A PHASE 2, MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF ASN002 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

PROTOCOL ASN002AD-201-EXT
IND # 133693

FINAL, VERSION 2.0
07 February 2019

Sponsor:	Asana BioSciences, LLC. [redacted]	
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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 08 August 2018	Initial version	N/A
2.0 / 07 February 2019	-To respond to FDA request to exclude placebo responders at Week 12 of the preceding ASN002AD-201 study from immediately being dosed in the open label extension protocol (ASN002AD-201EXT) until they have a flare.	1-Synopsis and Section 4, the following was added to clarify the restriction for exclusion of placebo responders: *"However, subjects who received the placebo in the study ASN002AD-201 will not be allowed to enter in the OLE study directly if they were responders at Week 12 based on EASI75. Placebo responders will be allowed to enter in the OLE study only if they have a flare within 2 months after their Week 12 visit, unless agreed to in writing by the Sponsor."* 2-Synopsis and Section 5.2, exclusion criterion added for placebo responders in study ASN002AD-201: *"Subject is a placebo responder at Week 12 based on EASI75 in preceding study ASN002AD-201. Subject will be allowed to enter the OLE only if a flare occurs within 2 months following Week 12 visit of the preceding study."* 3-Synopsis and Section 6.3, clarification about unblinding of placebo responders: *"The treatment assignment was designed to maintain the blind of the ASN002AD-201 study that will be conducted in parallel to the OLE study, except for the placebo responders who will be unblinded for the ASN002AD-201 study as they are prevented from entering directly in the OLE study."*
	- To revise the inclusion criterion related to body mass index (BMI) in order to allow wider pool of subjects access to the trial.	- Synopsis and Section 5.1, inclusion criterion #6 for subjects that are enrolled more than 2 weeks after their Week 12 visit in preceding ASN002AD-101 and ASN002AD-201 studies, BMI was revised to ≤ 38 kg/m^2.

	-To implement a discontinuation criterion regarding ineffective treatment during the study.	-Section 5.3.1, the following discontinuation criterion was added: *"The subject is not receiving benefit from the study drug. If, at any time during the study, either the Investigator or the subject determines there is no clinical or symptomatic benefit from receiving continued treatment with the study drug, the Investigator must discuss alternative treatment options that are available to the subject."*

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB) / ethic committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, local legal and regulatory requirements, the Declaration of Helsinki, and ICH GCP guidelines.

Sponsor: PPD

Feb 7, 2019
Date (DD-MMM-YYYY)

07-FEB-2019
Date (DD-MMM-YYYY)

Scientific Affairs:

12-Feb-2019
Date (DD-MMM-YYYY)

Study Statistician:

12-Feb-2019
Date (DD-MMM-YYYY)

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, the Declaration of Helsinki, ICH GCP guidelines, applicable Canadian regulations, applicable European regulations, applicable United States federal regulations, and local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
bid	twice a day
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CK	creatine kinase
CMH	Cochran Mantel Hansel
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
CPK	creatine phosphokinase
CRO	contract research organization
CV	coefficient of variation
DSMB	Data and Safety Monitoring Board
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	ethic committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDL	high-density lipoproteins
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	investigator brochure
ICH	International Council for Harmonisation
IGA	Investigator Global Assessment
IRB	institutional review board

ITT	intent-to-treat (population)
IV	intravenous
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDL	low-density lipoproteins
LMW	low molecular weight
JAK	janus kinase
Mapi	Mapi Life Sciences
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MPV	mean platelet volume
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	open label extension study
PK	pharmacokinetic
PLT	platelets
POEM	Patient-Oriented Eczema Measure
PP	per-protocol (population)
PPD	purified protein derivative
PUVA	psoralen-UV-A
QC	quality control
RBC	red blood cell (count)
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety (population)
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SYK	spleen tyrosine kinase
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet
VTE	venous thromboembolic event
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Asana BioSciences, LLC	**Name of Investigational Product:** ASN002	**Name of Active Ingredient:** ASN002

Title of Study:

A Phase 2, Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of ASN002 in Subjects with Moderate to Severe Atopic Dermatitis

Phase of Development:

Phase 2

Study Center(s):

Approximately 50 study centers located in the United States, Canada, and Germany will participate in this study.

Number of Subjects (planned):

This study is open to the subjects who participated in one of the preceding studies on ASN002 (ASN002AD-101 and ASN002AD-201). Therefore, it is anticipated that approximately 256 subjects will be included in this study. The actual sample size will depend on the number of subjects transitioning from prior ASN002 studies, so the anticipated number is not proposed as a fixed enrollment goal.

Duration of Study:

The maximum study duration per subject is up to 110 weeks (including up to 4 weeks for the screening period, up to 104 weeks (24 months) for the treatment period and a 2-week follow-up period).

Investigational Product, Dosage, and Mode of Administration:

ASN002 40, 60, or 80 mg orally administered once daily for up to 24 months. ASN002 will be available in 20-mg strength tablets.

Objectives:

Primary:

- To evaluate the long-term safety and tolerability of ASN002 in subjects with moderate to severe atopic dermatitis (AD) who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201)

Secondary:

- To evaluate the long-term efficacy of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201)
- To evaluate the effect of dose reduction at randomization in responder subjects with moderate to severe AD treated with ASN002 at 60 mg or 80 mg in study ASN002AD-201
- To evaluate the effect of dose increase at randomization in non-responder subjects with moderate to severe AD treated with ASN002 at 40 mg or 60 mg in study ASN002AD-201

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- To assess population PK of ASN002 in AD subjects via a population PK analysis approach

Exploratory:

- To explore the relationships between PK exposure and clinical measurement (e.g., efficacy and safety) as appropriate

Endpoints:

Primary Endpoint:

- Number and rate (events per 100 patient-years) of treatment-emergent adverse events (TEAEs)

Secondary Endpoints:

