AN OPEN LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF EVO756 IN ADULTS WITH CHRONIC INDUCIBLE URTICARIA

Protocol Number	EVO756-CIU001
Protocol Final Date	FINAL v1.0 31May2024
Protocol Amendment 1	FINAL v2.0 23Jul2024
Protocol Amendment 2	FINAL v3.0 03Sep2024
Protocol Amendment 3	FINAL v4.0 10Jan2025
Study Drug	EVO756
IND Number	167423
Sponsor	Evommune, Inc. 1841 Page Mill Road Suite 100 Palo Alto, CA 94304 USA

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 3 (Protocol Version 4), are summarized in the following table. Administrative changes such as corrections to typographical and grammatical errors are made throughout the document.

Section(s)	Modification	Rationale
[redacted]	[redacted]	[redacted]
4.4.2	Added interim safety results from EVO756-CIU001.	Update to available clinical safety data from the ongoing trial.
[redacted]	[redacted]	[redacted]
8.2.6.1, Table 4, 13.4.1	Added serum chemistry and hematology evaluations at the Week 2 and Week 3 study visits.	[redacted]
[redacted]	[redacted]	[redacted]
6.1, Table 4, 13.6	Added PK sample collection at Week 3 visit.	To evaluate EVO756 concentrations in plasma at all visits.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
13.6	Deleted descriptive statistics from the PK statistical analyses.	PK samples are collected at random timepoints; therefore, descriptive statistics will not be summarized.

PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 2 (Protocol Version 3), are summarized in the following table. Administrative changes such as corrections to typographical and grammatical errors are made throughout the document.

Section(s)	Modification	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Changes to the protocol, introduced in Amendment 1 (Protocol Version 2), are summarized in the following table. Administrative changes such as corrections to typographical and grammatical errors are made throughout the document.

Section(s)	Modification	Rationale
4.1, 4.3	Study background and summary of nonclinical data is revised.	To more fully describe the study background and nonclinical data as presented in the IB.
4.4	Clinical experience from the recently completed EVO756-HV001 clinical study is updated.	To reflect the most current clinical experience with EVO756 in alignment with the revised IB and describe the rationale for the selected dose.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
8.2.6	Clarification added that on Day 1, blood samples will be collected prior to study drug administration.	To provide guidance on timing of baseline blood sample collection relative to the first dose.
10.4	Additional detail regarding study drug administration. Additional information to sites and subjects on recording missed doses and the timing of their last dose prior to the Week 1, 2, and 4 provocation tests on a form are added.	Added clarification on dosing instructions.
11.2.3	The statement “If no valid reason exists for suggesting a relationship, then the AE should be classified as ‘not related’…” is removed.	To clarify the requirements for assessing relatedness of AEs to study drug.
[redacted]	[redacted]	[redacted]
Table 4	The Week 4 visit window is changed to -3 days.	The previous window of ± 3 days was an oversight. Because provocation testing is conducted at Week 4, the visit cannot occur after treatment completion.

SPONSOR SIGNATURE PAGE

AN OPEN LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF EVO756 IN ADULTS WITH CHRONIC INDUCIBLE URTICARIA

Protocol Number: **EVO756-CIU001**

Protocol Final Date: **31May2024**

Protocol Amendment 1: **23Jul2024**

Protocol Amendment 2: **03Sep2024**

Protocol Amendment 3: **10Jan2025**

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 Conference on 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:

_____ _____

Sponsor Signature Date

[redacted]

