TrialSpark

CLINICAL STUDY PROTOCOL

Protocol Number:	ASN008-201
Protocol Title:	A Randomized, Double-Blind, Vehicle-Controlled, Phase 2 Trial to Evaluate the Anti-pruritic Efficacy, Safety, Tolerability, and Pharmacokinetics of ASN008 in Adults with Mild to Moderate Atopic Dermatitis
Compound:	ASN008
Version:	3.0
Version Date:	05 July 2023
Study Phase:	Phase 2
Sponsor Name:	TrialSpark, Inc
Legal Registered Address:	16 E 34th Street, 10th Floor New York, NY 10016, USA
IND:	137975
NCT #:	NCT05870865

SPONSOR SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, Vehicle-Controlled, Phase 2 Trial to Evaluate the Anti-pruritic Efficacy, Safety, Tolerability, and Pharmacokinetics of ASN008 in Adults with Mild to Moderate Atopic Dermatitis

The information contained in this protocol is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research that have their origins in the Declaration of Helsinki and are described in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E6(R2), Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, and 312, and applicable local regulations.

The trial will be conducted in accordance with ICH Good Clinical Practice (GCP), applicable United States (US) CFR, and applicable local regulations.

Sponsor Signatories

[redacted]

7/5/2023 | 12:54:50 PM EDT

Date

[redacted]
Chief Medical Officer, TrialSpark

[redacted]

7/5/2023 | 1:32:55 PM EDT

Date

[redacted]
Vice President, Biostatistics and Data Management

PROTOCOL VERSION SUMMARY

Document	Version	Date
Original Protocol	Version 1.1	20 January 2023
Global Amendment 1	Version 2.0	30 March 2023
Global Amendment 2	Version 3.0	05 July 2023

Summary of Protocol Amendment Changes

Description of Change	Sections Impacted	Brief Rationale
Global Amendment 2, Version 3.0 (05 July 2023)		
Removed Investigator Signature Page	N/A	Investigator signatures are being collected on a separate form
Removed requirement to apply IP at site on Days 8, 15, and 22	Table 2	Ensure consistent IP application regardless of study visit timing
Corrected eDiary verification time points (not performed on Days 1 and 56)	Table 2	Correct error
Added a footnote to the Schedule of Assessments on recommended order of procedures at study visits	Table 2	Provide clarification
Revised requirement for Randomization Visit to occur up to Day -7	Table 2, Figures 1 & 2 Section 5.5	Requirements around timing of the Randomization Visit were modified to ensure maximal flexibility in scheduling the Day 1 visit. Clinically, the timing of randomization is not important as long as the participant is confirmed eligible and drug is able to be at the site prior to Day 1.
Added section on study requirements and procedures such as emollient use, daily eDiary entries, and recommended order of procedures at study visits	Section 3.2 (new)	Provide clarifications to ensure consistency across sites and improve compliance with eDiary entries
Updated inclusion criterion #2 to specify need for documented Investigator confirmation of AD diagnosis when medical records are not available	Section 4.1 (and Synopsis)	Provide clarification
Removed note from inclusion criterion #10	Section 4.1 (and Synopsis)	The note was specific to use of the eDiary and not specific to inclusion criteria; this information is now covered in the new Section 3.2.2.
Updated exclusion criteria #17 and #26 to clarify that ECG and BP measurements at the Screening and Day 1 visits are to be considered for eligibility	Section 4.2 (and Synopsis)	Provide clarification
Clarified recommendations and expectations regarding administration of study drug	Section 6.1	Provide clarification
Updated text to ensure consistent use of “Peak Pruritus NRS” terminology	Section 7 and 7.1	Correct inconsistency
Added clarifications regarding recording on NRS data	Section 7.1	Provide clarification

Description of Change	Sections Impacted	Brief Rationale
Removed requirement to assess vIGA before the morning dose	Section 7.4	No longer applicable since dose administration at the site is no longer required at most visits
Added clarification on repeat vital sign assessments	Section 8.1.1	Provided clarification
Added creatine phosphokinase to list of laboratory parameters	Table 7	Correct oversight
Replaced PK parameter of "oral clearance" with "apparent systemic clearance"	Global	Correct error
Minor edits for grammar (i.e., spelling, punctuation) and consistent terminology	Global	Correct grammatical errors and inconsistencies
Incorporated changes in Administrative Letter 2	Global	Provide clarification

Description of Change	Sections Impacted	Brief Rationale
Global Amendment 1, Version 2.0 (30 March 2023)		
Corrected exclusion criteria numbering	Synopsis	Correct error
Revisions to Schedule of Assessments: • Corrected visit window for Week 4 (-2 days) and Week 8/ET (±2 days) • Updated footnote d (on ECG collection) • Updated footnote reference and footnote wording for IP administration (footnote h)	Tables 2 and 3	Correct errors and provide clarification
Added paragraph on dose justification	Section 1.1	Provide clarification
Clarified that the last dose of study treatment on Day 28 is to be applied during the study visit	Section 3.1 (and Synopsis)	Provide clarification
Added statement that participants are not to receive study treatment for more than 28 days	Section 3.1 (and Synopsis)	Provide clarification
Updated inclusion criterion 7 to specify Vitamin C as an exclusionary emollient	Sections 4.1 and 5.2.1 (and Synopsis)	Correct inconsistency with Table 6 (Prohibited Therapies and Procedures)
Updated exclusion criteria 2, 9, 11, and 12 on prior/ concomitant therapies; Added exclusion criterion 28	Section 4.2 (and Synopsis)	Correct inconsistency with Table 6 (Prohibited Therapies and Procedures)
Added possible reasons for withdrawal and information regarding loss to follow up	Section 4.3	Provide clarification
Added antihistamines to Table 6 (Prohibited Therapies or Procedures)	Section 5.2.3	Correct inconsistency with exclusion criterion 9
Updated study restrictions to be consistent with other protocol sections	Section 5.4	Correct inconsistency
Removed format for participant ID numbers	Section 5.5	Correct error
Removed Appendices and referenced their inclusion in the Investigator site files	Sections 7 and 12	Limit distribution of duplicative information
Added respiration rate to vital sign assessments	Section 8.1.1	Correct oversight
Minor edits for grammar (i.e., spelling, capitalization, punctuation) and abbreviation use	Global	Correct grammatical errors and inconsistencies
Incorporated changes in Administrative Letter 1	Global	Provide clarification

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LIST OF ABBREVIATIONS

AD	Atopic dermatitis
AE	Adverse event
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CFR	Code of Federal Regulations
CL/F	Apparent systemic clearance
CV	Coefficient of variance
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
ED_{50}	Median effective dose
ET	Early Termination
FTU	Fingertip unit
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JAK	Janus kinase
MCPMod	Multiple Comparison Modelling
NRS	Numerical rating scale
PK	Pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PP	Per protocol
QD	Once daily
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TRPA1	Transient Receptor Potential-A1
TRPV1	Transient Receptor Potential-V1
ULN	Upper limit of normal
Vd/F	Apparent volume of distribution
vIGA	Validated Investigator Global Assessment

SYNOPSIS

Name of Sponsor/Company: TrialSpark, Inc	**Name of Investigational Product:** ASN008	

Title of Trial:

A Randomized, Double-Blind, Vehicle-Controlled, Phase 2 Trial to Evaluate the Anti-pruritic Efficacy, Safety, Tolerability, and Pharmacokinetics of ASN008 in Adults with Mild to Moderate Atopic Dermatitis

Phase of Development: Phase 2

Trial Centers:

Approximately 25 US trial centers will participate in this trial.

Population:

Sample Size: Approximately 120 participants will be enrolled.

Target Population: The trial population includes adults with mild to moderate atopic dermatitis (AD, validated Investigator Global Assessment [vIGA] of 2 or 3) body surface area (BSA) ≤20%, and pruritus numerical rating scale (NRS) ≥7 at baseline (Day 1).

Duration of Trial:

The trial duration per participant is up to 12 weeks (84 days): including up to 4 weeks (28 days) for the screening period, 4 weeks (28 days) for the treatment period, and up to 4 weeks (28 days) for the follow-up period.

Investigational Product, Dosage, and Route of Administration:

ASN008 topical gel (1.25, 2.5, and 5%) or matching vehicle applied twice daily (BID).

Route of administration: Topical application

Objectives:

Primary Objective:

- To evaluate the anti-pruritic effect of ASN008 topical gel compared to matching vehicle in participants with AD following BID topical application for 4 weeks (28 days).

Secondary Objectives:

- To evaluate the therapeutic effect of ASN008 topical gel on AD.
- To evaluate the local and systemic safety and tolerability of ASN008 topical gel in participants with AD following BID topical application.
- To evaluate the pharmacokinetic (PK) profile of ASN008 topical gel in participants with AD following BID topical application.

Endpoints:

Primary Efficacy Endpoint:

- Percent change of 7-day average daily peak pruritus NRS from Baseline to Week 4.

Secondary Efficacy Endpoints:

- Percent change of 7-day average daily peak pruritus NRS from Baseline to Week 1, 2, and 3.
- Change of 7-day average daily peak pruritus NRS from Baseline to Week 1, 2, 3 and 4.
- Change and percent change from baseline in daily peak pruritus NRS to Days 1 to 7.
- Pruritus response defined as 7-day average of daily peak pruritus NRS reduction ≥4 points from Baseline at Week 1, 2, 3, and 4.
- Change from baseline in 5-D Pruritus Scale at Week 2 and 4.
- Change and percent change from baseline in the Eczema Area and Severity Index (EASI) score at Week 2, and 4.
- Change from baseline in total BSA at Week 2, and 4.
- Change from baseline in the Dermatology Life Quality Index (DLQI) at Week 2, and 4.
- Change from baseline in the Patient-Oriented Eczema Measure (POEM) at Week 2 and 4.

Exploratory Efficacy Endpoints

- Change from baseline in vIGA at Week 2 and 4.
- At least a 50% reduction from baseline in EASI (EASI-50) at Week 2 and 4.
- At least a 75% reduction from baseline in EASI (EASI-75) at Week 2 and 4.
- At least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA at Week 2 and 4.
- Change from baseline in hourly pruritus NRS score at Hour 1 to 24.

Safety and Tolerability Endpoints

- Number of treatment-emergent adverse events (TEAEs).
- Number of Investigational Product related TEAEs.
- Changes in vital signs, physical examinations, electrocardiogram (ECG), and safety laboratory tests.
- Incidence of treatment-emergent serious adverse events from first dose through completion of the follow-up period (up to a maximum of 56 days).
- Incidence of TEAEs leading to treatment discontinuation from first dose through completion of follow-up period (up to a maximum 56 days).

Secondary PK Endpoints

- ASN008 PK will be characterized using population-based methods. Apparent systemic clearance (CL/F), apparent volume of distribution (Vd/F), inter- and intra-subject variability of these parameters will be estimated.