Secondary safety endpoints include:

- Number and rate (events per 100 patient-years) of drug-related TEAEs
- Proportion of subjects withdrawing from worsening AD at each visit
- Changes in vital signs, physical examinations, electrocardiogram (ECG), and safety laboratory tests

Secondary efficacy endpoints include:

- Change and percent change from baseline in Eczema Area and Severity Index (EASI) score at each visit
- Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at each visit
- Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at each visit
- Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at each visit
- Time to achieve EASI50, EASI75, and EASI90 relative to baseline only in subjects who received the placebo in the previous study
- Proportion of subjects maintaining EASI75 in responder subjects in ASN002AD-201 randomized to a reduced dose of ASN002 in ASN002AD-201-EXT
- Proportion of subjects achieving EASI75 in non-responder subjects in ASN002AD-201 randomized to an increased dose of ASN002 in ASN002AD-201-EXT
- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator's Global Assessment (IGA) at each visit
- Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at each visit
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit
- Change from baseline in SCORing Atopic Dermatitis (SCORAD) at each visit
- Change from baseline in 5-D Pruritus Scale at each visit
- Change and percent change from baseline in pruritus Numeric Rating Scale (NRS) at each visit
- Proportion of subjects achieving at least a 4-point reduction from baseline in pruritus NRS at each visit

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- Change and percent change from baseline in Body Surface Area (BSA) involved with AD at each visit
- Change from baseline in Patient-Oriented Eczema Measure (POEM) at each visit
- Change from baseline in Dermatology Life Quality Index (DLQI) at each visit
- Number and percentage of subjects with dose increase after randomization in the present study
- Time to first AD flare

Secondary PK endpoint includes:

- Measurement of plasma concentrations of ASN002

Exploratory Endpoints:

Exploratory endpoints include:

- Characterization of population PK parameters via nonlinear mixed-effects modeling
- Characterization of the relationship between PK exposure and efficacy and safety parameters

Study Design:

This is a Phase 2, multicenter, open-label extension (OLE) study designed to investigate the long-term safety, tolerability, efficacy, and pharmacokinetics of ASN002 in the treatment of moderate to severe AD.

Approximately 256 subjects with AD who participated in one of the preceding studies on ASN002 (ASN002AD-101 and ASN002AD-201) will be included in this study. Subjects will be eligible to enter the OLE study if they (1) participated in ASN002AD-101 study OR (2) participated in ASN002AD-201 study, completed at least the first 4 weeks without the use of prohibited treatments for AD, and completed the study visits up to Week 12 (subjects who started prohibited systemic medication and who had the study product discontinued in ASN002AD-201 study are allowed to enroll in the OLE study but not earlier than 12 weeks after Day 1 of the ASN002AD-201 study). Subjects who received the placebo in the other preceding studies are allowed to be enrolled in the OLE study. However, subjects who received the placebo in the study ASN002AD-201 will not be allowed to enter in the OLE study directly if they were responders at Week 12 based on EASI75. Placebo responders will be allowed to enter in the OLE study only if they have a flare within 2 months after their Week 12 visit, unless agreed to in writing by the Sponsor.

All subjects will sign an informed consent specific for the OLE study before initiating any trial-related procedures. Subjects will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria.

For subjects who participated in the preceding ASN002AD-201 study, Day 1 visit should preferably occur on the same day of the Week 12 visit of the preceding study (or at least 12 weeks after Day 1 of ASN002AD-201 study for subjects who started prohibited systemic medications) or can be delayed up to 2 weeks after, if needed, to minimize treatment interruption. In both cases, subjects will not have to perform the Screening visit in the OLE study, and assessments that are common to both visits (Screening and Day 1 visits) will be performed only once. If the Week 12 visit of the preceding ASN002AD-201 study and Day 1 of the OLE study are performed on the same day, assessments that are common to both visits will be performed also only once. All subjects from the preceding ASN002AD-201 study who are

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enrolled in the OLE study more than 2 weeks after their Week 12 visit will have to perform a complete screening evaluation no more than 30 days prior to Day 1. The Screening visit should not be performed more than 2 months after the subject's Week 12 visit for subjects who participated in the ASN002AD-201 study, unless agreed to in writing by the Sponsor.

Subjects who participated in the preceding ASN002AD-101 study will have to perform the Screening visit. Enrolment of subjects who participated in the preceding ASN002AD-101 study will be allowed until the last subject from the ASN002AD-201 study has performed his Week 12 visit.

Eligible subjects will be randomized on Day 1 to receive ASN002 once daily for up to 24 months. After 12 months of ASN002 study treatment, study treatment may be extended to 24 months contingent on Sponsor's decision based on emerging ASN002 clinical trial data.

Subjects from the preceding ASN002AD-101 study will be randomized in a 1:1:1 ratio to receive either ASN002 40 mg, 60 mg, or 80 mg, regardless of the treatment received or the response observed in the ASN002AD-101 study.

Subjects from the preceding ASN002AD-201 study will be randomized according to the rules described in the below table. The treatment assignment was designed to maintain the blind of the ASN002AD-201 study that will be conducted in parallel to the OLE study, except for the placebo responders who will be unblinded for the ASN002AD-201 study as they are prevented from entering directly in the OLE study.

Treatment/dose received in preceding ASN002AD-201 study	**Response in preceding ASN002AD-201 study[1]**	**Dose to be received in the OLE**		
		ASN002 40 mg	**ASN002 60 mg**	**ASN002 80 mg**
Placebo	Non-responder		X	X
	Responder	X		
ASN002 40 mg	Non-responder		X	X
	Responder	X		
ASN002 60 mg	Non-responder			X
	Responder	X	X	
ASN002 80 mg	Non-responder			X
	Responder	X	X	X

[1] Response in preceding ASN002AD-201 study based on EASI75 at Week 12 or last assessment before the start of a prohibited medication.

