUDY PROCEDURES BY VISIT

The procedures required for subject evaluation at each study visit are outlined below and in the study Schedule of Visits and Procedures. The timing of each study day is relative to the day of initial dosing/application (Baseline/Day 1). Visit windows are provided, where allowed, to allow study sites flexibility in maintaining the study visit schedule for participating subjects.

10.1. Screening Period

The screening evaluation period may take up to 30 days in order to provide adequate washout time for subjects taking certain medications. The purpose of the Screening visit is to ensure that appropriate subjects are entered into the study and remain stable during the pre-treatment period. Questions on subject eligibility will be referred to the Sponsor or their designee. Screen failures may not be re-screened unless approved by the Sponsor.

- Obtain written informed consent.
- Collect demographic information.
- Complete medical history.
- Review inclusion/exclusion criteria.
- Query subject for prior and concomitant medication use.
- Perform a physical examination.
- Record height and weight.
- Measure vital signs.
- COVID-19 test.
- 12-lead ECG.
- Draw blood samples for laboratory tests and urine for urinalysis and urine pregnancy test.
- Collect IGA, BSA and EASI.
- Upload and instruct on e-diary for pruritus-NRS.
- Collect AEs
- Schedule next visit.

10.2. Baseline (Day 1)

- Collect concomitant medication information.
- Measure vital signs.
- Medical history: update medical history if appropriate.
- Perform a physical examination.
- Conduct urine pregnancy test.

- Draw blood sample for pharmacokinetic analysis.
- Collect IGA, BSA and EASI.
- Collect AEs.
- Collect LSRs pre and post study drug application.
- Confirm pruritus-NRS diary data is complete.
- Confirm subject eligibility and enrollment.
- Instruct subject on study medication application and e-diary completion.
- Apply first application in clinic and record in diary.
- Dispense study drug and Subject AD Mapping Image.
- Schedule next visit.

10.3. Week 2

- Collect AEs
- Collect concomitant medication information.
- Measure vital signs.
- Conduct urine pregnancy test.
- Draw blood sample for pharmacokinetic analysis.
- Collect IGA, BSA and EASI.
- Collect LSRs.
- Confirm compliance with pruritus-NRS diary.
- Confirm compliance with study drug application.
- Dispense study drug.
- Schedule next visit.

10.4. Week 4

- Collect AEs
- Collect concomitant medication information.
- Measure vital signs.
- Conduct urine pregnancy test.
- Collect IGA, BSA and EASI.
- Collect LSRs.
- Confirm compliance with pruritus-NRS diary.

- Confirm compliance with study drug application.
- Dispense study drug.
- Schedule next visit.

10.5. Week 8 (Study Exit/Early Withdrawal)

- Perform physical exam.
- Collect AEs.
- Collect concomitant medication information.
- Measure vital signs.
- Collect ECG.
- Draw blood samples for laboratory tests and urine for urinalysis and urine pregnancy test.
- Draw blood sample for pharmacokinetic analysis.
- Collect IGA, BSA and EASI.
- Collect LSRs.
- Confirm compliance with pruritus-NRS diary.
- Confirm compliance with study drug application.
- Close e-diary and exit subject from study.

10.6. Unscheduled Visit

Additional visits may be scheduled as necessary to ensure the safety and well-being of subjects who experience AEs. Physical exam and laboratory evaluations, if necessary, should be conducted. Laboratory evaluations should be collected and analyzed using the central laboratory for this study. Data will be recorded in the eCRF.

11. ASSESSMENT OF EFFICACY

11.1. Investigator Global Assessment (vIGA™)

The IGA is a static assessment and rates the severity of the subject's AD and is a 5-point scale ranging from 0 (clear) to 4 (severe). A score is selected using descriptors that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under the morphological description be present. A single assessor should be assigned to each individual subject for as many visits as possible, to avoid inter-assessor variability in scoring. Assessors must be trained and certified by the Sponsor prior to conducting this assessment. The IGA must be conducted prior to conducting EASI and BSA assessments.

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point.