Trial Design:

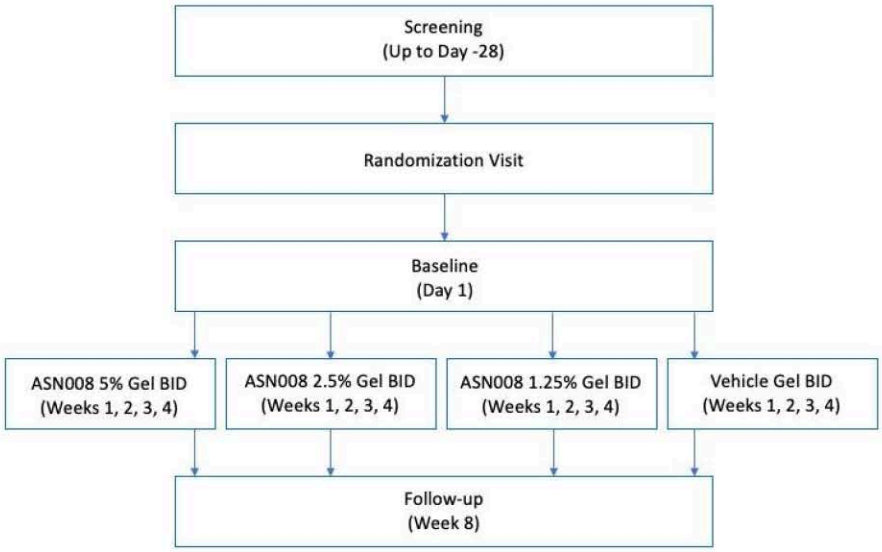
Approximately 120 participants, at least 18 years of age, with mild to moderate AD (vIGA of 2 or 3), BSA of ≤20% involved, and a pruritus NRS ≥7 at Screening and at Day 1 (pre-dose), will be included in this randomized, double-blind, placebo-controlled, multicenter, Phase 2 trial.

All participants will sign an informed consent form and undergo screening (within 28 days prior to Day 1). During the screening period, all treatments for AD and/or itch will be stopped to allow for wash out, as applicable and according to eligibility requirements (see Section 5.2.3). Participants may be re-screened once if they fail the initial screening evaluation for reasons related to incidental transitory conditions and if they met (and continue to meet) the disease severity and pruritus level specified in the inclusion criteria.

Consistent daily or BID use of a non-prescription emollient (participant's choice, excluding those containing hydrocortisone, urea, antihistamines, anesthetics, antibiotics, cannabidiol, or Vitamin C) is required at least 7 days prior to Day 1 and throughout the trial until the follow-up (Week 8). During the study, participants should apply the emollient to all areas other than those where the trial product has been applied. Every effort should be made to use the same emollient throughout the trial. The commercial name of the selected emollient(s) will be recorded in the source document and electronic case report forms. No other products, including, but not limited to, topical corticosteroids, calcineurin inhibitors, biologics, or Janus kinase (JAK) inhibitors (topical or oral) may be used during the trial.

Eligible participants will be randomized in a 1:1:1:1 ratio to receive ASN008 gel 1.25%, ASN008 gel 2.5%, ASN008 gel 5%, or matching vehicle BID for 4 weeks (28 days), followed by a 4-week (28-day) follow-up period. Participants will be required to participate in 8 scheduled visits: Screening; Randomization (remote visit); Day 1; Week 1 (Day 8); Week 2 (Day 15); Week 3 (Day 22); Week 4 (Day 28); and Week 8 (Day 56)/early termination. See Study Schema (Figure 1).

Figure 1 Trial Design



Participants who meet all the inclusion criteria and none of the exclusion criteria will be accepted into the trial. Eligible participants will be enrolled in 1 of 4 cohorts (Table 1), with approximately 30 participants per cohort.

Table 1 Trial Cohorts

Cohort	Participants (N)	Dose
1	30	ASN008 5.0% BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days)
2	30	ASN008 2.5% BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days)
3	30	ASN008 1.25% BID daily topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days)
4	30	ASN008 matching vehicle BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days)

N=number of participants; BID=twice daily.

Participants will be randomized to receive ASN008 gel 1.25%, 2.5%, 5% or matching vehicle applied BID to the AD lesions as instructed for a treatment period of 4 weeks (28 days). The first dose will be applied on Day 1 and the last dose will be applied during the Day 28 study visit; participants are not to receive study treatment for more than 28 days.

Safety monitoring: Adverse events will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (Version 25.1 or later). All safety data (scheduled and unscheduled) will be presented in data listings.

Safety will be assessed by collecting TEAEs, recording vital signs, performing complete and brief physical examinations, ECGs, and evaluating clinical laboratory results and local tolerability assessments.

Any safety concerns arising during the study will be evaluated by the Medical Monitor and Sponsor to determine the appropriate course of action (e.g., treatment discontinuation, stopping enrollment) for the remaining participants and communicated to the sites, if needed.

Participation in the PK part of the study is mandatory. Blood samples will be collected as follows:

- Day 1: Pre-dose (0), 1, 2, and 4 hours post-dose.
- Day 28: Pre-dose (0), 1, 2, and 4 hours post-dose.

Inclusion/Exclusion Criteria:

Inclusion criteria:

Participants are eligible to be included in the trial if ALL the following criteria apply:

1. Male or female participants, 18 years or older, at the time of informed consent.
2. Diagnosis of mild to moderate AD for at least 12 months according to American Academy of Dermatology Consensus Criteria with no significant disease flares for at least 4 weeks before Screening (based upon medical chart, treating physician, or participant report with documented clinical confirmation by the Investigator).
3. vIGA score of 2 or 3 at Screening and Day 1.
4. BSA ≤20% at Screening and Day 1.
5. NRS ≥7 at Screening and Day 1.
6. Body mass index ≤40 kg/m^2 at Screening.
7. Consistent daily or BID use of a non-prescription emollient (participant's choice, excluding those containing hydrocortisone, urea, antihistamines, anesthetics, antibiotics, cannabidiol, or Vitamin C) for at least 7 days prior to Day 1 and agrees to continued use of the same emollient at the same frequency throughout the trial on all areas other than those where trial product is applied.

   Note: on the day of scheduled trial visits, emollient should be withheld until after the trial visit.
8. For women of childbearing potential involved in any sexual activity that could lead to pregnancy, the participant must agree to use a highly effective contraceptive method from at least 4 weeks before Day 1 until at least 4 weeks after the last trial product administration. Highly effective contraceptive methods include either:
   a. Hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation,

      OR
   b. Double-barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.

   Note: Participants must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

   The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal activity throughout the trial. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

   A woman of nonchildbearing potential is defined as follows:
   a. Woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
   b. Woman who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
9. For men involved in any sexual activity that could lead to pregnancy, participant must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 8, from Day 1 until at least 4 weeks after the last trial product administration. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method must be used from at least 4 weeks before Day 1 until at least 4 weeks after the last trial product administration.
10. Ready access to a smartphone or other compatible electronic device on which the participant can receive text messages and complete assessments on web forms.
11. Participant is willing to participate for the duration of the trial, comply with all trial procedures, and is capable of giving informed consent.

    Note: consent must be obtained prior to any trial-related procedures.

Exclusion criteria:

Participants will be excluded from the study if ANY of the following apply:

1. Any female who is breastfeeding, pregnant, or who is planning to become pregnant during the trial.

2. Participant has received a marketed biological agent (ie, dupilumab) or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1; or participant has received a nonbiological product or device within 4 weeks prior to Day 1 (or 8 weeks prior to Day 1 if half-life is >15 days).
3. Active infection requiring treatment, including skin infections (including clinically infected AD).
4. History of skin disease or presence of a skin condition that, in the opinion of the Investigator, would interfere with trial assessments.
5. History of cancer or lymphoproliferative disease within 5 years prior to Day 1. Participants with successfully treated nonmetastatic cutaneous squamous cell, basal cell carcinoma, and/or localized carcinoma in situ of the cervix, are eligible to enroll.
6. Any medical or psychiatric condition which, in the opinion of the Investigator or the Sponsor's medical monitor, would place the participant at risk, interfere with trial participation, or interfere with the interpretation of trial results.
7. Psoralen-UV-A or UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
8. Doxepin, hydroxyzine, or diphenhydramine use within 1 week prior to Day 1.
9. Use of an antihistamine or any topical product containing urea within 1 week prior to Day 1.
10. Use of systemic antibiotic within 2 weeks, or topical antibiotics within 1 week, prior to Day 1.
11. Atopic dermatitis topical medication use within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach or oatmeal baths.
12. Topical or oral JAK inhibitor use or systemic medication use that could affect AD (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids) less than 4 weeks prior to Day 1. Intranasal corticosteroids, eye and ear drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
13. Current excessive sun exposure, planning a trip to a sunny climate during trial participation, or use of tanning beds/booths within 4 weeks prior to Day 1; or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products on non-treatment areas (except those containing Vitamin C) and protective apparel are recommended when exposure cannot be avoided.
14. Known hypersensitivity to ASN008 or its excipients.
15. Known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
16. Close affiliation with the Investigator (e.g., a close relative) including site staff, persons working at the contract research organization, or Sponsor employee.
17. Any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the Investigator, put the participant at undue risk or interfere with interpretation of trial results.
    a. Participant has 12-lead ECG abnormalities, at screening or Day 1, considered by the Investigator to be clinically significant or QTcF >450 ms, regardless of clinical significance. Abnormal ECG may be repeated once. For participants with QTcF >450 ms on initial ECG, the mean of the 2 QTcF assessments will determine eligibility.
18. History of congestive heart failure, defined as New York Heart Association class III or class IV.
19. History of significant arrythmias (e.g., supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia).
20. History of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or frequent intravenous treatment for skin infections over the last year.
21. History of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum at any time prior to enrollment.
22. Major surgery within 8 weeks prior to Day 1 or major surgery planned during the trial.
23. Known immune deficiency or immunocompromise.
24. Positive results for hepatitis B surface antigens, antibodies to hepatitis B core antigens, hepatitis C virus, or human immunodeficiency virus at the screening visit.
25. Presence of any of the following laboratory abnormalities at the screening visit:
    a. Hemoglobin <10 g/dL.

b. Platelet count $\leq 125 \times 10^3$ /μL.
c. Neutrophils $\leq 1.5 \times 10^3$ /μL.
d. Lymphocytes $\leq 1.0 \times 10^3$ /μL.
e. Aspartate aminotransferase/alanine aminotransferase >2 × the upper limit of normal (ULN).
f. Total bilirubin >1.5 × ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome).
g. Creatinine >1.0 × ULN.
h. Creatine phosphokinase >1.5 × ULN.

26. Uncontrolled treated/untreated hypertension at screening or Day 1 with systolic blood pressure (BP) >160 mmHg or diastolic BP >95 mmHg, confirmed by 1 repeat assessment, and/or failure to maintain hypertension therapy for 3-month period prior to screening.
27. Participant is currently receiving any other medication for AD (see medication washout requirements Section 5.2.3).
28. Participant has received a drug or substance known to be a strong inhibitor or inducer of CYP3A4 or CYP2D6 (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, bupropion, fluoxetine, paroxetine, quinidine) within 4 weeks prior to Day 1.

Statistical Methods:

Analysis Set:

Modified intent-to-treat set: this set includes all randomized participants who meet inclusion and exclusion criteria at the Day 1 visit; and participants will be attributed to the treatment they are randomized regardless of the actual treatment they receive.

Per protocol set: this set includes all randomized participants without major protocol deviations.

Safety set: this set includes all participants who receive at least 1 dose of treatment; and participants will be attributed to the treatment they receive.