Dose adjustment will be permitted after evaluation of the subject's condition every 3 months. Based on the subject's response to the study treatment, the dose may be increased to the next highest dose if the subject and the investigator agree that this is needed to achieve the desired response. Dose reduction will not be permitted.

For scheduled study visits, subjects will come to the study center up to 12 occasions: Screening; Day 1; Months 1, 3, 6, 9, 12, 15, 18, 21, 24, and Follow-up/Early Termination (ET). For subjects who participated in the preceding ASN002AD-201 study and are enrolled in the OLE study within 2 weeks after their Week 12 visit, the Screening visit will not be performed, and they will come to the study center for up to 11 visits (the assessments that are common to both visits will be performed only once at Day 1).

Safety will be assessed by adverse events (AEs), physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.

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Efficacy will be assessed using IGA, EASI, SCORAD, BSA, pruritus NRS, and 5-D pruritus scale. Quality of life will be evaluated using POEM and DLQI.

ASN002 exposure will be monitored via sparse PK samples (trough and 3-hour post-dose samples) on the study visits. Exposure-response relationships between ASN002 exposure and selected safety and efficacy data may be explored.

Inclusion/Exclusion Criteria:

For subjects who participated in the preceding ASN002AD-201 study and for which the Day 1 visit is performed on the same day as Week 12 visit or up to 2 weeks after, the following inclusion and exclusion criteria will be applied at Day 1:

Inclusion criteria:

In order to be eligible to participate in this study, a subject must meet all of the following criteria **at Day 1 visit**, unless specified otherwise:

1. Subject with a history of moderate to severe atopic dermatitis who participated in the preceding ASN002AD-201 study, who completed at least the first 4 weeks without the use of prohibited treatments for AD, and completed the study visits up to Week 12.
2. Subject must be a candidate for prolonged open label ASN002 treatment according to the investigator's judgment.
3. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
4. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to continue using a highly effective contraceptive method until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

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

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 of the preceding ASN002AD-201 study and will continue to be abstinent from penile-vaginal intercourse throughout the OLE study. 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.

   Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

   Note: A woman of nonchildbearing potential is as follows:

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

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b. Woman who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels). FSH testing not required if already performed in the preceding study (data is available on file) and confirmed nonchildbearing potential.

5. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #4, from Day 1 until at least 90 days after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives method listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 of the preceding ASN002AD-201 study until at least 90 days after the last study product administration of the present study.
6. Female of childbearing potential has had a negative urine pregnancy test at Day 1.
7. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
8. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A subject who meets any of the following criteria **at the Day 1 visit**, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has any clinically significant medical condition or physical/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.
8. Subject has a 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
9. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
10. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
11. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.

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12. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
13. Subject is known to have immune deficiency or is immunocompromised.
14. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
15. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
16. Subject has a known history of diverticulitis.
17. Subject has uncontrolled diabetes.
18. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
19. Subject has used dupilumab within 12 weeks prior to Day 1.
20. Subject has used doxepin within 1 week prior to Day 1.
21. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
22. Subject has used topical products containing urea within 1 week prior to Day 1.
23. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
24. Subject has used oral corticosteroids for the treatment of AD within 2 weeks prior to Day 1.
25. Subject has used systemic treatments (other than biologics and oral corticosteroids) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
26. Subject has received any marketed or investigational biological agent targeting the immune system or that could have an effect on the immune system within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
27. Subject is currently receiving any other systemic medication for AD.
28. Subject is currently receiving a nonbiological investigational product, other than ASN002, or device or has received one within 4 weeks prior to Day 1.
29. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
30. Subject had prior treatment with a systemic SYK or JAK inhibitor, other than ASN002, for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
31. Subject was withdrawn from the preceding study for which ASN002 has been stopped for safety reasons.
32. Subject has a known hypersensitivity to ASN002 or its excipients.
33. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.

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34. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO or subject is an employee of the sponsor.
35. Subject is institutionalized because of legal or regulatory order.
36. Subject is a placebo responder at Week 12 based on EASI75 in preceding study ASN002AD-201. Subject will be allowed to enter the OLE only if a flare occurs within 2 months following Week 12 visit of the preceding study.

For subjects who participated in the preceding ASN002AD-101 study and for subjects who participated in the preceding ASN002AD-201 study but are enrolled more than 2 weeks after their Week 12 visit, the following inclusion and exclusion criteria will be applied at the Screening and Day 1 visits:

Inclusion criteria:

In order to be eligible to participate in this study, a subject must meet all of the following criteria **at the Screening and Day 1 visits**, unless specified otherwise:

1. Subject with a history of moderate to severe atopic dermatitis who:
    a. participated in ASN002AD-101 study
    OR
    b. participated in ASN002AD-201 study, completed at least the first 4 weeks without the use of prohibited treatments for AD, and completed the study visits up to Week 12 (subjects who started prohibited systemic medication and who had the study product discontinued in ASN002AD-201 study are allowed to enroll in the OLE study but not earlier than 12 weeks after Day 1 of the ASN002AD-201 study).
2. For subjects who participated in the preceding ASN002AD-101 study only: Subject has an EASI score ≥ 16 at Day 1.
3. For subjects who participated in the preceding ASN002AD-101 study only: Subject has moderate to severe atopic dermatitis at Day 1, as defined by an IGA ≥ 3.
4. For subjects who participated in the preceding ASN002AD-101 study only: Subject has atopic dermatitis covering $\geq 10\%$ of the BSA on Day 1.
5. Subject must be a candidate for prolonged open label ASN002 treatment according to the investigator's judgment.
6. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
7. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
8. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject 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 study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

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

Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. 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.

Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

Note: A woman of nonchildbearing potential is 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 (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels). FSH testing not required if already performed in the preceding study (data is available on file) and confirmed nonchildbearing potential.

9. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #8, from Day 1 until at least 90 days after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives method listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 until at least 90 days after the last study product administration.
10. Female of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
11. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
12. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A subject who meets any of the following criteria **at the Screening and Day 1 visits**, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.

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6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or QTc F ≥ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeat assessment. For subjects with QTcF≥450 msec on initial ECG, the mean of the two QTc F assessments will determine eligibility.
8. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.
9. Subject has a 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
10. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
11. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
12. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.
13. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
14. Subject is known to have immune deficiency or is immunocompromised.
15. If not performed within 1 year prior to Screening visit:

    Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at the Screening visit.
16. Presence of any of the following laboratory abnormalities at the Screening visit:
    a. Hemoglobin < 11 g/dL;
    b. White blood cell (WBC) < 3.0 x 10^3 /μL;
    c. Platelet count < 125 x 10^3 /μL;
    d. Neutrophils < 1.8 x 10^3 /μL;
    e. Lymphocytes < 1.0 x 10^3 /μL;
    f. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 x the upper limit of normal (ULN);
    g. Total bilirubin > 1.2 x ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome);
    h. Creatinine > ULN.
17. Subjects has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure >160 mm Hg or diastolic BP >95 mm Hg, confirmed by one repeat assessment.
18. If not performed within 1 year prior to Screening visit:

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Subject has a known active tuberculosis or a positive tuberculosis (TB) infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent TB (with negative chest x-ray findings for active TB).

19. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
20. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
21. Subject has a known history of diverticulitis.
22. Subject has uncontrolled diabetes.
23. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
24. Subject has used dupilumab within 12 weeks prior to Day 1.
25. Subject has used doxepin within 1 week prior to Day 1.
26. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
27. Subject has used topical products containing urea within 1 week prior to Day 1.
28. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
29. Subject has used oral corticosteroids for the treatment of AD within 2 weeks prior to Day 1.
30. Subject has used systemic treatments (other than biologics and oral corticosteroids) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
31. Subject has received any marketed or investigational biological agent targeting the immune system or that could have an effect on the immune system within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
32. Subject is currently receiving any other systemic medication for AD.
33. Subject is currently receiving a nonbiological investigational product, other than ASN002, or device or has received one within 4 weeks prior to Day 1.
34. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
35. Subject had prior treatment with a systemic SYK or JAK inhibitor, other than ASN002, for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
36. Subject was withdrawn from the preceding study for which ASN002 has been stopped for safety reasons.
37. Subject has a known hypersensitivity to ASN002 or its excipients.

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38. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
39. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO or subject is an employee of the sponsor.
40. Subject is institutionalized because of legal or regulatory order.
41. Subject is a placebo responder at Week 12 based on EASI75 in preceding study ASN002AD-201. Subject will be allowed to enter the OLE only if a flare occurs within 2 months following Week 12 visit of the preceding study.

Statistical methods:

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

Safety Analyses:

The safety analysis will include reported AEs and other safety information (i.e., clinical laboratory evaluations, vital signs, physical examination, and 12-lead ECG results). A summary of safety results will be presented for each treatment group. The treatment group for safety will be determined as the last dose received prior to the AEs or prior to the safety results. Thus, a subject may be assigned to more than one treatment group, depending on the safety results assessed.

Efficacy Analyses:

The efficacy endpoints will be summarized with descriptive statistics for each treatment group. All subjects will be analyzed according to the treatment group to which they were initially randomized at the start of the OLE study (regardless of dose increase after randomization during the study).

PK Analyses:

ASN002 concentration data will be summarized based on nominal timepoints using descriptive statistics, such as mean, SD, CV%, median, minimum and maximum.

Population PK analysis will be performed using nonlinear mixed-effects modeling approach with first-order conditional methods.

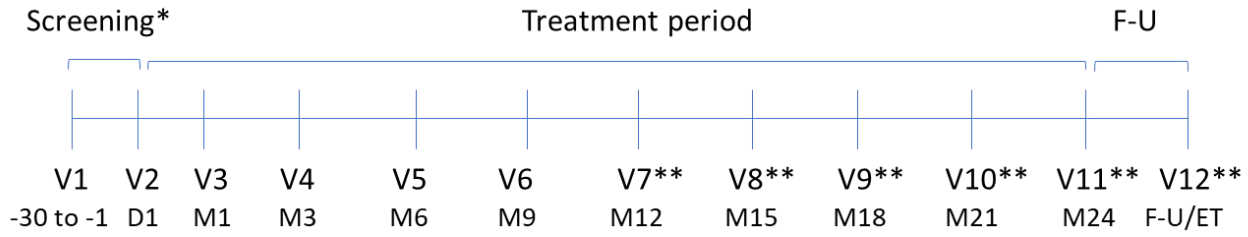
PK-efficacy and PK-safety relationships will be explored.

Sample Size Consideration:

No formal sample size or power calculations were performed for this study. The sample size is based on the completion of the preceding ASN002AD-101 and ASN002AD-201 studies and the consenting for the extension.

1.2 Study Diagram

Figure 1: Study Diagram



D=Day; ET=Early Termination; F-U=Follow-up; M=Month; V= Visit
*For subjects who participated in the preceding ASN002AD-201 study, Day 1 visit should preferably occur on the same day of the Week 12 visit of the preceding study or can be delayed up to 2 weeks after, if needed, to minimize treatment interruption. In both cases, subjects will not have to perform the Screening visit in the OLE study, and assessments that are common to both visits (Screening and Day 1 visits) will be performed only once.
** V7 through V11: Study treatment may be extended up to 24 months contingent on Sponsor's decision based on emerging ASN002 clinical trial data. V12 may thus occur at Week 54 or Week 106.

1.3 Schedule of Events

All subjects will sign an informed consent specific for the OLE study before initiating any trial-related procedures. Subject will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria.