INVESTIGATOR'S AGREEMENT

AN OPEN LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF EVO756 IN ADULTS WITH CHRONIC INDUCIBLE URTICARIA

Protocol Number: EVO756-CIU001

Protocol Final Date: 31May2024

Protocol Amendment 1: 23Jul2024

Protocol Amendment 2: 03Sep2024

Protocol Amendment 3: 10Jan2025

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, Inc. All rights of publication of the results reside with Evommune, Inc. unless other agreements were made in a separate contract.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
24-Hour Emergency Contact	[redacted]	[redacted]
Sponsor Physician	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company: Evommune, Inc		
Name of Investigational Product: EVO756		
Protocol Number: EVO756-CIU001	**Phase:** 2a	**Country**: United States
Title of Study: An Open Label Study Evaluating the Safety, Tolerability, and Efficacy of EVO756 in Adults with Chronic Inducible Urticaria		
Primary Objective: • To evaluate the safety and tolerability of EVO756 in subjects with chronic inducible urticaria (CIndU). **Secondary Objectives:** • To assess the efficacy of EVO756 in reducing wheal formation following a standardized provocation test in CIndU (cold urticaria or symptomatic dermographism). • To assess the efficacy of EVO756 in reducing pruritus at the site of urticaria provocation tests. [redacted]		
Study Design: EVO756-CIU001 is a multi-center Phase 2a open label study evaluating the safety, tolerability, and efficacy of EVO756 in adults with chronic inducible urticaria (CIndU). Subjects will be treated with EVO756 for 4 weeks and evaluated weekly on an outpatient basis. Subjects will return for a Study Exit visit approximately 2 weeks after treatment completion.		
Number of subjects (planned): Approximately 30 adults with CIndU, having either cold induced urticaria or symptomatic dermographism, will be enrolled in this study.		
Key Study Population Criteria: Inclusion Criteria: • Male or female aged ≥ 18 to ≤ 65 years, at the time of consent. • Capable of providing informed consent and willing and able to comply with study requirements. • Confirmed CIndU diagnosis with either cold urticaria or symptomatic dermographism for ≥ 3 months. • Positive provocation test result at Screening and Day 1 visits (see Section 8.2.6.5) o For subjects with cold urticaria, wheal formation at temperatures ≥16 °C using the TempTest.		

- For subjects with symptomatic dermographism, TFS of ≥ 2 using the FricTest.

Exclusion Criteria:

- Any clinically significant abnormality in laboratory evaluations, physical examinations, vital signs, or ECG at Screening in the opinion of the Investigator.
- AST, ALT, alkaline phosphatase, or total bilirubin above the ULN at Screening.
- History of hypersensitivity to EVO756, its components, or drugs of similar classes.
- Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days (or 5 half-lives, whichever is longer) or within 120 days (or 5 half-lives, whichever is longer) for investigational biologics prior to Day 1, or concomitant participation in an investigational study involving no drug or device administration. Participation in non-interventional registries or epidemiological studies is allowed.
- Concomitant use of the following medications for the timeframes specified below and while on study:
  - Biologics (e.g., omalizumab, dupilumab, tezepelumab, ligelizumab) for 120 days or 5 half-lives (whichever is longer) prior to Day 1,
  - Cyclosporine, methotrexate, sulfonamides, systemic glucocorticoids (e.g., prednisone), or mycophenolate mofetil for 28 days prior to Day 1,
  - A live or live-attenuated vaccine for 14 days prior to Day 1,
  - Leukotriene inhibitors (e.g., montelukast, zafirlukast) for 14 days prior to Day 1 (if being used to treat CIndU or CSU),
  - H2-receptor antagonists [e.g., ranitidine, famotidine]) for 14 days prior to Day 1 (if being used to treat CIndU or CSU),
  - Long-acting antihistamines (e.g. H1-receptor antagonists such as, loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) for 7 days prior to the first provocation test during the screening period,
  - Short-acting antihistamines (e.g., H1-receptor antagonists such as hydroxyzine, diphenhydramine) for 3 days prior to the first provocation test during the screening period.
- History of diseases other than CIndU or Chronic Spontaneous Urticaria (CSU) with urticaria or angioedema symptoms, such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema.
- Any other skin disease or skin markings (e.g., extensive scarring, tattoos) that might confound the assessment of CIndU provocation or pruritus evaluation in the Investigator's opinion.
- Significant medical history, other than CIndU, or sequelae of gastrointestinal (e.g., peptic ulcer, gastrointestinal bleeding), liver or kidney disease, uncontrolled cardiovascular disease, or any other condition which might interfere with the evaluation of safety or provocation of CIndU.

[redacted]

Criteria for evaluation:

Safety:

Safety will be assessed through an evaluation of treatment emergent adverse events (TEAEs), physical exams, vital signs, laboratory tests (serum chemistry, hematology, and urinalysis), and 12-lead ECGs.

Efficacy:

Efficacy of EVO756 in reducing wheal formation following standardized provocation will be assessed:

- In subjects with cold induced urticaria, the TempTest will be used to induce wheals and the Critical Temperature Threshold will be measured. The CTT determines the highest temperature sufficient for inducing symptoms.
- In subjects with symptomatic dermographism, the FricTest will be used to induce wheals and the Total Fric Score (TFS) will be measured. The TFS represents the number of wheals induced following the test, from 0 to 4.
- Efficacy of EVO756 in reducing the severity of pruritus at the provocation test site [redacted]

[redacted]

Statistical methods:

Sample size justification:

The sample size of this study is based on clinical considerations only.

Analyses for primary and secondary objectives:

Safety and tolerability:

Descriptive summary statistics will be prepared and reported for TEAEs. Changes from baseline will be summarized for vital signs, 12-lead ECG, and clinical laboratory parameters.

Efficacy:

In subjects with cold urticaria, mean absolute change from baseline in CTT and proportion of subjects who are complete responders will be calculated at Weeks 1, 2, and 4.