Pharmacokinetic set: this set includes all participants who receive at least one dose of treatment and have ASN008 concentration data.

Efficacy Analyses:

The aim of the analyses of the primary endpoint, percent change from baseline at Week 4 in 7-day average of daily peak pruritus NRS, is to test for treatment effect, characterize the gel concentration-response curve, and to estimate the minimum effective and optimal concentration. The Multiple Comparison Modelling approach will be applied to the analyses.

Candidate gel concentration-response models which will be used in the analysis include the following:

- Linear model.
- Quadratic model with maximum effect reached at 3.5%, the model parameter is -0.1428571.
- Exponential model which reaches 20% of the effects at 2.5%, the model parameter is 1.803368.
- E_{max} model with ED_{50}=2.5%.
- Sigmoid E_{max} model with ED_{50}=2.5% and Hill's parameter =2.5.
- Logistic model which reaches 20% and 95% effects at concentrations 2.5% and 5%, respectively, the model parameters are $ED_{50\%}$ =3.3002654, delta =0.5772694.

The minimum effective concentration is defined as the lowest concentration whose standardized effect size is at least 0.25 and is significantly different from placebo at a 2-sided significance level of 0.2.

The optimal concentration is defined as the highest concentration of ASN008 used in this clinical trial without safety concerns for linear and exponential models or the lowest concentration which maintains 90% of the maximum effect for the rest of candidate models.

Safety Analyses:

The safety analysis will include reported local and systemic TEAEs and other safety information (i.e., clinical laboratory evaluations, vital signs, physical examinations, ECGs, and local tolerability assessments results). A summary of safety results will be presented for each cohort.

PK Analyses: ASN008 concentration data and PK parameters will be summarized per cohort based on nominal timepoints using descriptive statistics, such as mean, standard deviation (SD), geometric mean, coefficient of variance, median, minimum, and maximum. Population-based analysis to determine inter- and intra-individual variability of PK parameters (CL/F and Vd/F) will be conducted.
Sample Size Consideration: Using analysis outlined above for the primary endpoint, N=24/cohort will give 80% power to detect a standardized effect of 0.72 with 2-sided significance level of 0.1 (28.8% improvement over placebo in percent change from baseline in pruritus, assuming SD = 40%).

Table 2 Schedule of Events

Study Visits	Screening (up to D-28)	Randomization[a] (phone)	Treatment Period					Follow-up/ET (Day 56/Week 8)
			D1	D8 (Week 1)	D15 (Week 2)	D22 (Week 3)	D28 (Week 4)	
Window (days)			0 days	±1 day	±2 days	±2 days	-2 days	±2 days
Informed consent	X							
Demographics	X							
Medical and surgical history	X		X					
Inclusion-exclusion criteria	X		X					
Pregnancy test (WOCBP only)	Serum		urine	urine	urine	urine	urine	urine
Clinical laboratory tests (biochemistry, hematology, urinalysis)	X		X		X		X	X
Body weight and height, BMI[b]	X		X		X		X	X
Serology (HIV, HBV, HCV)	X							
Physical examination	X		X		brief		X	brief
Vital signs	X		X	X	X	X	X	X
Electrocardiogram (12-lead, central reading)	X[c]		X[d]		X		X[d]	X[e]
vIGA	X		X		X		X	X
BSA (excluding palms, scalp, axillae, groin, genitals, and folds)	X		X		X		X	X
EASI	X		X		X		X	X
5-D pruritus scale			X		X		X	X
DLQI			X		X		X	X
POEM			X		X		X	X
Pruritus NRS[f]	X		X	X	X	X	X	
Randomization		X						
Investigational Product Application at study site			X				X	
Investigational Product BID Application Daily[g]			X----------X[g]					
Participant Daily e-Diary[h]			X----------X					
Investigational product distribution			X	X	X	X		
Collection of investigational product				X	X	X	X	X[e]
Verification of daily diary				X	X	X	X	
Emollient use	-7 days	X[a]	X----------X					
Local tolerability assessments			X	X	X	X	X	X
PK samples collection			See Table 3					
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events evaluation	X	X	X----------X					

BID=twice daily; BMI=body mass index; BSA=body surface area; D=day; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; ET=early termination; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; NRS=numerical rating scale; PK=pharmacokinetics; POEM =Patient-Oriented Eczema Measure; vIGA= Validated Investigator Global Assessment; WOCBP=women of childbearing potential.

Note: In general, non-invasive procedures should be completed prior to invasive procedures. Unless otherwise specified, the study assessments scheduled during the study visits will be performed before the study product application. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order, when possible: vital signs, 12-lead ECG, local tolerability, pruritus NRS, and blood draw for PK evaluation.

[a] The Randomization visit will be conducted remotely via phone after all screening assessments have been completed and the results of those assessments are determined to be in line with the trial entry criteria (i.e., based on central read ECG, central laboratory results, and all clinical outcome assessments and patient-reported outcome assessments). During

this remote check-in, study staff will verify the participant's desire to continue in the trial, record any adverse events, assess concomitant medications, and confirm that non-prescription emollient has been (or will be) used consistently for at least 7 days prior to Day 1. Study staff will then acquire a randomization number for eligible participants, which will prompt shipment of investigational product to the study site. The interval between the Randomization Visit and Day 1 Visit should allow enough time for the investigational product to arrive at the study site (i.e., approximately 1 week).

[b] Height will be measured only at screening and the same value will be used for BMI calculation at other visits.

[c] If participant has clinically significant 12-lead ECG abnormalities (per Investigator) or QTcF >450 ms, abnormal ECG may be repeated once. For participants with QTcF >450 ms on initial ECG, the mean of the 2 QTcF assessments will determine eligibility.

[d] On Day 1 and Day 28, ECGs will be time matched with PK sample collection and will be performed at time 0 (pre-dose, within 1 hour of dosing), 1 (±15 min), 2 (±30 min), and 4 (±1 hour) hours post-dose. The ECG should be performed prior to the PK sample collection.

[e] ET only.

[f] Hourly starting immediately post dose until bedtime on Day 1 only.

[g] Should not be applied to palms, scalp, axillae, groin, genitals, or folds. The last dose of investigational product should be applied during the Day 28 study visit; participants are not to receive study treatment for more than 28 days.

[h] Participant will complete daily e-diary onsite during visit if not already completed.

Table 3 Pharmacokinetic Sampling

Window	Predose	Post IP Administration		
		1 hour	2 hours	4 hours
	within 1 hour of dosing	± 15 min	± 30 min	± 1 hour
Day 1	X	X	X	X
Day 28 (-2 days)	X	X	X	X

IP=investigational product

1. INTRODUCTION

ASN008 is formulated as a topical gel with minimal systemic exposure intended for twice daily (BID) topical application. It is a sodium channel blocker, and like other known neuronal sodium channel blockers, is believed to block the sodium channel by binding to an intracellular channel site. Because ASN008 is a permanently charged quaternary amine, it cannot gain efficient entry into the interior of the cell via passive permeation through the cell membrane, however, ASN008 does gain entry into cells through open Transient Receptor Potential (TRP)-V1 and TRPA1 channels. These channels are opened by a variety of stimuli, including heat, acidic pH, and exposure to any number of irritants or inflammatory mediators such as those involved in many pathological conditions that have associated acute or chronic itch. The transmission of such itch signals is mediated through sodium channels in afferent C and Aδ nerve fibers. Furthermore, TRPV1 and TRPA1 channels are selectively expressed in C and Aδ fibers of sensory afferent neurons but are not found in motor neurons. Because of this selective expression pattern, ASN008 is capable of sensory nerve type selective blockade of sodium channel signaling, making it an inviting strategy for developing a selective and well tolerated therapy for pruritus.

1.1. Study Rationale and Dose Justification

The nonclinical pharmacology data obtained for ASN008 topical gel provide a strong rationale for continued development as a treatment for itch associated with several pathological conditions, such as atopic dermatitis (AD). The data from nonclinical studies with ASN008 topical gel suggested that it was safe and well-tolerated at the doses selected in this trial. Several nonclinical safety pharmacology and toxicology studies via systemic and dermal routes were conducted to support the Phase 1 clinical trial of ASN008 via topical dermal route.

A Phase 1, multicenter, double-blind, randomized, single and multiple ascending doses, vehicle-controlled trial of ASN008 topical gel in healthy volunteers (Part A) and participants with AD (Part B) has been completed (ASN008-101). A total of 32 healthy volunteers were randomized into 4 cohorts in Part A and 25 AD participants were randomized into Part B (10 participants to ASN008 2.46% 2 mg/cm^2 once daily (QD), 9 participants ASN008 2.46% 2 mg/cm^2 BID, and 6 participants to placebo).

ASN008 topical gel was well tolerated at all doses following single application on healthy skin (Part A) and multiple applications (QD or BID) on AD lesions (Part B). All treatment-emergent adverse events (TEAEs) reported were of mild severity. No TEAEs at the application area were reported in Part A and only 2 participants (ASN008 BID group) experienced mild TEAEs at the application area in Part B. Both events resolved by the time of trial completion and were considered treatment related. All systemic TEAEs reported were considered not related to the trial product.

Trial results suggest minimal systemic exposure following a single topical application of ASN008 in healthy volunteers, or after repeated (QD or BID topical application of active ASN008 [corresponding to a dose of active moiety of ~49.2 µg/cm^2]) in participants with AD. Preliminary efficacy results showed ASN008 was able to reduce pruritus in AD in participants with a body surface area (BSA) of 1-10%. Participants had a rapid reduction in pruritus following a single application on Day 1, which was sustained up to 8 hours post-dose in QD

participants, and up to 12 hours post-dose in the BID group. The difference between ASN008 QD and vehicle in pruritus was statistically significant on Day 1, at the 4-, 6-, and 8-hour timepoints ($p < 0.05$).

Assessment of the 5% gel as the top dose in this Phase 2 dose-response study is justified based on 1) negligible systemic exposure, safety and tolerability in humans in the Phase 1/1b study; 2) high systemic safety margin based on lack of adverse finding after IV and topical administration in rats and minipigs, respectively; and 3) an application rate in $\mu g/cm^2$ that is lower than that at dermal no observed adverse effects level in minipigs after topical administration an lower than application rates previously evaluated in the Phase 1/1b study. Additional details regarding completed clinical and nonclinical studies can be found in the Investigator's Brochure (IB).

1.2. Background

Atopic dermatitis is a chronic inflammatory skin disease. Pruritus is the most burdensome and prevalent symptom in patients suffering from AD. Treating atopic itch has historically been a challenge due to multiple underlying mechanisms within its pathogenesis and an incomplete understanding of them. AD is characterized clinically by inflammation, pruritus, papules, lichenification, excoriations, xerosis, and oozing (Williams 1995, Lipman 2021). Onset of symptoms typically occurs in children and can improve in adulthood, however, late onset can also occur (Eichenfield 2014). Atopic dermatitis affects 10-20% of children and 1-3% of adults (Eichenfield 2014, Leung 2014). Recent studies suggest that the prevalence of AD in adults could be much higher (Silverberg 2014). Prevalence has also been observed to be higher in industrialized countries, suggesting, at least partially, an environmental link (Cabanillas 2017). The quality of life and psychological state of patients with AD can be greatly impacted by this disease (Lewis-Jones 2006, Marciniak 2017).