For subjects who participated in the preceding ASN002AD-201 study, Day 1 visit should preferably occur on the same day of the Week 12 visit of the preceding study or can be delayed up to 2 weeks after, if needed, to minimize treatment interruption. In both cases, subjects will not have to perform the Screening visit in the OLE study, and assessments that are common to both visits (Screening and Day 1 visits) will be performed only once. If the Week 12 visit of the preceding ASN002AD-201 study and Day 1 of the OLE study are performed on the same day, assessments that are common to both visits will be performed also only once. All subjects from the preceding ASN002AD-201 study who are enrolled in the OLE study more than 2 weeks after their Week 12 visit will have to perform a complete screening evaluation no more than 30 days prior to Day 1. The Screening visit should not be performed more than 2 months after the subject's Week 12 visit for subjects who participated in the ASN002AD-201 study, unless agreed to in writing by the Sponsor.

Subjects who participated in the preceding ASN002AD-101 study will have to perform the Screening visit. Enrolment of subjects who participated in the preceding ASN002AD-101 study will be allowed until the last subject from the ASN002AD-201 study has performed his Week 12 visit.

For subjects who have to perform the Screening visit, the Day 1 visit must occur, at the latest, 30 days after the Screening visit.

Table 1 provides a description of the procedures to be performed at each visit. Unless specified otherwise, the study assessments scheduled during the study visits will be performed before the study drug administration. If assessments are scheduled at the same time, then the assessments should occur in the following order:

- Vital signs
- 12-lead ECG
- Blood draws for PK samples (time window vs drug administration detailed in footer of Table 1)

Table 1: Schedule of Events

Study Visits	**Screening[1]**	**Baseline[1]**	**Treatment Period**									**Follow-up/ET**
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7***	**V8***	**V9***	**V10***	**V11***	**V12***
Month (M)			**M1**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	
Week (W)		**D1**	**W4**	**W13**	**W26**	**W39**	**W52**	**W65**	**W78**	**W91**	**W104**	**W54 or W106**
Day (D)			**D29**	**D92**	**D183**	**D274**	**D365**	**D456**	**D547**	**D638**	**D729**	**D743**
Window (days)	-30 to -1		±7	±7	±7	±7	±7	±7	±7	±7	±7	±2
Informed consent[2]	X	X										
Demographics[3]	X	X										
Medical and surgical history[4]	X	X										
Inclusion-exclusion criteria	X	X										
Pregnancy test[5]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X[6]			X[6]		X[6]		X[6]		X[6]	X
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X	X			X		X		X	X
Clinical laboratory tests (hematology, chemistry, and urinalysis)	X	X		X	X	X	X	X	X	X	X	X
Serology (HIV, HBV, HCV)[8]	X											
Tuberculosis evaluation[8,9]	X											
BSA	X	X	X	X	X	X	X	X	X	X	X	
IGA	X	X	X	X	X	X	X	X	X	X	X	
EASI	X	X	X	X	X	X	X	X	X	X	X	
SCORAD		X	X	X	X	X	X	X	X	X	X	
Pruritus NRS		X	X	X	X	X	X	X	X	X	X	
5-D pruritus scale		X	X	X	X	X	X	X	X	X	X	
DLQI		X	X	X	X	X	X	X	X	X	X	
POEM		X	X	X	X	X	X	X	X	X	X	
Randomization		X										
Study product administration at study center		X	X	X	X	X	X	X	X	X		
Study product administration daily[10]		X----------									----------X	
Blood sampling for PK evaluation[11]		X	X	X	X		X					
Dispensing of study product		X	X	X	X	X	X	X	X	X		

Study Visits	**Screening[1]**	**Baseline[1]**	**Treatment Period**									**Follow-up/ET**
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7***	**V8***	**V9***	**V10***	**V11***	**V12***
Month (M)			**M1**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	
Week (W)		**D1**	**W4**	**W13**	**W26**	**W39**	**W52**	**W65**	**W78**	**W91**	**W104**	**W54 or W106**
Day (D)			**D29**	**D92**	**D183**	**D274**	**D365**	**D456**	**D547**	**D638**	**D729**	**D743**
Window (days)	-30 to -1		±7	±7	±7	±7	±7	±7	±7	±7	±7	±2
Collection of study product			X	X	X	X	X	X	X	X	X	
Study product accountability/ compliance		X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events evaluation	X	X	X	X	X	X	X	X	X	X	X	X

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; IGA=Investigator Global Assessment; M=month; NRS=numeric rating scale; PK=pharmacokinetics; POEM=Patient-Oriented Eczema Measure; SCORAD=SCORing Atopic Dermatitis; V=visit.

* V7 through V11: Study treatment may be extended up to 24 months contingent on Sponsor's decision based on emerging ASN002 clinical trial data. V12 may thus occur at Week 54 or Week 106.

[1] For subjects who participated in the preceding ASN002AD-201 study, Day 1 visit should preferably occur on the same day of the Week 12 visit of the preceding study or can be delayed up to 2 weeks after, if needed, to minimize treatment interruption. In both cases, subjects will not have to perform the Screening visit in the OLE study, and assessments that are common to both visits (Screening and Day 1 visits) will be performed only once. All subjects from the preceding ASN002AD-201 study who are enrolled in the OLE study more than 2 weeks after their Week 12 visit and subjects who participated in the preceding ASN002AD-101 study will have to perform a complete screening evaluation.

[2] For subjects performing the Day 1 visit within 2 weeks of Week 12 visit of the ASN002AD-201 study, inform consent will be signed on Day 1 since no Screening visit will be performed. For the other subjects, informed consent must be signed at the Screening visit.

[3] The subject's demographic data, including date of birth, gender, race, and ethnicity collected at the Screening visit of the preceding study will be used in the present study and do not need to be collected again.

[4] Medical and surgical history collected in the preceding study will be used in the present OLE study. Only new information and updates will need to be collected at Screening /Day 1 visit(s).