In subjects with symptomatic dermographism, mean absolute change from baseline in TFS and proportion of subjects who are complete responders will be calculated at Weeks 1, 2, and 4.

Worst pruritus-NRS score at the provocation test site will be assessed. [redacted]

Additional details will be described in the Statistical Analysis Plan (SAP).

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
BID	Twice daily
CIndU	Chronic inducible urticaria
CSU	Chronic Spontaneous Urticaria
CTT	Critical Threshold Temperature
[redacted]	[redacted]
GCP	Good Clinical Practice
EOT	End of Treatment
IB	Investigator's Brochure
IC90	90% inhibition concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IRB	Institutional Review Board
MC	Mast cells
MRGPRX2	Mas-related G-protein coupled receptor member X2
NRS	Numeric Rating Scale
OAE	Other significant adverse event
OTC	Over the counter
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
QD	Once daily
SAE	Serious adverse event
TFS	Total Fric Score
[redacted]	[redacted]

4. INTRODUCTION

4.1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted].

[redacted]

[redacted]

[redacted]

5. TRIAL OBJECTIVES AND EFFICACY ENDPOINTS

5.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of EVO756 in subjects with CIndU.

5.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of EVO756 in reducing wheal formation following a standardized provocation test in CIndU (cold urticaria or symptomatic dermographism).
- To assess the efficacy of EVO756 in reducing pruritus at the site of the urticaria provocation tests.

[redacted]

5.4. Endpoints

5.4.1. Safety

Safety will be assessed through an evaluation of treatment emergent adverse events (TEAEs), physical exams, vital signs, laboratory tests (serum chemistry, hematology, and urinalysis), and 12-lead ECGs.

5.4.2. Efficacy

Efficacy of EVO756 in reducing wheal formation following standardized provocation will be assessed by:

- In subjects with cold urticaria, [redacted]
- In subjects with symptomatic dermographism, [redacted]
- Worst pruritus-NRS score at the provocation test site [redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a multi-center Phase 2a open label study evaluating the safety, tolerability, and efficacy of EVO756 in approximately 30 adult subjects with CIndU. During screening, subjects will be evaluated for cold urticaria or symptomatic dermographism by the TempTest or the FricTest to determine baseline sensitivity to a cold or pressure provocation, respectively. [redacted] Subjects will be evaluated for IgE levels at Screening and will be identified as either an IgE low subject [redacted] or an IgE high subject [redacted]

Subjects will be seen on an outpatient basis at the study center at Screening, Day 1, Week 1, Week 2, Week 3, and Week 4 (End of Treatment). Subjects will return to the study center for a Study Exit visit at Week 6.

Efficacy will be assessed using a TempTest for subjects with cold urticaria or FricTest for subjects with symptomatic dermographism, and [redacted] pruritus-NRS at the site of the urticaria provocation test for all subjects.

Safety will be assessed through an evaluation of treatment emergent adverse events (TEAEs), physical exams, vital signs, laboratory tests (serum chemistry, hematology, and urinalysis), and 12-lead ECGs.

[redacted]

6.2. Number of Subjects

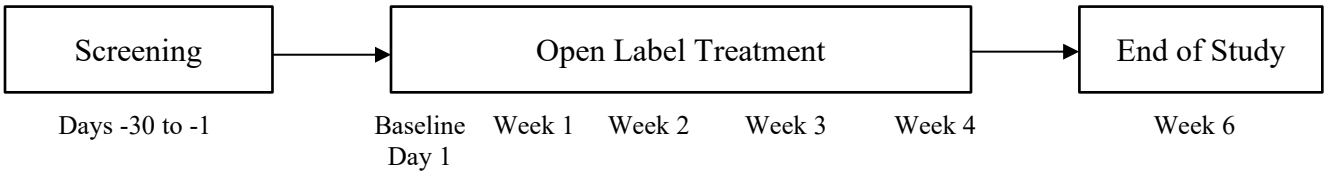
Approximately 30 subjects with CIndU will be enrolled in this study.

6.3. Duration of the Study

The duration of participation for each subject is expected to be approximately 10 weeks (up to 30 days for screening, 4 weeks of treatment, and 2 weeks of follow-up).

See Figure 1 for a schema of the study design.