Table 4: vIGA

Score	Clinical Definition[1,2]
0-Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1-Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2-Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3-Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4-Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

[1] In indeterminate cases, please use extent to differentiate between scores.
[2] Excoriations should not be considered when assessing disease severity

11.2. Eczema Severity and Area Index (EASI)

EASI is used to assess the severity and extent of AD; it is a composite index with scores ranging from 0 to 72, with the higher values indicating more severe and/or extensive disease. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

11.3. Body Surface Area (BSA) Involvement

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the subject palm = 1% rule. Assessors must be trained and certified by the Sponsor prior to conducting this assessment.

11.4. Pruritus-NRS Scale

Pruritus will be assessed using a Pruritus Numerical Rating Scale (NRS). The Pruritus NRS is an 11-point scale used by subjects to rate their worst itch severity over the past 24 hours with 0 indicating “No itch” and 10 indicating “Worst itch imaginable.” Subject assessments will be captured daily using an electronic diary.

Subjects will be provided with an electronic diary at least 7 days prior to the baseline visit and instructed to enter their pruritus scores daily subjects may be provided the electronic diary at the first Screening visit. Pruritus diary compliance will be checked by the study site staff and subjects will be counseled for non-compliance. At least 4 of the 7 days prior to the baseline visit, the diary must be completed in order for the subject to be eligible for study participation.

12. BASELINE DEMOGRAPHICS, ATOPIC DERMATITIS AND MEDICAL HISTORY

12.1. Demographics and Other Baseline Characteristics

At the screening visit, demographic information including age, gender, race and ethnicity will be collected and recorded in the eCRF for each subject.

12.1.1. Atopic Dermatitis Prior Medications History

All prior AD medications will be collected.

12.1.2. Other Atopic Diseases History

Prior and concomitant atopic disease history will be collected including asthma, allergic rhinitis, food allergies, chronic rhinosinusitis with or without polyposis, and eosinophilic esophagitis.

12.2. Medical History

A complete medical history will be collected as part of the screening assessment and include all clinically relevant past or coexisting medical conditions (including COVID-19 infection and vaccination) or surgeries. The medical history will be updated prior to treatment at Baseline should new findings be present since the screening visit. Findings will be recorded in the eCRF.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

13.1.1. Vital Signs

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the subject in the seated position, after sitting for at least 5 minutes. Any abnormal findings which are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

13.1.2. Physical Examination

A complete physical examination will be conducted at screening and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. A symptom directed physical exam may be performed at each subsequent visit, if needed, to assess the subject. Height and weight will be recorded as part of the screening physical exam and only the subject's weight will be recorded with the end of study physical exam. Findings will be recorded in the eCRF.

13.1.3. Electrocardiogram (ECG)

12-lead ECG measurements will be obtained in all subjects. The subject should rest quietly for at least 5 minutes in a supine position prior to ECG collection. The ECG should be obtained either prior to the time of blood collection, or at least 15 minutes afterwards.

At screening, the Investigator will use the machine-read ECG to determine subject eligibility. The medical monitor may be consulted if needed for interpretation of ECGs.

All study sites will be supplied with standardized, validated digital 12-lead ECG (12 lead at 25 mm/sec reporting rhythm, ventricular rate, the RR interval, the PR interval, QRS duration, QT, QTcF and QTcB intervals) equipment capable of recording, storing, and printing producing high resolution 12-lead ECG. Study sites will be trained on the use of the equipment prior to study start.

Machine-read ECG recordings will be collected and analyzed centrally. Data will be transferred electronically to the database. Additional details regarding subject preparation, ECG procurement and data transmission may be provided in a separate study manual.

13.1.4. Laboratory Assessments

Laboratory tests will be collected to evaluate safety in all study subjects and analyzed using a central laboratory. Laboratory samples will be collected per the Schedule of Visits and Procedures, and as clinically indicated. Laboratory samples are to be shipped on the same day as collected. Laboratory tests are described below.

COVID-19: molecular (RT-PCR) test or antigen test for COVID-19 infection.

Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell count and differential (%), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin

concentration (MCHC), mean corpuscular volume, RBC morphology, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils.