Atopic dermatitis is a heterogeneous disease with a wide spectrum of clinical phenotype and a complex pathophysiology (Bieber 2017, Brunner 2017). The precise etiology of AD remains unclear but is likely to be multifactorial in nature, involving genetics, abnormalities in the skin barrier, immune system defects, and environmental triggers (e.g., allergens, irritants, microbes, diet, stress, and air quality) (Leung 2014, Eichenfield 2014). Pruritus prevalence in AD patients is greater than 80% and seriously impairs their quality of life by causing sleep and psychological disturbances (Lipman 2021).

1.3. Benefit/Risk Assessment

1.3.1. Known Potential Risks

ASN008 is formulated as a topical gel intended for BID topical application. The data from both nonclinical studies and the Phase 1 clinical trial with ASN008 support the evaluation of ASN008 at the doses to be administered in this trial. Additional information related to previous studies is available in the IB.

1.3.2. Known Potential Benefits

It is anticipated that participants will experience an improvement in pruritus as a result of participating in this trial, if they are randomized to active investigational product (IP). Participation in this trial may help generate future benefit for larger groups of patients with AD.

1.3.3. Assessment of Risks and Benefits

All quality, pharmacology, and toxicology data, and safety and tolerability data from nonclinical studies and the 2-part Phase 1 clinical trial, are considered sufficient to expect a positive benefit/risk ratio for the treatment of pruritus associated with AD with ASN008, and therefore to initiate this trial.

The risk to participants in this trial will be minimized by compliance with the eligibility criteria, proper trial design, and close monitoring.

More detailed information about the known and expected benefits and risks, and reasonably expected TEAEs of ASN008, may be found in the IB.

2. OBJECTIVES AND ENDPOINTS

Trial objectives and endpoints are presented in Table 4.

Table 4 Trial Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To evaluate the anti-pruritic effect of ASN008 topical gel compared to matching vehicle in participants with AD following BID topical application for 4 weeks (28 days).	• Percent change of 7-day average daily peak pruritus NRS from Baseline to Week 4.
Secondary Efficacy	
To evaluate the therapeutic effect of ASN008 topical gel on AD.	• Percent change of 7-day average daily peak pruritus NRS from Baseline to Week 1, 2, and 3. • Change of 7-day average daily peak pruritus NRS from Baseline to Week 1, 2, 3, and 4. • Change and percent change from baseline in daily peak pruritus NRS to Days 1 to 7. • Pruritus response defined as 7-day average of daily peak pruritus NRS reduction $\geq$ 4 points from Baseline at Week 1, 2, 3, and 4. • Change from baseline in 5-D Pruritus Scale at Week 2 and 4. • Change and percent change from baseline in the EASI score at Week 2 and 4. • Change from baseline in total BSA at Week 2 and 4. • Change from baseline in the Dermatology Life Quality Index (DLQI) at Week 2 and 4. • Change from baseline in the Patient-Oriented Eczema Measure (POEM) at Week 2 and 4.

Objectives	Endpoints
Pharmacokinetics	
To evaluate the pharmacokinetic (PK) profile of ASN008 topical gel in participants with AD following BID topical application.	• ASN008 PK will be characterized using population-based methods. Apparent systemic clearance (CL/F), apparent volume of distribution (Vd/F), inter- and intra-subject variability of these parameters will be estimated.
Safety	
To evaluate the local and systemic safety and tolerability of ASN008 topical gel in participants with AD following BID topical application.	• Number of TEAEs. • Number of IP-related TEAEs. • Changes in vital signs, physical examinations, ECG, and safety laboratory tests. • Incidence of treatment-emergent serious adverse events (SAEs) from first dose through completion of the follow-up period (up to a maximum of 56 days) • Incidence of TEAEs leading to treatment discontinuation from first dose through completion of follow-up period (up to a maximum 56 days).
Exploratory	
To further explore the degree of efficacious effect of ASN008 gel on the AD.	• Change from baseline in vIGA at Week 2 and 4. • At least a 50% reduction from baseline in EASI (EASI-50) at Week 2 and 4. • At least a 75% reduction from baseline in EASI (EASI-75) at Week 2 and 4. • At least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA at Week 2 and 4. • Change from baseline in hourly pruritus NRS score at Hour 1 to 24

AD=atopic dermatitis; BID=twice daily; BSA=body surface area; CL/F=apparent systemic clearance; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI-50=50% reduction from baseline in EASI; EASI-75=75% reduction from baseline in EASI; ECG=electrocardiogram; IP=investigational product; NRS=numerical rating scale; PK=pharmacokinetic; POEM=Patient-Oriented Eczema Measure; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Vd/F=apparent volume of distribution; vIGA=validated Investigator Global Assessment.

3. INVESTIGATIONAL PLAN

3.1. Overall Design

Approximately 120 participants, at least 18 years of age, with mild to moderate AD (validated Investigator Global Assessment [vIGA] of 2 or 3), BSA of ≤20% involved, and a pruritus numerical rating scale (NRS) ≥7 at Screening and at Day 1 (pre-dose), will be included in this randomized, double-blind, placebo-controlled, multicenter, Phase 2 trial.

All participants will sign an informed consent form (ICF) and undergo screening (within 28 days prior to Day 1). With approval from the medical monitor, the screening period may be extended to 7 days in certain situations (i.e., IP shipping delays, laboratory or electrocardiogram (ECG) re-tests, or other logistical or unforeseen issues) that would cause the Day 1 visit to need to occur more than 28 days after the screening visit). During the screening period, all treatments for AD and/or itch will be stopped to allow for wash out, as applicable and according to eligibility requirements (see Section 5.2.3). Participants may be re-screened once if they fail the initial screening evaluation for reasons related to incidental transitory conditions and if they met (and continue to meet) the disease severity and pruritus level specified in the inclusion criteria (Section 4.1).

Eligible participants will be randomized in a 1:1:1:1 ratio to receive ASN008 gel 1.25%, ASN008 gel 2.5%, ASN008 gel 5.0%, or matching vehicle BID for 4 weeks (28 days), followed by a 4-week (28-day) follow-up period. The first dose of study treatment will be applied on Day 1 and the last dose will be applied during the Day 28 study visit; participants are not to receive study treatment for more than 28 days. See Study Schema (Figure 2).

Participants will be required to participate in 8 scheduled visits: Screening; Randomization (remote visit); Day 1; Week 1 (Day 8); Week 2 (Day 15); Week 3 (Day 22); Week 4 (Day 28); and Week 8 (Day 56)/early termination (ET). Consistent daily or BID use of a non-prescription emollient is required at least 7 days prior to Day 1 and throughout the trial until the follow-up (Week 8); refer to Section 3.2.1 for further details. During the 28-day treatment period (Day 1 to Day 28), participants will be required to make daily entries in an electronic diary (eDiary) as described in Section 3.2.2.

The trial duration per participant is up to 12 weeks (84 days): including up to 4 weeks (28 days) for the screening period, 4 weeks (28 days) for the treatment period, and up to 4 weeks (28 days) for the follow-up period.

A participant is considered to have reached the end of the trial when they have completed their Day 56 (Week 8) or ET visit. The trial will be considered complete when the last participant has completed their last trial visit.

3.2. Study Requirements and Procedures

3.2.1. Emollient Use

Consistent daily or BID use of a non-prescription emollient (participant's choice, excluding those containing hydrocortisone, urea, antihistamines, anesthetics, antibiotics, cannabidiol, or Vitamin C) is required at least 7 days prior to Day 1 and throughout the trial until the follow-up (Week 8).

During the screening period and follow-up period, participants must apply the emollient to all dry skin areas of the body **including** on AD lesions. During the treatment period, participants must apply the emollient to all dry skin areas **except** those where the IP has been applied.

Every effort should be made to use the same emollient throughout the trial. The commercial name of the selected emollient(s) will be recorded in the source document and electronic case report form (eCRF). No other products, including, but not limited to, topical corticosteroids, calcineurin inhibitors, biologics, or Janus kinase (JAK) inhibitors (topical or oral) may be used during the trial.

During the treatment period, participants will document their emollient use daily in the eDiary.

3.2.2. Daily eDiary Entries

Participants will be required to complete eDiary entries to record information related to drug administration, emollient use, and peak pruritus NRS. Entries will be made in the web-based eDiary using the participant's own electronic device (smart phone, tablet, or any device with internet access and ability to receive text messages). On Day 1, site staff will assist with creating an eDiary account for the participant, ensuring that the participant can access the account using their own device, and providing instructions on making entries. At the Day 28 or End of Treatment Visit (after administration and documentation of the last dose of study drug), site staff will lock the participant's eDiary account and no further entries will be made.

On Day 1, eDiary entries will be made hourly from first dose to bedtime. After Day 1, eDiary entries will be made twice daily (at the time of dose administration) until Day 28. The following information will be recorded in the eDiary at the specified times:

- At the time of the morning dose administration, information on IP application and peak pruritus NRS will be recorded
- At the time of the evening dose administration, information on IP application and emollient use will be recorded

If for any reason a participant is unable to complete their eDiary (ie, the device battery dies, service is lost, etc.), they will record the information on a paper form. Any paper forms used for eDiary entries should be filed in the participant's source files.

Participants should recall and record missed eDiary information on the paper form as soon as they realize the entry was missed. In order to ensure the accuracy of the data, every effort should be made to record missed NRS data on the paper form within 24 hours of the missed entry. Sites are encouraged to work with the participant to complete a paper back-up diary for missed entries regarding IP application and emollient use at their in-clinic visits if not already completed by the participant. Recall of NRS should not exceed 24 hours.

At each study visit, participants should be reminded that they are required to make entries in the eDiary twice per day. Site staff will assess treatment compliance and eDiary completion compliance at each visit. Participants who are not compliant will be re-educated on the proper use of the study drug and the eDiary.

3.2.3. Order of Assessments

At each study visit, non-invasive procedures should, in general, be completed prior to invasive procedures. Unless otherwise specified, the study assessments scheduled during the study visits will be performed before the study product application. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order, when possible: vital signs, 12-lead ECG, local tolerability, pruritus NRS, and blood draw for PK evaluation.

3.3. Number of Participants

This trial will enroll approximately 120 adult participants.

3.4. Treatment Assignment

Eligible participants will be enrolled in 1 of 4 cohorts (see Table 5).