Figure 1: Study Design



7. STUDY POPULATION

7.1. Subject Inclusion Criteria

1. Male or female aged ≥18 to ≤65 years, at the time of consent.
2. BMI >18.0 and ≤35.0 kg/m^2 at Screening.
3. Capable of providing informed consent and willing and able to comply with study requirements. Note: consent must be obtained prior to any study-related procedures.
4. Confirmed CIndU diagnosis with either cold urticaria or symptomatic dermographism for ≥ 3 months.
5. Positive provocation test result at Screening and Day 1 visits (see Section 8.2.6.5)
    a. For subjects with cold urticaria, wheal formation at temperatures ≥16 °C using the TempTest.
    b. For subjects with symptomatic dermographism, TFS of ≥ 2 using the FricTest.
6. WOCBP (childbearing potential females are defined as women that are neither postmenopausal nor surgically sterile) who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized since at least 6 months prior to screening) must be willing to use highly effective contraceptive methods at least 28 days prior to Day 1 and throughout the study and for 90 days after the last study drug administration.
    a. The following are highly effective contraceptive methods: combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable, implantable) 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.
    b. Female subjects who are not WOCBP must be either post-menopausal (at least 12 months of amenorrhea in the absence of other biological causes with a documented serum FSH confirming nonchildbearing potential as per laboratory ranges confirmatory levels at Screening) or surgically sterilized (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy).
7. Male subjects who are not vasectomized for at least 6 months prior to screening, and who are sexually active with a WOCBP must be willing to use an effective barrier method of contraception from the first study drug administration until at least 90 days after the last study drug administration. Female partners of male subjects who are WOCBP should use acceptable contraceptive methods at least 28 days prior to Day 1, throughout the study, and for 90 days after the last study drug administration.

8. Male subjects must not donate sperm from the first study drug administration until 90 days following the last study drug administration.
9. Female subjects must not donate oocytes or undergo in vitro fertilization from the first study drug administration until 90 days following the last study drug administration.

7.2. Subject Exclusion Criteria

1. Any clinically significant abnormality in laboratory evaluations, physical examinations, vital signs, or ECG at Screening, in the opinion of the Investigator.
2. Known history of HIV, hepatitis B, or hepatitis C.
3. AST, ALT, alkaline phosphatase, or total bilirubin above the ULN at Screening.
4. History of renal disease, creatinine level 1.25x above ULN, or creatinine clearance <60 ml/min (using the Cockcroft-Gault or CKD-EPI equation) at Screening.
5. History of hypersensitivity to EVO756, its components, or drugs of similar classes.
6. History of clinically significant drug or alcohol abuse in the last year prior to Day 1.
7. Positive pregnancy test or breastfeeding at Screening and Day 1.
8. Women planning a pregnancy within the study period.
9. History of a major surgery within 8 weeks prior to Day 1, or major surgery planned during the study.
10. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days (or 5 half-lives, whichever is longer) or within 120 days (or 5 half-lives, whichever is longer) for investigational biologics prior to Day 1, or concomitant participation in an investigational study involving no drug or device administration. Participation in non-interventional registries or epidemiological studies is allowed.
11. Concomitant use of the following medications for the timeframes specified below and while on study:
    a. Biologics (e.g., omalizumab, dupilumab, tezepelumab, ligelizumab) 120 days or 5 half-lives (whichever is longer) prior to Day 1,
    b. Cyclosporine, methotrexate, sulfonamides, systemic glucocorticoids (e.g., prednisone), or mycophenolate mofetil 28 days prior to Day 1,
    c. A live or live-attenuated vaccine 14 days prior to Day 1,
    d. Leukotriene inhibitors (e.g., montelukast, zafirlukast) 14 days prior to Day 1 (if being used to treat CIndU or CSU),
    e. H2-receptor antagonists [e.g., ranitidine, famotidine]) 14 days prior to Day 1 (if being used to treat CIndU or CSU),
    f. Long-acting antihistamines (e.g. H1-receptor antagonists such as, loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) 7 days prior the first provocation test during the screening period,

g. Short-acting antihistamines (e.g., H1-receptor antagonists such as hydroxyzine, diphenhydramine) for 3 days prior to the first provocation test during the screening period.

12. History of diseases other than CIndU or CSU with urticaria or angioedema symptoms, such as urticarial vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa), and hereditary or acquired angioedema.
13. Any other skin disease or skin markings (e.g., extensive scarring, tattoos) that might confound the assessment of CIndU provocation or pruritus evaluation in the Investigator's opinion.
14. History of malignancy of any organ system (other than fully treated localized basal cell carcinoma or squamous cell of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
15. Significant medical history, other than CIndU, or sequelae of gastrointestinal (e.g., peptic ulcer, gastrointestinal bleeding), liver or kidney disease, uncontrolled cardiovascular disease, or any other condition which might interfere with the evaluation of safety or provocation of CIndU.
16. Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study or being compliant with study procedures.

8. STUDY PROCEDURES

The procedures required for subject evaluation at each study visit are presented in the Schedule of Assessments, [redacted] The timing of each study day is relative to the day of initial dosing (Day 1). Visit windows are provided where allowed to allow flexibility in maintaining the study visit schedule for participating subjects.