Chemistry: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, uric acid, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin (total and direct), and non-fasting glucose.

Urine pregnancy testing (beta human chorionic gonadotropin [β-hCG]): performed in all females unless post-menopausal/sterile.

Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase. A microscopic examination of urine will be performed if clinically indicated in the opinion of the Investigator based on the findings of the urinalysis or clinical signs and symptoms. Any clinically significant laboratory result is to be recorded as an AE after study drug dosing.

Screening laboratory values must be reviewed by the Investigator prior to subject enrollment. Subjects will be screen failed for clinically significant laboratory values. Screening laboratory tests may be repeated one time in order to confirm out of range results or clinical significance at the discretion of the investigator. Subjects with a positive test result for COVID-19 may be rescreened for the trial eligibility.

The central laboratory should be used for any laboratory testing required for a subject during study participation, including laboratory testing needed for unscheduled visits. Clinically significant laboratory results must be recorded on the AE eCRF, preferably as a diagnosis rather than individual test results. Any subject who has a clinically significant laboratory test result will be evaluated by the PI and will be treated and/or followed up at the discretion of the PI until the value returns to clinically acceptable levels.

13.1.4.1. Local Skin Reactions (LSRs)

A static assessment of local skin reactions will be conducted in all subjects at each study visit. LSRs include burning/stinging, pruritus, edema, erythema, dryness and scaling. Each LSR will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe).

Burning/stinging and pruritus will be assessed by the subject and edema/swelling, erythema, dryness, and scaling will be assessed by the Investigator/designee. Subjects will be read the definition of each subject-assessed LSR and asked to select the appropriate definition. The corresponding grade will be assigned by the site and entered in the eCRF.

At the Baseline visit, LSRs are collected prior to study drug application and approximately 15 minutes (+30 minutes) following the first application of study drug.

When assessing the LSRs, the underlying disease involving the skin should be considered in the overall score. Local skin reaction assessments subsequent to study drug application, that are greater than the Baseline visit pre-application assessment score are to be recorded as an AE. The stop date for the AE is the date that the score is less than or equal to the pre-application Baseline Day 1 visit score.

Table 5: Subject Assessed Local Skin Reactions

Score	Grade	Burning/Stinging	Pruritus
0	None	No stinging/burning	No pruritus
1	Mild	Slightly warm, tingling sensation; not really bothersome	Occasional, slight itching/scratching
2	Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome	Intermittent itching/scratching which does not disturb sleep
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort	Bothersome itching/scratching which disturbs sleep

Table 6: Investigator Assessed Local Skin Reactions

Score	Grade	Edema	Erythema	Dryness	Scaling
0	None	No edema	No erythema present	None	None
1	Mild	Slight, barely perceptible edema	Slight erythema: very light-pink	Perceptible dryness with no flakes or fissure formation	Slight diffuse scaling
2	Moderate	Distinct presence of edema	Dull red, clearly distinguishable	Easily noted dryness and flakes but no fissure formation	Diffuse scaling
3	Severe	Marked, intense edema	Deep/dark red	Easily noted dryness with flakes and fissure formation	Prominent, dense scaling

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

13.2.1.2. Serious Adverse Event (SAE)

An AE or suspected AE reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- Immediately life-threatening;

An AE or suspected AE is considered "life threatening" if, in view of either the Investigator or Sponsor, its occurrence places the study subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires in-patient hospitalization or prolongation of existing hospitalization.

Any hospital admission will be considered an in-patient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for a pre-planned procedure or social or situational reasons (e.g., no place to stay, lives too far away to come for hospital visits) will not be considered in-patient hospitalizations.

- Persistent or significant disability or incapacity.
- Congenital abnormality or birth defect.
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalizations, or the development of drug dependency.

13.2.2. Reporting of Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.

Non-serious AEs should be recorded on the eCRF from the time the subject has signed informed consent through the last study visit, unless otherwise specified. Any changes in the subject's status between signing informed consent, up to the time administration of the first dose of study drug will be recorded as a pre-treatment AE. Any AE occurring after administration of the first dose of study drug will be considered a treatment emergent AE (TEAE).