[5] Females of childbearing potential only. Serum pregnancy test at screening and urine pregnancy test at other visits.

[6] Brief physical examinations.

[7] Including weight and BMI. Height collected at the Screening visit of the preceding study will be used in the present study and does not need to be collected again. The same value for the height will be used for BMI calculation at each visit.

[8] If not performed within 1 year prior to Screening visit.

[9] If PPD is used, a second visit will be necessary for PPD reading only.

[10] Study products will be taken at home daily for up to 24 months, except on study visit days when the study products will be administered on site (and except on Visit 11 where no study product will be administered).

[11] For Day 1, Months 1, 6, and 12, PK samples will be collected at pre-dose and 3 hours post dose; the 3-hour sample can be collected between 2-8 hours post-dose. For Month 3, visit, only a pre-dose sample will be collected. For ET visit, one PK sample will be collected at the time of visit if the ET visit occurs during the first 12 months only (if the ET is after, the PK sample is not required). No PK sample is required at the Follow-up visit.

2 INTRODUCTION

2.1 Background

2.1.1 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Inflammation, pruritus, papules, lichenification, excoriations, xerosis, and oozing clinically characterize AD.(1) Onset typically occurs in children and can improve in adulthood; however, late onset can also occur.(2) Atopic dermatitis affects 10-20% of children and 1-3% of adults.(2, 3) Moreover, recent studies suggest that the prevalence of AD in adults could be much higher.(4) Prevalence has also been observed to be higher in industrialized countries, suggesting, at least partially, an environmental link.(5) The quality of life and psychological state of patients with AD, as well as the parents of patients can be greatly impacted by this disease.(6, 7) Pruritus prevalence in AD patients is greater than 80% and greatly impairs their quality of life by causing sleep and psychological disturbance.(8)

It is a heterogeneous disease with a wide spectrum of clinical phenotype and a complex pathophysiology.(9, 10) 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, air quality).(3, 11)

In recent years, the understanding of the clinical characterization of AD phenotypes and molecular mechanisms of the disease has advanced greatly giving hope for the development of new therapeutic agents.(5, 10, 12, 13) Janus kinase (JAK) and Spleen tyrosine kinase (SYK) are tyrosine kinases that have been shown to be implicated in the pathogenesis of various types of autoimmune and inflammatory diseases.(14, 15) It is understood that AD is primarily a T cell-driven disease.(16) Atopic dermatitis was shown to have a strong Th2 response where IL-4 promotes the differentiation of Th2 cells, which are regulated by the JAK signaling pathway. Moreover, activation of SYK leads to the release of various inflammatory mediators and plays a role in downstream signaling involved in the pathology of several allergic and autoimmune diseases.(14, 17) Therefore, targeting both JAK and SYK kinases may provide a new therapeutic approach in the treatment of inflammatory disorders, such as atopic dermatitis.

2.1.2 ASN002 in Atopic Dermatitis

ASN002 is an orally bioavailable, potent dual inhibitor of JAK and SYK kinases with 50% inhibitory concentrations (IC_{50} values) of 5-46 nM in biochemical assays. In cell-based mechanistic assays, the compound showed inhibition of IgE-immune complex induced degranulation and phosphorylation of LAT (Linker for Activation of T cells) a substrate of SYK, and also IL-6 induced phosphorylation of STAT3 (IC_{50} range 14–143 nM). In a collagen-induced arthritis model, ASN002 demonstrated a significant reduction in arthritic, histopathology and radiographic scores when compared to vehicle. The compound also showed broad antiproliferative activity in a panel of cell lines representing both solid and leukemia/lymphoma tumor types. The data from both in vitro (cell line) and in vivo efficacy studies with ASN002

provide strong rationale for its evaluation in subjects with atopic dermatitis. In the Phase 1b study (ASN002AD-101), plasma concentrations of ASN002 were measured in subjects with atopic dermatitis following single and repeated once daily oral administration at 20, 40 and 80 mg. At steady state, C_{max} and AUC were dose dependent with approximately 1.5-fold or less accumulation compared to those on Day 1, and the mean elimination $t_{1/2}$ were 7.3-13.7 hours. At 80 mg, the mean C_{max} and AUC_{tau} of ASN002 at steady state were 252 ng/ml and 3340 ng*hr/ml, respectively. The safety and tolerability profile of ASN002 at all dose levels was excellent. The most common adverse event (AE) observed was transient, mild headache, mostly restricted to Day 1 likely due to fasting. There were no clinically significant laboratory changes including hematological parameters observed in this study. ASN002 showed robust clinical efficacy with nearly all patients obtaining a 50% improvement in disease severity (EASI50) at 40 mg and 80 mg once daily, and substantial decreases in patient-reported itch measured by Numeric Rating Scale (NRS) after 4 weeks of treatment.

2.1.3 Study Rationale

In the previous Phase 1b clinical trial (ASN002AD-101), ASN002 has showed significant benefit for the treatment of atopic dermatitis, especially at 40 mg and 80 mg once-daily dosing regimens. A Phase 2b study (ASN002D-201) is currently ongoing to further investigate the benefit and risk of ASN002 at 40 mg, 60 mg and 80 mg once-daily dosing regimens in subjects with atopic dermatitis for a 12-week treatment duration.

Current therapies for AD provide relief of symptoms for most but not all patients. Additionally, they do not prevent or eradicate the disease. The development of medications that precisely target the molecular mediators of inflammation involved in AD is certainly a promising approach to treat this disease. There is definitely a need for new treatments in AD in order to increase the existing options available to clinicians.