8.1. Study Visits

8.1.1. Screening

The screening period may take up to 30 days to provide flexibility in scheduling and adequate washout time for subjects taking certain medications. Questions on subject eligibility will be referred to the Sponsor or their designee. Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the Investigator and Sponsor. Rescreened subjects will be re-consented and assigned a new subject number.

8.1.2. Day 1 through Study Exit

Subjects will complete all procedures as summarized in the Schedules of Assessments, [redacted] and detailed below on Day 1 through their Study Exit.

8.1.3. Unscheduled Visits

Additional visits may be scheduled, as necessary, and any safety procedures may be conducted at the discretion of the Investigator. All data collected will be recorded in the eCRF and laboratory database, as appropriate.

8.2. Study Procedures

8.2.1. Demographics/Medical History

Demographic information including age, gender, race, and ethnicity will be collected for each subject.

A complete medical history will be collected as part of Screening and should include all clinically relevant past or coexisting medical conditions or surgeries. History of CIndU, date of diagnosis, and any prior or current medications for CIndU will be recorded in the eCRF accordingly. Such history will be supported by medical records, as available.

The medical history will be updated prior to treatment, should new findings be present after the Screening visit.

8.2.2. Vitals 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.

When vital signs measurements coincide with a blood draw, they should be performed before the blood collection.

8.2.3. Height and Weight

Height will only be collected at Screening. Weight will be collected at all other timepoints as indicated in [redacted]

8.2.4. Physical Exam

A complete physical examination will be conducted at study visits as detailed in the Schedule of Assessments, [redacted]

The complete physical examination will cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems.

8.2.5. 12-Lead ECG

A 12-lead ECG will be conducted at study visits as detailed in the Schedule of Assessments, [redacted] Prior to measurement, subjects will be required to have rested for at least 10 minutes in a supine position. Study sites will use 12-lead ECG machines capable of recording ventricular rate, the PR, QRS, QT, QTcF, and RR intervals. The Sponsor or designee will help procure equipment for sites that do not have access to a 12-lead ECG. When ECGs coincide with a blood draw, they should be performed before the blood collection.

8.2.6. Laboratory Assessments

Laboratory tests will be collected as stipulated in the Schedule of Assessments, [redacted] will be analyzed at a central laboratory. Day 1 samples will be collected prior to study drug administration. Laboratory assessments may be repeated once during screening to qualify a subject for the study. All laboratory assessments, for screening and during the trial conduct, must be collected using the central laboratory. Sample handling, processing, and shipping information will be detailed in the Laboratory Manual.

8.2.6.1. Hematology, Blood Chemistry, and Urinalysis

Hematology, blood chemsitry, and urinalysis samples will be collected to evaluate safety. Analytes to be tested are summarized in [redacted]

Table 3: Laboratory Analytes for Safety Evaluation

Hematology	Blood Chemistry	Urinalysis
• Hematocrit • Hemoglobin • Red blood cell (RBC) count • White blood cell count and differential (%) • Mean corpuscular hemoglobin (MCH)	• Sodium • Potassium • Magnesium • Chloride • Calcium, phosphorus • CO2 • Uric acid	• pH • Specific gravity • Protein • Glucose • Ketones • Bilirubin • Blood

Hematology	Blood Chemistry	Urinalysis
• Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume • RBC morphology • Platelet count • Absolute neutrophils • Absolute lymphocytes • Absolute monocytes • Absolute eosinophils • Absolute basophils	• Blood urea nitrogen (BUN) • Creatinine • Total protein • Albumin • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase • Bilirubin (total, indirect, and direct) • Cystatin C • [redacted]	• Nitrite • Urobilinogen • Leukocyte esterase • Qualitative assessment of color and clarity • Microscopic analysis (as required)

8.2.6.2. Pregnancy Testing

Pregnancy testing will be performed for WOCBP. Serum pregnancy testing will be conducted at Screening, Week 4, and Week 6/Study Exit/Early Withdrawal. On Day 1 and unscheduled visits, pregnancy testing will be urine.

If a urine pregnancy test is positive prior to dosing, a serum pregnancy test may be drawn at the discretion of the Investigator to confirm the pregnancy. A negative urine or serum pregnancy test must be demonstrated to confirm subject eligibility prior to dosing.

A blood sample to test serum FSH will be collected from female subjects who are under 55 and post-menopausal (defined by 12 months of amenorrhea in the absence of other biological causes) at Screening.

8.2.6.3. Pharmacokinetic Sampling

A blood sample will be collected per the Schedule of Assessments, [redacted] at any time during the specified visit. Sample handling, processing, and shipping information will be detailed in the Laboratory Manual.