Table 5 Trial Cohorts

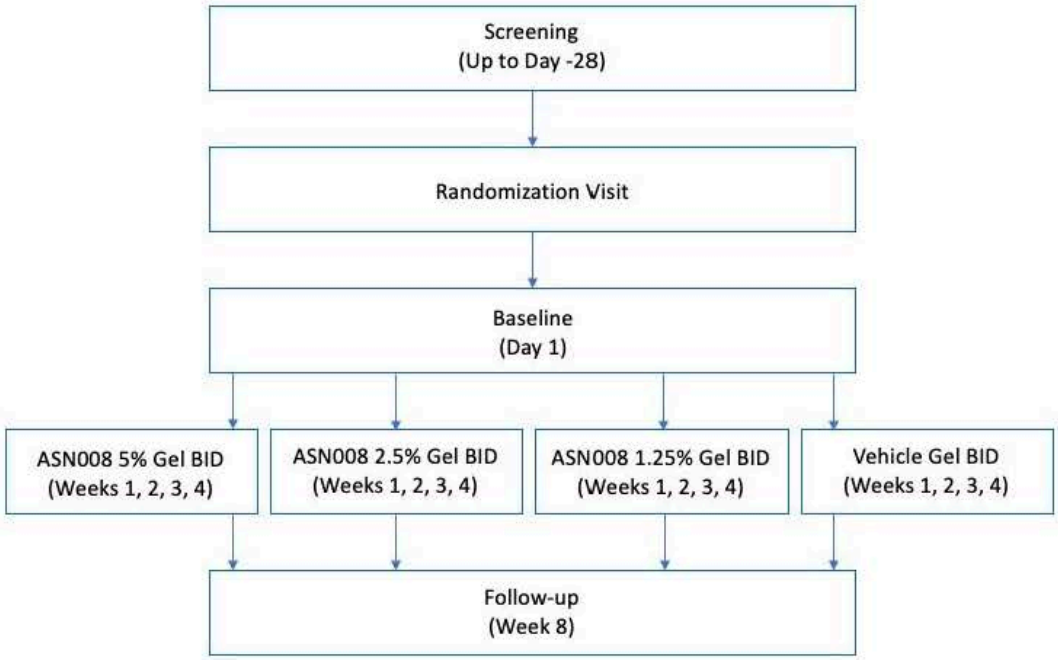
Cohort	Participants (N)	Dose
1	30	ASN008 5.0% BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days).
2	30	ASN008 2.5% BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days).
3	30	ASN008 1.25% BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days).
4	30	ASN008 matching vehicle BID topical application applied as a thin layer (approximately 2 mg/cm^2) for 4 weeks (28 days).

N=number of participants; BID=twice daily.

3.5. Dose Adjustment Criteria

No dose reductions or modifications are permitted in this trial.

Figure 2 Trial Design



4. STUDY POPULATION

Participants must meet all the following criteria at the Screening and Day 1 visits to participate in the trial, unless specified otherwise. Prospective approval of protocol deviations to enrolment criteria (i.e., waivers or exemptions) is not permitted.

4.1. Inclusion Criteria

Participants are eligible to be included in the trial if ALL the following criteria apply:

1. Male or female participants, 18 years or older, at the time of informed consent.
2. Diagnosis of mild to moderate AD for at least 12 months according to American Academy of Dermatology Consensus Criteria with no significant disease flares for at least 4 weeks before Screening (based upon medical chart, treating physician, or participant report with documented clinical confirmation by the Investigator).
3. vIGA score of 2 or 3 at Screening and Day 1.
4. BSA ≤20% at Screening and Day 1.
5. NRS ≥7 at Screening and Day 1.
6. Body mass index (BMI) ≤40 kg/m^2 at Screening.
7. Consistent daily or BID use of a non-prescription emollient (participant's choice, excluding those containing hydrocortisone, urea, antihistamines, anesthetics, antibiotics, cannabidiol, or Vitamin C) for at least 7 days prior to Day 1, and agrees to continued use of the same emollient at the same frequency throughout the trial on all areas other than those where trial product is applied.

   Note: on the day of scheduled trial visits, emollient should be withheld until after the trial visit.

8. For women of childbearing potential involved in any sexual activity that could lead to pregnancy, the participant must agree to use a highly effective contraceptive method from at least 4 weeks before Day 1 until at least 4 weeks after the last trial product administration. Highly effective contraceptive methods include either:
   a) hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation,

   Or

   b) double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.

   Note: Participants must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

   The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal activity throughout the trial. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

A woman of nonchildbearing potential is defined as follows:

a. Woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).

b. Woman who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

9. For men involved in any sexual activity that could lead to pregnancy, participant must agree to use 1 of the highly effective contraceptive methods listed in Inclusion Criterion 8, from Day 1 until at least 4 weeks after the last trial product administration. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method must be used from at least 4 weeks before Day 1 until at least 4 weeks after the last trial product administration.
10. Ready access to a smartphone or other compatible electronic device on which the participant can receive text messages and complete assessments on web forms.
11. Participant is willing to participate for the duration of the trial, comply with all trial procedures, and is capable of giving informed consent.

    Note: consent must be obtained prior to any trial-related procedures.

4.2. Exclusion Criteria

Participants will be excluded from the study if ANY of the following apply:

1. Any female who is breastfeeding, pregnant, or who is planning to become pregnant during the trial.
2. Participant has received a marketed biological agent (ie, dupilumab) or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1; or participant has received a nonbiological investigational product or device within 4 weeks prior to Day 1 (or 8 weeks prior to Day 1 if half-life is >15 days).
3. Active infection requiring treatment, including skin infections (including clinically infected AD).
4. History of skin disease or presence of a skin condition that, in the opinion of the Investigator, would interfere with trial assessments.
5. History of cancer or lymphoproliferative disease within 5 years prior to Day 1. Participants with successfully treated nonmetastatic cutaneous squamous cell, basal cell carcinoma, and/or localized carcinoma in situ of the cervix, are eligible to enroll.
6. Any medical or psychiatric condition which, in the opinion of the Investigator or the Sponsor's medical monitor, would place the participant at risk, interfere with trial participation, or interfere with the interpretation of trial results.
7. Psoralen-UV-A or UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
8. Doxepin, hydroxyzine, or diphenhydramine use within 1 week prior to Day 1.

9. Use of an antihistamine or any topical product containing urea within 1 week prior to Day 1.
10. Use of systemic antibiotic within 2 weeks, or topical antibiotics within 1 week, prior to Day 1.
11. Atopic dermatitis topical medication use within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach or oatmeal baths.
12. Topical or oral JAK inhibitor use or systemic medication use that could affect AD (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids) less than 4 weeks prior to Day 1. Intranasal corticosteroids, eye and ear drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
13. Current excessive sun exposure, planning a trip to a sunny climate during trial participation, or use of tanning beds/booths within 4 weeks prior to Day 1; or is not willing to minimize natural and artificial sunlight exposure during the trial. Use of sunscreen products on non-treatment areas (except those containing Vitamin C) and protective apparel are recommended when exposure cannot be avoided.
14. Known hypersensitivity to ASN008 or its excipients.
15. Known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
16. Close affiliation with the Investigator (e.g., a close relative) including site staff, persons working at the contract research organization, or Sponsor employee.
17. Any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the Investigator, put the participant at undue risk or interfere with interpretation of trial results.
    a. Participant has 12-lead ECG abnormalities, at screening or Day 1, considered by the Investigator to be clinically significant or QTcF >450 ms, regardless of clinical significance. Abnormal ECG may be repeated once. For participants with QTcF >450 ms on initial ECG, the mean of the 2 QTcF assessments will determine eligibility.
18. History of congestive heart failure, defined as New York Heart Association class III or class IV.
19. History of significant arrythmias (e.g., supraventricular tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia).
20. History of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or frequent intravenous treatment for skin infections over the last year.
21. History of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum at any time prior to enrollment.
22. Major surgery within 8 weeks prior to Day 1 or major surgery planned during the trial.
23. Known immune deficiency or immunocompromise.

24. Positive results for hepatitis B surface antigens, antibodies to hepatitis B core antigens, hepatitis C virus, or human immunodeficiency virus at the screening visit.
25. Presence of any of the following laboratory abnormalities at the screening visit:
    a. Hemoglobin <10 g/dL.
    b. Platelet count $\leq 125 \times 10^3$ /µL.
    c. Neutrophils $\leq 1.5 \times 10^3$ /µL.
    d. Lymphocytes $\leq 1.0 \times 10^3$ /µL.
    e. Aspartate aminotransferase/alanine aminotransferase >2 × the upper limit of normal (ULN).
    f. Total bilirubin >1.5 × ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome).
    g. Creatinine >1.0 × ULN.
    h. Creatine phosphokinase >1.5 × ULN.
26. Uncontrolled treated/untreated hypertension at screening or Day 1 with systolic blood pressure (BP) >160 mmHg or diastolic BP >95 mmHg, confirmed by 1 repeat assessment, and/or failure to maintain hypertension therapy for 3-month period prior to screening.
27. Participant is currently receiving any other medication for AD (see medication washout requirements Section 5.2.3).
28. Participant has received a drug or substance known to be a strong inhibitor or inducer of CYP3A4 or CYP2D6 (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, bupropion, fluoxetine, paroxetine, quinidine) within 4 weeks prior to Day 1.

4.3. Participant Withdrawal Criteria

Participants have the right to withdraw from the trial at any time for any reason without penalty. The Investigator also has the right to withdraw participants from the trial if they believe it is in the best interest of the participant, or if the participant is uncooperative or noncompliant.

Participation in this clinical trial may be discontinued for any of the following reasons:

- The participant withdraws consent or request discontinuation for any reason
- Any adverse event, illness, medical condition, or severe laboratory abnormality which indicates to the Investigator that continuation in the trial is not in the best interest of the participant
- Failure to comply with protocol requirements or trial-related procedures
- Pregnancy
- Trial terminated by the Sponsor

Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit.

The Investigator or designee should contact the participant to determine, as accurately as possible, the primary reason for their withdrawal.

A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the trial. If the reason for removal of a participant is an adverse event (AE) or an abnormal laboratory test result, the principal specific event or test must be recorded. If a participant withdraws from the trial, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

A participant will be considered lost to follow up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the clinical trial center. Before a participant is considered lost to follow up, the Investigator (or designee) must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These attempts should be documented in the participant's medical record.

5. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

5.1. Description of Study Drug

The ASN008 topical gel formulations are composed of the active pharmaceutical ingredient (ASN008), propylene glycol, Poloxamer 407, methylparaben (preservative), propylparaben (preservative), and sterile water. Three gel formulations in strengths of 1.25%, 2.5%, and 5.0% have been manufactured in support of this clinical trial.

Additional information for ASN008 topical gel and vehicle formulations is provided in the IB.

5.2. Concomitant Medications

All medications (including over the counter products including pills creams and topical treatments, vitamins, herbal/natural products [including cannabidiol], and antacids) taken within the 4 weeks prior to screening and throughout the trial must be recorded.

All past and current medications taken for AD (topical and systemic) will be documented as medication history for AD. The duration of the treatment and the reason for discontinuation will be documented.

Medication entries may be captured as generic names. Entries should include the following information if known: dose, unit, frequency of administration, route of administration, start date, discontinuation date, and indication. If the medication is discontinued or the dosage is changed, these details must be recorded.

5.2.1. Required Concomitant Therapy

Participants should apply a non-prescription emollient of their choice (participant's choice, excluding those containing hydrocortisone, urea, antihistamines, anesthetics, antibiotics, cannabidiol, or Vitamin C) daily or BID to any untreated lesions and all dry skin areas of the body for at least 7 days prior to Day 1 until the End of Study (Week 8) or ET visit. The emollient should be applied to any area needed except for the AD skin lesion(s) treated with the IP during the treatment period. On the day of scheduled visits, participants should not apply emollients before their scheduled visit time.

Every effort must be made to keep the same emollient throughout the trial. The commercial name of the selected emollient(s) must be recorded in the source document and the eCRF. No other products can be applied to the lesions during the trial. Emollient use should be recorded daily in the participant diary.