This trial is to collect long-term data on ASN002. The primary objective of this study is to assess the long-term safety and tolerability of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201). Long-term efficacy of ASN002 will also be evaluated as secondary endpoints. The doses to be administered in this study range between 40 and 80 mg, which were found to be well tolerated and safe in the previous Phase 1b study. Adverse events observed in the Phase 1b study were of mild or moderate intensity following 80 mg dose. One SAE was reported (anxiety attack), which was not related to the study drug, and one event led to treatment discontinuation for one subject (hypertension) in the 80-mg cohort (refer to Section 2.2.1 for more details). Once daily administration was chosen based on the data from the clinical studies in oncology subjects and healthy volunteers. Pharmacokinetic analyses indicate sufficient systemic exposure for ASN002 efficacy, and a half-life of ~10 hours is adequate for maintaining target trough concentrations.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The data from both nonclinical and clinical studies with ASN002 suggest that it is anticipated to be safe and well-tolerated at the doses to be administered in the present study.

In cancer subjects, ASN002 has been studied at daily doses up to 100 mg bid. The most common reported AEs were anemia, fatigue, chills, dizziness, and diarrhea, as expected in heavily pretreated and refractory cancer patients.

The safety of ASN002 has also been studied in a safety, tolerability, PK, and food effect study in healthy subjects at doses up to a single oral dose of 100 mg. The most common adverse event in this study was headache. One SAE, premature ventricular contractions, which was asymptomatic and mild, was experienced by one subject dosed with 50 mg ASN002 once. It resolved over 5 days without sequelae. This event was considered possibly related to study medication and unexpected.

The safety of ASN002 was also assessed in a previous Phase 1b study in AD patients. Adverse events observed in the Phase 1b study were mild or moderate at daily doses up to 80 mg for 4 weeks. There were no drug-related SAEs reported in this study. One SAE was reported (anxiety attack), which was not related to the study drug. In addition, one event led to treatment discontinuation for one subject (hypertension) in the 80-mg cohort. The corresponding patient was also on Ritalin and was observed with fluctuating blood pressure measurement results even after clearance of the study drug, suggesting Stage 1 hypertension levels. It is also important to note that the patient also had borderline high level of blood pressure at baseline. Considering the above, this study suggests that ASN002 is safe and well-tolerated at doses up to 80 mg.

Further information related to previous clinical studies is available in the Investigator Brochure.

2.2.2 Known Potential Benefits

Based on the Phase 1b clinical trial (ASN002AD-101), it is anticipated that subjects will benefit from the long-term treatment with ASN002 as a result of participating in this study. Participation in this study may help generate future benefit for larger groups of patients with atopic dermatitis.

2.2.3 Assessment of Risks and Benefits

All quality, pharmacology, and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and previous clinical studies are considered sufficient to expect a positive benefit/risk ratio following the long-term treatment of atopic dermatitis with ASN002, and therefore to initiate this study.

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

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the long-term safety and tolerability of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201)	Primary safety endpoint: • Number and rate (events per 100 patient-years) of treatment-emergent adverse events (TEAEs) Secondary safety endpoints: • Number and rate (events per 100 patient-years) of drug-related TEAEs • Proportion of subjects withdrawing from worsening AD at each visit • Changes in vital signs, physical examinations, electrocardiogram (ECG), and safety laboratory tests
Secondary	
To evaluate the long-term efficacy of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201)	Secondary efficacy endpoints: • Change and percent change from baseline in Eczema Area and Severity Index (EASI) score at each visit • Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at each visit • Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at each visit • Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at each visit • Time to achieve EASI50, EASI75, and EASI90 relative to baseline only in subjects who received the placebo in the previous study • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator's Global Assessment (IGA) at each visit • Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at each visit • Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit • Change from baseline in SCORing Atopic Dermatitis (SCORAD) at each visit • Change from baseline in 5-D Pruritus Scale at each visit • Change and percent change from baseline in pruritus Numeric Rating Scale (NRS) at each visit • Proportion of subjects achieving at least a 4-point reduction from baseline in pruritus NRS at each visit

OBJECTIVES	ENDPOINTS
	• Change and percent change from baseline in Body Surface Area (BSA) involved with AD at each visit • Change from baseline in Patient-Oriented Eczema Measure (POEM) at each visit • Change from baseline in Dermatology Life Quality Index (DLQI) at each visit • Number and percentage of subjects with dose increase after randomization in the present study • Time to first AD flare
To evaluate the effect of dose reduction at randomization in responder subjects with moderate to severe AD treated with ASN002 at 60 mg or 80 mg in study ASN002AD-201	• Proportion of subjects maintaining EASI75 in responder subjects in ASN002AD-201 randomized to a reduced dose of ASN002 in ASN002AD-201-EXT
To evaluate the effect of dose increase at randomization in non-responder subjects with moderate to severe AD treated with ASN002 at 40 mg or 60 mg in study ASN002AD-201	• Proportion of subjects achieving EASI75 in non-responder subjects in ASN002AD-201 randomized to an increased dose of ASN002 in ASN002AD-201-EXT
To assess population PK of ASN002 in AD subjects via a population PK analysis approach	Secondary PK endpoint: • Measurement of plasma concentrations of ASN002
Exploratory	
To explore the relationships between PK exposure and clinical measurement (e.g., efficacy and safety) as appropriate	• Characterization of population PK parameters via nonlinear mixed-effects modeling • Characterization of the relationship between PK exposure and efficacy and safety parameters

4 STUDY DESIGN

4.1 Overall Design

This study will be performed at approximately 50 study centers located in the United States, Canada, and Germany (sites who participated in preceding studies on ASN002, i.e. ASN002AD-101 and ASN002AD-201).

This is a Phase 2, multicenter, open-label extension (OLE) study designed to investigate the long-term safety, tolerability, efficacy, and pharmacokinetics of ASN002 in the treatment of moderate to severe AD.