[redacted]

8.2.6.5. Immunoglobulin E (IgE)

As part of the blood chemistry panel at Screening, pre-treatment IgE levels will be evaluated as a baseline characteristic for all subjects. The Sponsor will review screening IgE levels for all subjects [redacted]

8.2.7. Standardized Provocation Tests

Depending on the CIndU subtype, subjects will undergo provocation testing at the visits outlined in the Schedule of Assessments, [redacted] Details on how to perform the provocation tests will be outlined in the Provocation Test Manual. Each provocation test will be evaluated approximately 10 minutes after completion of provocation. The start and end time of the provocation test and the beginning of the provocation test evaluation will be recorded in the eCRF.

Provocation tests should be performed by the same administrator and evaluator, on the same arm for the duration of participation, whenever possible.

8.2.7.1. Cold Urticaria - TempTest

The TempTest is an instrument used to elicit symptoms of cold and heat urticaria. The instrument is a small device containing a single 2 mm wide 350 mm long U-shaped Peltier element generating a temperature gradient from 4° to 44 °C along its length. The subject will place the volar aspect of their forearm on the temperature gradient side of the device for approximately 5 minutes.

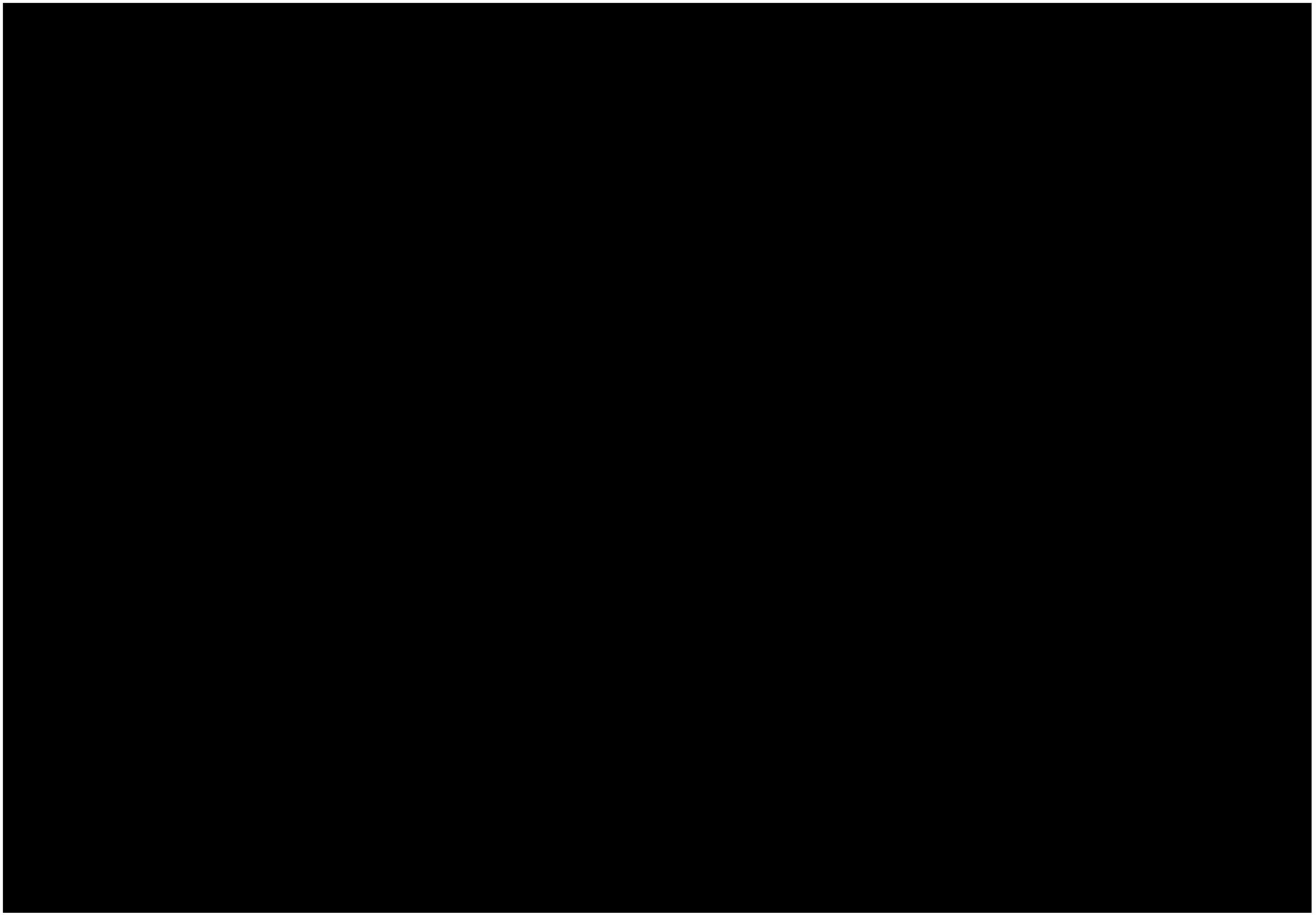
A positive response to the provocation test is defined as a palpable wheal at the test site. Approximately 10 minutes after completion of provocation (i.e., approximately 15 minutes from the start of the test), the resultant wheal will be outlined on the TempTest provided stencil. The critical threshold temperature (CTT), defined as the highest temperature that elicits a wheal response, will be determined and recorded. The stencil with wheal markings will be filed in the subject's source documents.