5.2.2. Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions were allowed. Eye and ear drops containing corticosteroids were allowed.
- Use of sunscreen products on non-treated areas (except those containing Vitamin C), and protective apparel are recommended when exposure cannot be avoided.

Drugs that were known to moderately inhibit CYP3A4 and CYP2D6 should be used with caution, and only following approval by the Medical Monitor. These drugs include amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, erythromycin, fluconazole fosamprenavir, imatinib, verapamil, cinacalcet, duloxetine, and terbinafine.

5.2.3. Prohibited Therapies

Table 6 lists prohibited medications not to be used from the defined washout periods before the first application of trial treatment (Day 1) through timepoint specified (end or treatment period or end of trial). Participants who start a prohibited medication or therapy as a treatment for AD or other reasons during the trial will be withdrawn from trial treatment and the medication must be recorded in the eCRFs.

For the purposes of this study, cannabis is considered a systemic treatment that may impact AD due to its effect on itch, potentially interrupting the itch/scratch cycle. As such, participants should not use any form of cannabis (e.g., inhaled, edible, topical, tincture) either medicinally or recreationally during the study.

Anti-histamines should be discontinued for at least 1 week ahead of Day 1, through the end of the treatment period.

Table 6 Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Minimal Interval Prior to First IP Dose	Timepoint Therapy may be Restarted
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)	After Day 56
Dupilumab	12 weeks	After Day 56
Nonbiological IP or device	4 weeks (or 8 weeks if $t_{1/2}$ >15 days)	After Day 56
Drug or substance known to be strong inhibitor or inducer of CYP3A4 or CYP2D6 (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, bupropion, fluoxetine, paroxetine, quinidine)	4 weeks	After Day 56
JAK inhibitor (oral or topical)	4 weeks	After Day 56
Systemic treatments (other than biologics) that could have affected AD (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids)	4 weeks	After Day 56

Prohibited medications, products, and procedures	Minimal Interval Prior to First IP Dose	Timepoint Therapy may be Restarted
Note: Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions were allowed. Eye and ear drops containing corticosteroids were allowed.		
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or had used tanning booths	4 weeks	After Day 56
Topical medicated treatment that could have affected AD including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach or oatmeal baths	2 weeks	After Day 56
Systemic antibiotics	2 weeks	After Day 56
Topical antibiotics	1 week	After Day 56
Antihistamine	1 week	After Day 28
Topical products containing urea	1 week	After Day 28
Hydroxyzine and diphenhydramine	1 week	After Day 28
Doxepin	1 week	After Day 28

AD=atopic dermatitis; CYP=cytochrome P450; IP=investigational product; JAK=Janus kinase; PUVA=psoralen-UV-A; $t_{½}$=half-life; UV=ultraviolet.

5.3. Treatment Compliance

Treatment compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the participant's dosing diary, and by maintaining adequate trial product dispensing and return records. Any deviation from the prescribed dosage regimen will be recorded in the source document and eCRF.

Participants who are significantly noncompliant with treatment (ie, administration of <80% of the expected treatments) based on IP accountability will be counseled and could be discontinued from the trial, at the discretion of the Investigator, following consultation with the Sponsor. A participant will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of trial product in the same time frame, as judged by the Investigator.

5.4. Study Restrictions

Participants should abstain from taking a bath/shower or swimming within 2 hours following each treatment application. If there are lesions on the hands, participants should abstain from washing their hands within 2 hours following each treatment application.

Participants should abstain from physical activity that could cause significant sweating within 2 hours following each treatment application.

Participants should be informed not to wear tight clothing on treated areas and to avoid touching the treated area(s) until areas of application were dry.

Participants should avoid eye contact with the trial products.

Participants should not consume grapefruit, grapefruit juice, or any grapefruit containing product within 4 weeks prior to Day 1 and throughout the entire trial duration.

Participants should avoid excessive sun exposure and refrain from sunbathing, receiving UV phototherapy or using a tanning booth during the study.

Participants should be informed not to change emollients during the study and that on the day of scheduled visits, emollients should not be applied before the scheduled visit time.

5.5. Assignment to Study Intervention

At the investigational site, each screened participant will be assigned a participant identifier number during screening that will be used on all participant documentation.

Participants will be randomized in a 1:1:1:1 ratio to receive either ASN008 gel at 1.25%, 2.5%, or 5.0%, or vehicle BID. Randomization will occur as part of the Randomization visit. The Randomization visit will be conducted remotely via phone once all screening assessments have been completed and the results of those assessments are determined to be in line with the trial entry criteria (i.e., based on central read ECG, central laboratory results, and all clinical outcome assessments and patient-reported outcome assessments). During this remote check-in, study staff will verify the participant's desire to continue in the trial, record any AEs, assess concomitant medications, and confirm that non-prescription emollient has been (or will be) used consistently for at least 7 days prior to Day 1. Study staff will then acquire a randomization number for eligible participants, which will prompt shipment of investigational product to the study site. The interval between the Randomization Visit and Day 1 Visit should allow enough time for the investigational product to arrive at the study site (i.e., approximately 1 week).

The randomization list will be generated using a validated software. The master randomization list will be kept secured until the trial blind is broken at the end of trial. This list will be uploaded into an Interactive Web Response System (IWRS). The Investigator or designee will be able to acquire a randomization number for eligible participants by connecting to the IWRS.

Further guidance and information can be obtained in the Pharmacy Manual.

5.6. Blinding

This trial will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the Sponsor's trial team until database lock is completed and all safety data has been cleaned and monitored. Investigators, participants, and clinical staff will remain blinded throughout the trial.

Blinding codes should only be broken in emergency situations for reasons of participant safety. If unblinding the treatment assignment for a participant is necessary due to a medical emergency (an unexpected serious adverse event [SAE] per product's safety profile) and other significant

medical situations such as pregnancy, the Investigator can make the decision to unblind the treatment assignment if knowing the treatment assignment will help the treatment decision of the particular AE. When the blind for a participant has been broken, the reason must be fully documented in the source document and eCRF. Whenever possible, the Investigator should contact the Sponsor or its designee before breaking the blind. If the blind is broken, the Investigator should promptly inform the medical monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

Emergency unblinding details are provided in the Pharmacy Manual.

The participant for whom the blind has been broken will be discontinued from the trial and undergo the ET procedures. In cases where there are ethical reasons to have the participant remain in the trial, the Investigator must obtain specific approval from the Sponsor or its designee for continuation. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug Administration

The topical gel should be applied to all AD lesions (except scalp, axillae, groin, genitals, and folds), with a maximum treated area of approximately 20% BSA. If new lesions on the soles of the feet appeared after Day 1 and initiation of treatment, then these lesions should be excluded from the BSA of treated area (should not be treated).

Participants should apply the gel as a thin layer using the fingertip unit (FTU) where a thin layer corresponded to approximately 2 mg/cm^2. A FTU is the amount of gel expressed from a tube applied from the distal skin-crease to the tip of the palmar aspect of the index finger and 1 FTU covers approximately 286 cm^2 (approximately 1.5% BSA) (Long 1991). The number of FTUs required to cover the treated area should be calculated for each participant and recorded at Day 1 and Day 15. Participants should be informed of how many FTUs they should apply on their AD lesions.

The topical gel will be applied to completely cover the lesions with a thin glistening layer. The gel may be applied on superficial abraded skin, but deeper wounds should be avoided. All original areas of involvement at Day 1 (even in the event of lesions clearing), and any new lesions (up to a maximum treated area of approximately 20% BSA) should be treated until Week 4. If new lesions appeared after Day 1, the new surface area to be treated (up to a maximum treated area of approximately 20% BSA) should be evaluated at every visit, and if applicable, the number of FTUs to be applied on AD lesions should be calculated and recorded. If new lesions on the soles of the feet appeared after Day 1 and initiation of treatment, then these lesions are excluded from the BSA of treated area (should not be treated).

The study treatment will be applied twice daily (except on Day 28), at approximately the same times each day; the date and time of each application will be recorded in the eDiary. It is recommended that the application times be approximately 12 hours apart (±2 hours). Participants should not shower or perform activities that may cause sweating for 2 hours post-application. Participants with AD lesions on hands should avoid washing their hands for approximately 2 hours post drug application. Participants without AD lesions on hands should wash their hands after treatment application.

If an application is missed participants should apply the study treatment as soon as they remember on the same day. However, if it is the next day, the missed application should be skipped and the next application should be applied as normal.

Participants will be trained on how to apply the study treatment on Day 1 with reminders given at each subsequent visit, which will be documented. Participants will apply their first dose (on Day 1) and their last dose (on Day 28) at the study site. When participants are dosed at the study site, they will self-apply the treatment under the direction and supervision of delegated study staff; the date and time of the application will be recorded by the site staff on the eCRF.

Participants are not to receive study treatment for more than 28 days.

6.2. Study Drug Packaging and Labeling

The test article (ASN008) and vehicle will be prepared with identical packaging and identical labels. The packaging will be laminate tubes. The labels will include an identification number, protocol number, and a statement that the products are for investigational use only.

6.3. Trial Drug Storage

Test article should be stored at 15°C to 30°C (59°F to 86°F), in a secured location with limited access.

6.4. Study Drug Accountability

Upon receipt of the test articles, the Investigator or designee will conduct an inventory. Designated trial staff will provide the test article to the participants in accordance with their sequentially assigned participant numbers and randomization. Participants should be instructed to bring all tubes of test article (used and unused) to each trial visit.

At each trial visit beginning at Week 1, all returned tubes will be weighed collectively on a calibrated scale. The number of tubes and collective weight should be recorded in the eCRF. If tubes are missing (e.g., X tubes dispensed and only Y returned) a note should be made on the eCRF explaining the discrepancy. Calibration logs should be current (per manufacturer) and available to the monitor for periodic review.

During the trial, the Investigator must maintain records of trial treatment dispensation and collection for each participant. This record must be made available to the trial monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. At the conclusion of the trial, the Investigator will be responsible for returning all used and unused trial supplies unless otherwise instructed by the Sponsor.

6.5. Study Drug Handling and Disposal

Investigational product(s) will be dispensed by the study site to the participant at the visits specified in Table 2. Participants are to return all investigational product (used and unused containers) to the study site. Each participant will be instructed on the importance of returning investigational product at the next study visit and on taking the product as prescribed. If a participant does not return investigational product, they will be instructed to return it as soon as possible.

The Investigator is responsible for maintaining accurate records of the investigational product initially received and dispensed/used. After verification of the investigational product accountability by the Sponsor or designee, used product will be stored safely until destruction/return. All study/investigational product must be documented on the accountability forms, including those that were accidentally or deliberately destroyed or returned to the Sponsor or designee. Any discrepancies between amounts dispensed and returned will be explained.

All investigational product accountability forms and treatment logs must be retained in the Investigator's study files. Product inventory and accountability records will be maintained as per International Council for Harmonisation (ICH) Good Clinical Practice (GCP). These records

must be available for inspection at any time by the Sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of investigational products are provided in the study manual.

7. ASSESSMENT OF EFFICACY

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given participant whenever possible.