The AE term should be reported in standard medical terminology when possible.

Any subject who has an AE (whether serious or non-serious) or clinically significant test value will be evaluated by the PI and will be treated and/or followed up until the symptoms or values return to normal or to clinically acceptable levels, as judged by the PI.

Unless a diagnosis is available, signs and symptoms must be reported as individual AEs in the eCRF; a diagnosis is preferred.

For each AE, the investigator will evaluate and report the onset date, resolution date, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, 2017. The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.2. An AE of severe intensity may not be considered serious significance (e.g., ‘severe’ headache). Seriousness of AEs is based on the outcome/action of an AE.

13.2.3. Reporting of Serious Adverse Events

SAEs must be reported to the Sponsor or designee within 24 hours of awareness of the event from the time the subject has signed informed consent through the last study visit, unless otherwise specified, using a SAE Reporting Form, provided for this study. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor or designee, must be made immediately, irrespective of the extent of information available. In all cases, the PI should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. The Investigator may be required to provide supplementary information as requested by the Sponsor or its designee.

When reporting SAEs, the following additional points should be considered:

- When the diagnosis of an SAE is known or suspected, the PI should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms; signs, symptoms and tests that support the diagnosis should be provided.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. If an autopsy was performed, the autopsy report should be provided.

The Sponsor will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor will assess the expectedness of each SAE to the study treatment. The current Investigator's Brochure will be used as the reference document to assess expectedness of the event to study drug.

13.2.4. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated or Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

The relationship of the AE to the study treatment will be based on the following two definitions:

Not related: An AE is defined as "not related" if the AE is not judged to be associated with the study drug and is attributable to another cause.

Related: An AE is defined as "related" where a causal relationship between the event and the study drug is a reasonable possibility (possibly or probably related). A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

13.3. Pregnancy Testing

Should a subject become pregnant during study participation, study drug dosing will be discontinued, and the subject will be withdrawn from study. The Investigator must perform medical assessments as clinically indicated and continue to follow the subject for at least 4 weeks after delivery. Details for both the mother and baby must be obtained. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities must be recorded as AEs or SAEs. The Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy. Pregnancy reporting forms will be provided to the study site.

13.4. Pharmacokinetic Sampling

Blood samples for pharmacokinetic (PK) anlaysis will be collected in all subjects. The procedural instructions will be provided in a separate pharmacokinetic instruction manual.

14. STUDY DISCONTINUATIONS

14.1. Discontinuation of the Study

The Sponsor has the right to terminate or to stop the study at any time. Should this be necessary, both the Sponsor and the Investigator will ensure that proper study discontinuation procedures are completed. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigator with the concurrence of the Sponsor or the sole opinion of the Sponsor, makes the continuation of the study unnecessary or unethical.
- The stated objectives of the study are achieved.
- The Sponsor discontinues the development of the study drug.

Regardless of the reason for withdrawal, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

14.2. Early Withdrawal of Study Subjects

The Investigator will make every reasonable effort to keep each subject in the study; however, a subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the study, the Investigator will attempt to schedule an Early Withdrawal Visit as soon as possible, determine the reason for discontinuation, and record the reason in the subject's study records and in the eCRF.

If at any time during the study, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator may discontinue a subject at any time if medically necessary. The Investigator may discontinue a subject's participation if the subject has failed to follow study procedures or, to keep follow-up appointments. Prior to discontinuing a subject from study participation, the Investigator will discuss his/her intentions with the Sponsor's Medical Monitor or designee. Appropriate documentation in the subject's study record and eCRF regarding the reason for discontinuation must be completed.

All subjects who fail to return to the study site for the required follow-up visits will be contacted by phone to determine the cause(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that subject contact the site regarding study follow-up.

Subjects will be discontinued early from the study if any of the following occur:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical AE, laboratory abnormality, or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the study is not in the best interest of the subject.
- Death.