8.2.7.2. Symptomatic Dermographism - FricTest

The FricTest is an instrument used to diagnose symptomatic dermographism (Mlynek 2013). The FricTest is a flat plastic comb (85 x 55 mm) with four round-ended plastic pins 3 mm in diameter, with lengths of 3.0, 3.5, 4.0, and 4.5 mm, respectively. For provocation, the comb is held perpendicular to the volar forearm and constant, sufficient pressure is applied so that all pins make contact with the skin and are almost, but not completely, invisible. The instrument is then stroked across the skin across approximately 60 mm. After about 10 minutes, the resultant wheals are evaluated. A clearly visible and palpable linear wheal with a width of ≥3 mm (the diameter of the pins) is considered a positive response. The total number of linear wheals with a width of ≥3 mm is the Total Fric Score (TFS).

8.2.8. Pruritus-Numerical Rating Scale (NRS)

Prior to and approximately 10 minutes after completion of the provocation test (i.e., immediately after the wheal evaluation), the subject will be asked to rate the severity of their pruritus at the site of the provocation test [redacted]



9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

[redacted]

9.2. Concomitant Medications

All medications (including over the counter [OTC] agents) taken by subjects after Screening until the last study day will be documented as concomitant medications in the eCRF.

The following medications are prohibited for the timeframe specified prior to the Day 1 visit and while on study:

- Biologics (e.g., omalizumab, dupilumab, tezepelumab, ligelizumab) 120 days or 5 half-lives (whichever is longer) prior to Day 1,
- Cyclosporine, methotrexate, sulfonamides, systemic glucocorticoids (e.g., prednisone), or mycophenolate mofetil 28 days prior to Day 1,
- A live or live-attenuated vaccine for 14 days prior to Day 1,
- Leukotriene inhibitors (e.g., montelukast, zafirlukast) 14 days prior to Day 1 (if being used to treat CIndU or CSU),
- H2-receptor antagonists [e.g., ranitidine, famotidine]) 14 days prior to Day 1 (if being used to treat CIndU or CSU),
- Long-acting antihistamines (e.g. H1-receptor antagonists such as, loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) 7 days prior the first provocation test during the screening period,
- Short-acting antihistamines (e.g., H1-receptor antagonists such as hydroxyzine, diphenhydramine) for 3 days prior to the first provocation test during the screening period.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

[redacted]

10.4. Study Drug Dispensation, Administration, and Return

Subjects will be dispensed study drug on Day 1, Week 1, Week 2, and Week 3 to support at-home dosing between clinic visits. Subjects will be administered their first dose of study drug at the study center.

For QD doses, subjects will be instructed to orally self-administer study drug with approximately 240 mL of water at approximately the same time every morning starting on Day 2 through Week 4.

For BID doses, subjects will be instructed to orally self-administer study drug with approximately 240 mL of water every morning and evening, approximately 12 hours apart. On study visit days, subjects will take study drug at the study center, as feasible. The investigator and study personnel should promote compliance by instructing the subject to take the study drug exactly as prescribed and by stating that compliance is necessary for the subject's safety and validity of the study. The subject will be instructed to contact the site if he/she is unable to take the study drug as prescribed for any reason. Compliance with study drug dosing will be reviewed at each visit and all remaining study drug must be returned to the site at each visit for study drug accountability. Adherence to treatment will be assessed by direct questioning and by maintaining adequate study product dispensing and return records. Subjects will be provided a paper diary to record any missing doses and to record the timing of the last administration of study drug prior the Week 1, 2, and 4 provocation tests. Missing doses and the time of administration prior to the provocation tests at Week 1, 2, and 4 will be recorded in the eCRF.

10.5. Study Drug Accountability and Disposal

The Investigator or designee will be responsible for documenting drug accountability at the study center. 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.

11. SAFETY MONITORING

11.1. Safety Parameters

Subjects will be monitored throughout the study by the clinical staff for AEs.

Safety parameters, including vital signs, physical exam results, laboratory results, and the 12-lead ECG, will be assessed by the Investigator or designee.

Subjects will be advised to notify their healthcare professional(s) that they are participating in a clinical research study on a drug called EVO756 before taking any medicines or undergoing any medical procedures.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. 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 causally 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.