The effect of ASN008 on pruritus will be measured by:

- Peak Pruritus NRS score
- 5-D Pruritus Scale

The effect of ASN008 on other parameters will be measured by:

- Eczema Area and Severity Index (EASI)
- Validated Investigator Global Assessment (vIGA)
- Body Surface Area (BSA) Involvement of AD
- Patient-Oriented Eczema Measure (POEM)
- Dermatology Life Quality Index Questionnaire (DLQI)

The assessments used in this trial are provided in the clinical scales section of the Investigator site files.

7.1. Peak Pruritus Numerical Rating Scale

The Peak Pruritus NRS is a single self-reported item designed to measure peak pruritus, or 'worst' itch, over the previous 24 h based on the following question: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?'

Participants will be trained on completion of the Peak Pruritus NRS scale at the first Screening Visit before the Peak Pruritus NRS measurements for eligibility are collected.

To be eligible for this study, participants must have a pruritus NRS score of $\geq$7 at screening and Day 1.

On Day 1, pruritus NRS will be assessed at several time points: pre-dose to confirm eligibility and then hourly in the eDiary starting immediately post-dose until bedtime. Following Day 1, participants will record the peak pruritus NRS daily in the eDiary before the morning investigational product application, and their compliance on the peak pruritus NRS will be followed at each clinic visit.

During study visits, the NRS data will be recorded by site staff in the eCRF.

7.2. 5-D Pruritus Scale

The 5-D Pruritus Scale is a 1-page, 5-question, validated questionnaire used in clinical trials to assess 5 dimensions of background itch: degree, duration, direction, disability, and distribution. Each question corresponds to 1 of the 5 dimensions of itch; participants will rate their symptoms over the preceding 2-week period as "present" or on a 1 to 5 scale, with 5 being the most affected. The 5-D Pruritus Scale will be recorded at the visits specified in Table 2.

7.3. Eczema Area and Severity Index

The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored from 0 to 3 separately) for each of 4 body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. The EASI will be assessed at the visits specified in Table 2.

7.4. Validated Investigator Global Assessment

The vIGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity.

The vIGA (excluding hands and feet) will be assessed as specified in Table 2.

7.5. Body Surface Area Involvement of Atopic Dermatitis

The overall BSA affected by AD (total BSA) will be evaluated (from 0% to 100%) at the visits specified in Table 2. The palmar surface of one hand represents 1% of participant's total BSA. In addition, at the screening and Day 1 visits, the BSA will be evaluated to verify each participant's eligibility, but excluding palms, scalp, axillae, groin, genitals, and folds. In addition, the BSA of treated area (include active, cleared, and new lesions) will be calculated at the visits specified in Table 2. The BSA of treated area will be used to calculate the number of FTUs to be applied by participants on AD lesions (except on scalp, axillae, groin, and genitals, and folds), with a maximum treated area of approximately 20% BSA. If new lesions on the soles of the feet appear after Day 1 and initiation of treatment, then these lesions should be excluded from the BSA of treated area (should not be treated).

To be eligible, participants must have a BSA (excluding palms, scalp, axillae, groin, genitals, and folds) of 1-20% at Day 1 visit. In addition, participants with presence of AD on soles at screening or Day 1 and participants with a ratio of BSA of intended area over total BSA of less than 80% on Day 1 will be excluded.

7.6. Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM), developed by Charman et.al., (Charman 2004) is a self-assessment of disease severity by the participant. The POEM has a maximum value of 28 based on the participant's response to seven questions scored from 0 to 4.

The POEM will be assessed at the visits specified in Table 2.

7.7. Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI) consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week.

The DLQI will be assessed for AD as specified in Table 2.

8. ASSESSMENT OF SAFETY

Safety will be assessed by collecting AEs, recording vital signs, performing complete and brief physical examinations, ECG, and evaluating clinical laboratory results and local tolerability assessments. Local tolerability assessments, at the site of application, will also be evaluated.

8.1. Safety Parameters

8.1.1. Vital Signs

The following vital signs will be recorded at the visits specified in Table 2 with the participant in a seated position, after having sat calmly for at least 5 minutes:

- Systolic and diastolic BP (mmHg)
- Pulse (beats per minute)
- Respiration rate (breaths per minute)
- Body temperature (°C)

The Investigator will review all vital sign results. Measurements of systolic BP >160 mmHg or diastolic BP >95 mmHg at Screening or Day 1 must be confirmed by 1 repeat assessment in order to determine eligibility. Values that are outside of the normal reference ranges at subsequent time points during the trial may be repeated at the discretion of the Investigator.

If deemed appropriate by the Investigator, clinically significant findings in the vital signs will exclude a participant from study participation. Any abnormal finding related to vital signs that the Investigator considers to be clinically significant must be recorded as an AE.

8.1.2. Weight and Height

Weight (kg) and height (cm) will be collected to calculate the BMI and will be recorded as specified in Table 2. The height will only be recorded at the screening visit and the same value will be used for BMI calculation at subsequent visits.

8.1.3. Physical Examination

At a minimum, the following sites/systems should be included in the complete physical examination:

- General appearance
- Dermatological
- Head, eyes, ears, nose, throat
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

At a minimum, the following sites/systems should be included in the brief physical examination:

- General appearance

- Dermatological
- Respiratory
- Cardiovascular
- Abdominal

The physical examinations performed during the course of the trial are specified in Table 2.

Information for all physical examinations must be included in the source document. If deemed appropriate by the Investigator, clinically significant findings in the physical examination may exclude a participant from trial participation. Any significant change should be reported as an AE in the source document and eCRF.

8.1.4. Electrocardiogram

Twelve-lead ECGs with a central reading should be performed as a safety assessment at the visits specified in Table 2 with the participant in a supine position, after lying calmly for at least 5 minutes.

Clinically significant findings in the ECG may exclude a participant from trial participation (as deemed appropriate by the Investigator and according to the exclusion criteria Section 4.2). Any clinically significant change during the study should be reported as an AE.

8.1.5. Laboratory Assessments

Laboratory tests should be performed at the visits specified in Table 2. Tests include urinalysis, hematology with differential, a standard chemistry panel (chemistry included liver function tests), serology, and serum pregnancy test (screening) for females of childbearing potential. In addition, a serum or urine pregnancy test should be performed for females of childbearing potential (conducted at the trial site) at the visits specified in Table 2. The specific tests in these panels are listed in Table 7.

Table 7 Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, PLT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, creatinine (enzymatic), creatine phosphokinase, GGT, glucose random, LDH, potassium, sodium, total bilirubin, urea (BUN), uric acid
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen and microscopic analysis (as required)
Pregnancy test	For females of childbearing potential (serum pregnancy test (β-hCG) at screening and serum or urine pregnancy test at other visits)
Laboratory tests required at screening only	FSH levels for females who had a cessation of menses for at least 12 months without an alternative medical cause Serology (HBV [HBsAg, anti-HBc], HCV, HIV)

ALT=alanine aminotransferase; anti-HBc=antibody to hepatitis B core antigen; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl-transferase; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCT=hematocrit; HCV=hepatitis C virus; Hgb=hemoglobin; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PLT=platelets; RBC=red blood cell (count); WBC=white blood cell (count).

Participants who do not qualify to participate in the trial due to a screening laboratory value abnormality may repeat the test once within the original screening time window, if the Investigator believes there is a reasonable possibility that the participant may be eligible if re-tested.

If deemed appropriate by the Investigator, clinically significant findings in clinical laboratory testing may exclude a participant from trial participation. Any clinically significant change should be reported as an AE.

8.1.6. Local Tolerability Assessment

Local tolerability assessments will be performed at specified time points for each AD lesion treated with study drug at the visits specified in Table 2. Local tolerability will be assessed by evaluation of erythema, stinging, itching, burning, desquamation, edema, and pain using a 4-point ordinal scale (0, 1, 2, 3) for local toxicity. Any assessment with a score of 3 should be reported as an AE.

Assessment of local tolerability may be performed by the Investigator or an appropriately qualified designee; however, at a minimum, any identified intolerance should be confirmed by the Investigator and reported as an AE. When intolerance is noted at the site of more than one AD lesion, separate AEs should be reported (ie, an AE corresponding to each AD lesion site).

Any participant with an identified intolerance which indicates to the Investigator that continuation in the trial is not in the best interest of the participant should be evaluated for discontinuation.

8.2. Adverse Events, Serious Adverse Events, and other Safety Reporting

8.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a trial product, whether or not considered related to the trial product. AEs and SAEs will be collected from the time of informed consent signature until the final visit / contact.

In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no trial treatment has been administered.

All AEs that occur after any participant has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether or not they are related to the trial, must be recorded on forms provided by TrialSpark.

8.2.2. Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the trial product but appeared following first dose, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.2.3. Definition of Serious Adverse Event

A serious AE or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should also usually be considered serious.

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

All SAEs that occur after any participant has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether or not they are related to the trial, must be recorded on forms provided by TrialSpark.

8.2.4. Relationship to Study Drug

The Investigator will establish causality of the AE to the experimental treatment. The Investigator should take into account the participant's history, most recent physical examination and/or ophthalmology findings, and concomitant medications.

The degree of "relatedness" of the AE to the trial medication must be described using the following scale:

Not related indicates that there is not a reasonable possibility for relationship of the event to the trial medication.

Possibly related indicates that a direct cause and effect relationship between trial medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the trial medication.

Probably related indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the trial medication.

The statement **"reasonable possibility for relationship"** means that there are facts (e.g., evidence such as de-challenge/re-challenge/temporal relationship, exposure, likely cause due to known safety profile, etc.) to suggest a positive causal relationship. The Investigator may also change their opinion for causality after follow-up information and may provide a follow-up SAE report with the revised causality assessment.

8.2.5. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the trial personnel or revealed by observation will be recorded during the trial at the investigational site. Adverse events that lead to discontinuation of administration of trial drug or withdrawal from study must be reported and recorded as an AE. Information about AEs will be collected from signing of consent form until the end of the trial. Serious adverse event information will be collected from signing of consent form until Week 8 (Day 56), 4 weeks following the last dose of trial drug. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the trial.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 8.2.3. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on TrialSpark's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the trial.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

8.2.6. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the first administration of trial drug until the last trial visit. Any SAEs considered possibly or probably related to the IP and discovered by the Investigator at any time after the trial should be reported. All SAEs must be reported to TrialSpark within 1 business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to TrialSpark.

Additional follow-up information, if required or available, should all be faxed to TrialSpark within 1 business day of receipt, and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or trial file.

TrialSpark is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the Institutional Review Board or Independent Ethics Committee of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

8.2.7. Pregnancy Reporting

If a female participant or a female partner of a male participant becomes pregnant during the trial, the participant should inform the trial site as soon as possible. Upon confirmation of the pregnancy, the female participant will be discontinued from the trial. The Investigator must complete a trial specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance vendor (PrimeVigilance) within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The vendor will report all cases of pregnancy to the Sponsor and PrimeVigilance in a timely manner. Post-treatment follow up should be done to ensure participant safety. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. 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. The Investigator will notify the vendor and PrimeVigilance of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the Sponsor and, when applicable, to the ethics committee.

In the case of an SAE or pregnancy, the participant treatment assignment may be unblinded if judged necessary by the Investigator and/or medical monitor in consultation with the Sponsor.

Once the participant treatment assignment is unblinded, the participant for whom the blind has been broken will be discontinued from the trial and undergo the ET procedures.