- Serious protocol violation, including persistent non-compliance, subjects requiring prohibited medications or procedures allowing subjects to receive the appropriate medical attention. In such cases, the Investigator must contact the Sponsor or designee, as the final decision to withdraw the subject will be taken by the Sponsor.
- Discontinuation of the study by the Sponsor.

14.3. Study Drug Discontinuation

Subjects who discontinue or have their study drug discontinued prematurely should continue to have all protocol-specified safety assessments and end of study procedures collected.

The Investigator should stop study drug treatment in the following instances:

- Inter-current illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.
- Any AE which is clinically significant, is deemed persistent, is probably or definitely related to study drug in the judgment of the Investigator.
- Unacceptable toxicity.

15. STATISTICAL CONSIDERATIONS

15.1. General Statistical Methodology

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. All statistical tests will be one-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

The primary method of handling missing efficacy data will be based on MCMC; additional details, including details on sensitivity analyses will be provided in the SAP.

The pruritus-NRS weekly mean will be calculated as follows: The mean of each subject's baseline and post-baseline pruritus-NRS scores will be computed for each week based on the previous 7 days. The weekly mean will be calculated if a subject has responses for pruritus-NRS on at least 4 of the 7 days of the week. If the subject has 3 or fewer pruritus-NRS responses, the mean value for that item will be considered missing. All pruritus-NRS efficacy endpoint analyses will be conducted on the weekly mean.

Demographic data will be summarized by treatment group using descriptive statistics. Subjects' baseline characteristics related to efficacy analyses will be compared with descriptive statistics among treatment groups to ensure comparable results.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

15.2. Populations Analyzed

All subjects who are randomized will be included in the intent-to-treat (ITT) population.

Per-protocol (PP) population: All subjects in the ITT population who complete the Week 8 evaluation without any significant protocol violations

PK population: All subjects who had blood collected for PK analysis will be included in the PK population.

All subjects who are randomized and receive at least one confirmed dose of study drug will be included in the safety population.

The primary efficacy analysis and the analysis of all secondary endpoints will be performed using the ITT population Additional supportive efficacy analyses will be performed using the PP population. In all efficacy analysis, subjects will be included in the treatment arm to which they

were randomized. Safety analyses will be performed using the safety population. In all safety analyses, subjects will be analyzed based on the treatment that was received.

15.3. Exposure and Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the expected number of applications while enrolled in the study.

15.4. Efficacy Measures

15.4.1. Primary Efficacy Analysis

The primary efficacy analysis will be conducted with an analysis of variance (ANOVA) model with the percentage change from Baseline to Week 8 in EASI score as the dependent variable and treatment group and the randomization stratification variable as factors. The two arms will be compared using a one-sided test at the alpha=0.05 level of significance.

15.4.2. Secondary Efficacy Analyses

All secondary endpoints defined as the percentage change from baseline will be analyzed using the same type of ANOVA model as specified for the primary analysis. All change from baseline secondary endpoints will be analyzed using analysis of covariance (ANCOVA) models with treatment group and the randomization stratification variable as factors and with the baseline value of the corresponding endpoint as a covariate. Secondary endpoints that are defined as proportion variables will be analyzed using Pearson's chi-square test or (if more than 25% of expected cell frequencies are less than 5) Fisher's exact test. All secondary analyses will be conducted using one-sided tests at the alpha=0.05 level of significance, with no adjustments for multiplicity.

15.5. Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. TEAEs are defined as AEs with an onset on or after the date of the first study drug application. AEs noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

All information pertaining to an AE noted during the study will be listed by subject, detailing the verbatim term given by the Investigator or designee, preferred term, system organ class, onset date, resolution date, severity, seriousness, action taken, outcome and drug relatedness. The event onset will also be shown relative (in number of days) to date of first application.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, system organ class, preferred term, severity, relationship to study drug (causality) and seriousness. When summarizing AEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs will be summarized by treatment group, severity and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

15.5.1. Local Skin Reactions

Local Skin Reaction assessments (LSRs) include burning/stinging, pruritus, edema/swelling, erythema, dryness, and scaling. LSRs will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe).