Abnormal laboratory, vital signs, physical exam, and ECG findings may be assessed as AEs only if they are found to be clinically significant by the investigator, correlate with a clinically relevant presentation, and/or require intervention.

11.2.1.2. 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;
- 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.

11.2.2. 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 study center.

AEs should be recorded on the eCRF from the time the subject has signed informed consent through the last study visit. 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 Investigator or designee and will be treated and/or followed up until the symptoms or values return to normal or to clinically acceptable levels, or stabilize, as judged by the Investigator.

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 or stabilization 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 11.2.1.2. An AE of severe intensity may not be considered serious (e.g., 'severe' headache). 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 or until resolution, whichever is sooner, using SAE form. 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.

Reporting should be done by sending the completed SAE form to the following email address (faxing can also be done as a second option in case emailing is not possible).

[redacted]

In all cases, the Investigator 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 Investigator 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 or designee will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will decide 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.

11.2.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (not related, 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.

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 have a reasonable possibility to be associated with the study drug and/or is attributable to another cause.

Related: An AE is defined as "related" where a causal relationship between the event and the study drug is reasonably likely. 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, the AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the known characteristics of the subject's clinical state.

11.3. Pregnancy

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 inform the Sponsor (or designee) and complete a study-specific pregnancy form within 24 hours of the confirmation of pregnancy (contact information to be used is the same as for SAE reporting). Pregnancy reporting forms will be provided to the site. The Investigator will follow the pregnancy until completion or until pregnancy termination, and in the case of a live-born offspring, to 1 month of age in that infant. Details for both the mother and baby must be obtained. In the event that the female partner of a male subject were to become pregnant, the Investigator must obtain consent prior to collecting medical information on the pregnancy. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities must be recorded as AEs or SAEs.

[redacted]

12. STUDY DISCONTINUATIONS

12.1. 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 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, including reason(s) for discontinuation, must be recorded in the eCRF.

12.2. 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 Termination/Study Exit 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 Physician 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 center 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.

12.3. 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:

- [redacted]
- 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.

13. STATISTICS

13.1. General Statistical Methodology

A statistical analysis plan (SAP), describing all statistical analyses, will be provided as a separate document. [redacted]

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.

Demographic data will be summarized using descriptive statistics.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal will be summarized using frequencies and percentages.

[redacted]

13.3. Exposure and Compliance

The extent of exposure to study drug will be summarized by the dose of study drug administered per dose, total number of days of exposure, total number of doses, number of missed doses, and number and percentage of subjects who are compliant. [redacted]

13.4. Safety Measures

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 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/stabilization date, severity, seriousness, action taken, outcome and relationship to study drug. The event onset will also be shown relative (in number of days) to date of first dose.

Treatment-emergent AEs will be summarized for all subjects by 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 for all subjects, 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.

13.4.1. Other Safety Data

Laboratory test results will be summarized descriptively by visit . Additionally, shifts by study visit to Week 4 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 as observed values and changes from Day 1 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 drug class and preferred term.

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

Descriptive statistics by 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.

13.5. Efficacy Measures

In subjects with cold urticaria, mean absolute change from baseline in CTT will be calculated at Weeks 1, 2, and 4. Additionally, proportion of complete responders ([redacted] will be calculated at Weeks 1, 2, and 4.

In subjects with symptomatic dermographism, mean absolute change from baseline in TFS will be calculated at Weeks 1, 2, and 4. Additionally, proportion of complete responders [redacted] will be calculated at Weeks 1, 2, and 4.

Worst pruritus-NRS at the provocation test site will be assessed. [redacted] Additional details will be provided in the SAP.

13.6. Pharmacokinetic Analysis

Plasma concentration data will be tabulated for Day 1, Week 2, Week 3 and Week 4.

13.7. Exploratory Measures

[redacted]

14. ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

During the study, a monitor or Sponsor representative will have regular contacts with the study center, for the following:

- 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 reported;
- Confirm AEs and SAEs have been properly documented on CRFs, confirm that the Sponsor has been informed of all SAEs, and assess if SAEs have been reported to the IRB, as appropriate.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice. Centralized monitoring, which consists of remote review of accumulating data from all sites may also be performed.

14.2. Audits and Inspections

Authorized representatives of the Sponsor (or designee), a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of Sponsor (or designee) 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 Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

16. ETHICS

16.1. Ethics Review

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

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB 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 will provide this information to the Principal Investigator.

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

16.2. 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, and applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits 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 Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

16.4. 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 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; the Sponsor or designee; and, if required, Regulatory Authority(ies).

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

16.5. 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 as required by protocol 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.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor (or 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.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation or based on local regulations. If it becomes necessary for the Sponsor (or designee) or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

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

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