8.2.8. Overdose

Trial drug overdose is any accidental or intentional use of trial drug in an amount higher than the dose indicated per protocol for a given participant. Trial intervention compliance (see Section 5.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any trial drug overdose during the trial should be recorded on the source document and eCRF. In the event of overdose, the participant should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the AE eCRF and reported using the procedures detailed in Section 8.2.6 even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner but should be noted as non-serious on the form and the AE eCRF. The excess quantity and duration of the overdose should be recorded.

9. STATISTICS

9.1. Sample Size Determination

Using analysis outlined above for the primary endpoint, N = 24 / group will give 80% power to detect a standardized effect of 0.72 with 2-sided significance level of 0.1 (28.8% improvement over placebo in percent change from baseline in pruritus, assuming standard deviation [SD] = 40%).

9.2. Populations for Analyses

Modified intent-to-treat analysis set: this set includes all randomized participants who meet inclusion and exclusion criteria at the Day 1 visit; participants will be attributed to the treatment they are randomized regardless of the actual treatment they receive.

Per protocol (PP) set: this set includes all randomized participants without major protocol deviations.

Safety set: this set includes all participants who receive at least 1 dose of treatment; participants will be attributed to the treatment they actually receive.

Pharmacokinetic (PK) set: this set includes all participants who receive at least 1 dose of treatment and have ASN008 concentration data.

9.3. Statistical Analyses

Significance level for this trial is set to be 0.05 unless otherwise specified. Continuous variables will be summarized using the number of participants, mean, SD, median, minimum, and maximum; additionally, for PK data, geometric mean and percent of coefficient of variance (CV%) will be presented. Categorical variables will be presented using frequencies and percentages. A Statistical Analysis Plan will provide additional details on the approach to the analysis and data displays.

9.3.1. Efficacy Analyses

The aims of the analyses of the primary endpoint – percent change from baseline at Week 4 in 7-day average of daily peak pruritus NRS – is to test for treatment effect, to characterize the gel concentration-response curve, and to estimate the minimum effective and optimal concentration. The Multiple Comparison Modelling (MCPMod) approach will be applied to the analyses.

Candidate gel concentration-response models which will be used in the analysis include the following:

- Linear model.
- Quadratic model with maximum effect reached at 3.5%, the model parameter is -0.1428571.
- Exponential model which reaches 20% of the effects at 2.5%, the model parameter is 1.803368.
- E_{max} model with ED_{50}=2.5%.
- Sigmoid E_{max} model with ED_{50}=2.5% and Hill's parameter = 2.5.

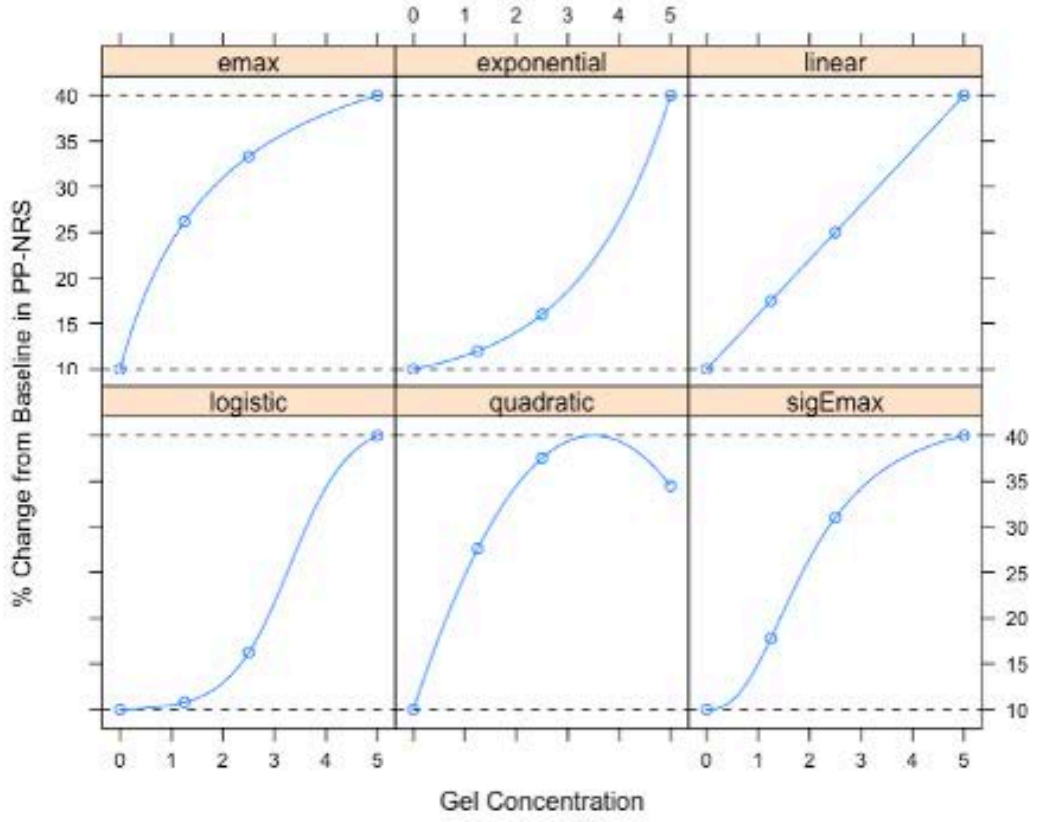
- Logistic model which reaches 20% and 95% effects at concentrations 2.5% and 5%, respectively, the model parameters are $ED_{50\%} = 3.3002654$, delta = 0.5772694.

The minimum effective concentration is defined as the lowest concentration whose standardized effect size is at least 0.25 and is significantly different from placebo at a 2-sided significance level of 0.2.

The optimal concentration is defined as the highest concentration of ASN008 used in this clinical trial without safety concerns for linear and exponential models, or the lowest concentration which maintains 90% of the maximum effect for the rest of candidate models.

Figure 3 depicts the shapes of curves for each candidate model, assuming the vehicle effect is 10% and treatment effect is 40% (30% improvement over vehicle).

Figure 3 Candidate Concentration - Response Models



Analysis of primary endpoint consists of the following steps:

Mean and variance estimation: A Mixed model repeated measures with visit, treatment, baseline disease severity, and visit by treatment interactive and fixed effects, baseline NRS as covariate, participant as random effects will be fitted first, the least-squares means and their variance-covariance matrix at Week 4 will be estimated using the fitted model.

1. MCP-step: the candidate models are tested using the estimated means and their variance-covariance matrix from the previous step. If any of the models is statistically significant at

2-sided significance level of 0.1, the treatment effect is established, the analysis moves to the next step.

2. Mod-step: the concentration-response curve will be characterized, and the minimum effective concentration and optimal concentration will be estimated. All significant models indicated by the previous step will be fitted, and minimum effective concentration and optimal concentration will be estimated based on the fitted models.
3. Finally, weighted estimates for minimum effective concentration and optimal concentration will be calculated using weighing in Buckland et al. (Buckland 1997).

The above analysis will be performed on the modified intent-to-treat set and PP set; the modified intent-to-treat set will be used as the primary analysis set.

The change from baseline and percent change from baseline in Pruritus NRS will be analyzed using a mixed effects model with baseline pruritus NRS as covariable, treatment, visit, treatment by visit as fixed effects, participant as random effects. With fitted model, the least square means and their 95% confidence intervals, the least mean differences between each active treatment and placebo and their 95% confidence intervals will be calculated for Week 1, 2, 3, and 4.

The change from baseline and percent change from baseline in Pruritus NRS will also be summarized by treatment and visit using descriptive statistics.

The above analysis will be performed on the modified intent-to-treat and PP sets.

Pruritus response, which is defined as improvement (reduction) of 7-day average of daily hand peak pruritus NRS $\geq$4 from Baseline, will be analyzed using the Cochran Mantel Hansel test, controlling for NRS at baseline, at Week 1, 2, 3, and 4.

Pruritus response will also be summarized descriptively by treatment and visit.

Pruritus response will be analyzed on both the modified intent-to-treat and PP sets.

All other continuous variables will be analyzed in a similar manner as the percent change from baseline in Pruritus NRS; all other binary variables will be analyzed in a similar manner as the Pruritus response.

All efficacy variables will be listed for each participant by visit.

9.3.2. Pharmacokinetic Analyses

ASN008 concentration data and PK parameters will be summarized per cohort based on nominal timepoints using descriptive statistics, such as mean, SD, geometric mean, CV%, median, minimum and maximum. PK parameters (apparent systemic clearance [CL/F], apparent volume of distribution [Vd/F], and distribution clearance) will be calculated using population-based methods (e.g., Nonlinear Mixed Effects Modeling) appropriate for sparse samples. Measures of inter- and intra-individual variability will be estimated.

PK-safety and efficacy relationships may be explored using linear regression, loess plots, Hills functions, or logistic regression, as appropriate.

9.3.3. Safety Analyses

The safety analysis will include reported local and systemic TEAEs and other safety information (i.e., clinical laboratory evaluations, vital signs, physical examinations, ECGs and local tolerability assessments results). A summary of safety results will be presented for each treatment group. Adverse events will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (Version 25.1 or later). All safety data (scheduled and unscheduled) will be presented in data listings.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following, as applicable:

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

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

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

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 14 days from the previous ICF signature date.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, and by inspectors from regulatory authorities.

The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in an eCRF completion guidelines document.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan and/or site contracts.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for two years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and data origin can be found in the monitoring guidelines which will follow the principles of being attributable, legible, contemporaneous, original, and accurate (ALCOA).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Sponsor or designee will perform monitoring to confirm that data entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7. Study and Site Closure/Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The study will be registered on ClinicalTrials.gov prior to the first participant enrolled.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Study results will be posted to registries such as www.ClinicalTrials.gov and EudraCT as required by local regulations. Additionally, there may be publications in relevant medical journals based on the results from the study.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11. LIST OF REFERENCES

Bieber T, D'Erme AM, Akdis CA, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? *J Allergy Clin Immunol.* 2017;139(4S):S58-S64.

Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol.* 2017;139(4S):S65-S76.

Buckland, ST, Burnham KP, Augustin, NH. Model selection: An integral part of inference. *Biometrics.* 1997;53:603-18.

Cabanillas B, Brehler AC, Novak N. Atopic dermatitis phenotypes and the need for personalized medicine. *Curr Opin Allergy Clin Immunol.* 2017;17(4):309-315.

Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Archives of Dermatology.* 2004;140(12):1513-9.

Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71(1):116-132.

Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol.* 2014;134(4):769-779.

Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract.* 2006;60(8):984-992.

Lipman ZM, Labib A, Yosipovitch G. Current Clinical Options for the Management of Itch in Atopic Dermatitis. *Clin Cosmet Investig Dermatol.* 2021 Aug 3;14:959-969.

Long CC, Finlay AY. The finger-tip unit--a new practical measure. *Clin Exp Dermatol.* 1991;16(6):444-447.

Marciniak J, Reich A, Szepietowski JC. Quality of Life of Parents of Children with Atopic Dermatitis. *Acta Derm Venereol.* 2017;97(6):711-714.

Silverberg JI. Persistence of childhood eczema into adulthood. *JAMA Dermatol.* 2014;150(6):591-592.

Williams HC. Atopic eczema. *BMJ.* 1995;311(7015):1241-1242.

12. APPENDICES

None.