LSRs will be summarized by visit using descriptive statistics. A by-subject listing of subjects with any LSR scored as 3 will be presented.

15.6. Other Safety Data

Laboratory test results will be summarized descriptively at baseline and Week 8. Additionally, shifts from baseline to Week 8 in laboratory test results based on normal ranges will be summarized with descriptive statistics. Individual laboratory test results will be presented in a by-subject listing. Any clinically significant laboratory abnormalities will be captured as AEs.

Vital signs will be presented by treatment group as observed values and changes from baseline using descriptive statistics.

Medical histories will be coded using the MedDRA dictionary and presented in a by-subject listing.

Concomitant medications will be coded using the WHO-Drug dictionary. Concomitant medications will be summarized by treatment, drug class and preferred term.

Physical examination data will be presented in a by-subject listing.

Descriptive statistics by treatment group and visit will be provided for the following ECG parameters: heart rate (HR), RR duration, QRS duration, PR duration, QT duration and QTcF and QTcB duration.

15.7. Pharmacokinetic Analysis

Plasma concentration data will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, SD, and % coefficient of variation) by treatment group for each visit at which samples were taken.

15.8. Sample Size Determination

The assumed true standard deviation of the percentage change from Baseline to Week 8 in the EASI score is 50%. Based on the use of a one-sided test at the alpha=0.05 level of significance, a total sample size of 118 subjects (59 subjects/treatment arm) will provide greater than 90% power to detect a mean between-group difference of 30 percentage points.

16. ACCESS TO SOURCE AND STUDY RELATED DOCUMENTS

16.1. Study Monitoring

The Sponsor or designee will ensure that all study sites are qualified to participate and enroll subjects in this trial and will ensure that the facilities are adequate to conduct the trial and site staff are trained on the protocol. The study will be discussed with the investigator(s) and other personnel with regard to their responsibilities, protocol adherence, and the responsibilities of the Sponsor or its representatives.

During the study, the Sponsor or its designee will have regular contact with the study site to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously identified.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm all SAEs have been forwarded to the Sponsor or its designee and, as appropriate, forwarded to the institutional review board (IRB).

Subject confidentiality will be always maintained. The monitor will be available between visits if the investigator(s) or other staff needs information or advice. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected during the monitoring visits are resolved.

16.2. Audits and Inspections

Authorized representatives of the Sponsor or its designee, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor's audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Council for Harmonisation, and any applicable regulatory requirements. The investigator should contact the Sponsor or its designee immediately if contacted by a regulatory agency about an inspection.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The investigator must submit written approval to the Sponsor or its designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol, in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable with all local regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator(s) at each study site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

17.4. Compliance with the Protocol and Protocol Amendments

The study shall be conducted as described in this protocol. All revisions to the protocol must be prepared by the Sponsor. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/EC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented and submitted to the IRB/EC; the Sponsor or designee; and, if required, Regulatory Authority(ies).

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to the Sponsor and/or designee.

17.5. Study Documentation and the Case Report Form

The Investigator is responsible for ensuring that data are properly recorded in the eCRFs and on related documents. All entries must be supported by the subject's medical records or source notes. The Investigator who has signed the protocol signature page is to ensure that the observations and findings are recorded correctly and completely.

All Investigator observations/assessments must be reported in the eCRF. The original reports and any traces and films must be reviewed, signed, and dated and retained by the Investigator for future reference.

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported in the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator must certify that the data are complete and accurate at the time the subject ends the study or as instructed by the Sponsor or designee by applying an electronic signature to the eCRF study completion page.

18. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

19. DATA HANDLING AND RECORD KEEPING

19.1. Inspection of Records

The Sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

19.2. Retention of Records

The Investigator must retain study drug disposition records, copies of eCRFs and all study-related source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study. Following the study close-out visit, data will be provided to the Investigator to store with the Investigator's study file for archiving purposes.

20. PUBLICATION POLICY

Publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

21. LIST OF REFERENCES

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22. APPENDICES

Appendix 1. Subject AD Mapping Image