Approximately 256 subjects with AD who participated in one of the preceding studies on ASN002 (ASN002AD-101 and ASN002AD-201) will be included in this study. Subjects will be eligible to enter the OLE study if they (1) participated in ASN002AD-101 study OR (2) participated in ASN002AD-201 study, completed at least the first 4 weeks without the use of prohibited treatments for AD, and completed the study visits up to Week 12 (subjects who started prohibited systemic medication and who had the study product discontinued in ASN002AD-201 study are allowed to enroll in the OLE study but not earlier than 12 weeks after Day 1 of the ASN002AD-201 study). Subjects who received the placebo in the other preceding studies are allowed to be enrolled in the OLE study. However, subjects who received the placebo in the study ASN002AD-201 will not be allowed to enter in the OLE study directly if they were responders at Week 12 based on EASI75. Placebo responders will be allowed to enter in the OLE study only if they have a flare within 2 months after their Week 12 visit, unless agreed to in writing by the Sponsor.

All subjects will sign an informed consent specific for the OLE study before initiating any trial-related procedures. Subjects will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria.

For subjects who participated in the preceding ASN002AD-201 study, Day 1 visit should preferably occur on the same day of the Week 12 visit of the preceding study (or at least 12 weeks after Day 1 of ASN002AD-201 study for subjects who started prohibited systemic medications) or can be delayed up to 2 weeks after, if needed, to minimize treatment interruption. In both cases, subjects will not have to perform the Screening visit in the OLE study, and assessments that are common to both visits (Screening and Day 1 visits) will be performed only once. If the Week 12 visit of the preceding ASN002AD-201 study and Day 1 of the OLE study are performed on the same day, assessments that are common to both visits will be performed also only once. All subjects from the preceding ASN002AD-201 study who are enrolled in the OLE study more than 2 weeks after their Week 12 visit will have to perform a complete screening evaluation no more than 30 days prior to Day 1. The Screening visit should not be performed more than 2 months after the subject's Week 12 visit for subjects who participated in the ASN002AD-201 study, unless agreed to in writing by the Sponsor.

Subjects who participated in the preceding ASN002AD-101 study will have to perform the Screening visit. Enrolment of subjects who participated in the preceding ASN002AD-101 study will be allowed until the last subject from the ASN002AD-201 study has performed his Week 12 visit.

Eligible subjects will be randomized on Day 1 to receive ASN002 once daily for up to 24 months. After 12 months of ASN002 study treatment, study treatment may be extended to 24 months contingent on Sponsor's decision based on emerging ASN002 clinical trial data.

For scheduled study visits, subjects will come to the study center up to 12 occasions: Screening; Day 1; Months 1, 3, 6, 9, 12, 15, 18, 21, 24, and Follow-up/Early Termination (ET). For subjects who participated in the preceding ASN002AD-201 study and are enrolled in the OLE study within 2 weeks after their Week 12 visit, the Screening visit will not be performed, and they will come to the study center for up to 11 visits (the assessments that are common to both visits will be performed only once at Day 1).

Safety will be assessed by adverse events (AEs), physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.

Efficacy will be assessed using IGA, EASI, SCORAD, BSA, pruritus NRS, and 5-D pruritus scale. Quality of life will be evaluated using POEM and DLQI.

ASN002 exposure will be monitored via sparse PK samples (trough and 3-hour post-dose samples) on the study visits. Exposure-response relationships between ASN002 exposure and selected safety and efficacy data may be explored.

No formal interim analyses are planned for this open-label study, except for the review of safety data on regular basis.

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the long-term safety and tolerability and to evaluate the long-term efficacy of ASN002 study product in subjects with atopic dermatitis.

4.3 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1.

The end of the study is defined as completion of the last visit or procedure shown in the schedule of event for the last enrolled subject in the trial globally for all sites.

4.4 Safety Monitoring Criteria for Individual Subject Treatment Interruption/Discontinuation

In the event of an adverse event or laboratory abnormality, individual subject study treatment may be temporary or permanently discontinued based on the Investigator's judgement in accordance with the guidelines described in this section.

Treatment may be resumed upon recovery to baseline or mild levels after the condition leading to suspension of dosing resolves, at the discretion of the principal investigator in consultation with the medical monitor. A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study

treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation/interruption. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

Any retreatment should only be considered upon written agreement between the investigator and the sponsor. This information pertaining to discontinuation or interruption of study medication and the reasons for it must be recorded in the case report form.

Dose adjustment is not permitted other than as defined in the present protocol, as described in Section 6.3.

4.4.1 Interruption criteria

A subject who meets either of the below criteria will have the study drug interrupted until laboratory retesting is performed and/or event resolution.

- neutrophils > 0.5 x 10^3 /µL but < 1 x 10^3 /µL;
- platelet count > 50 x 10^3 /µL but < 100 x 10^3 /µL;
- lymphocytes < 0.5 x 10^3 /µL but > 0.2 x 10^3 /µL;
- CPK >10 x ULN;
- an infection requiring IV treatment with antiviral, antibiotic, antiprotozoal, antiparasite or requiring oral medications of those longer than 2 weeks;
- AST/ALT > 5 x ULN.

Decision to restart the medication following any laboratory abnormality described above will be made in consultation with the study sponsor and medical monitor.

4.4.2 Permanent study discontinuation

Adverse events or laboratory abnormalities that meet either of the below criteria will result in permanent study discontinuation of the subject. Treatment with the study product will be immediately stopped and the subject withdrawn from this study.

- serious opportunistic infection such as tuberculosis;
- hypertension that cannot be controlled with additional antihypertensive medication(s);
- neutrophils ≤ 0.5 x 10^3 /µL;
- lymphocytes ≤ 0.2 x 10^3 /µL;
- platelets ≤ 50 x 10^3 /µL;
- diagnosis of malignancy;
- venous thrombo-embolic event or major cardiovascular event.

4.5 Safety Monitoring

The primary medical monitor and sponsor clinical team will review the safety data on a regular basis. An independent Data and Safety Monitoring Board (DSMB) is not required for the study.

However, recommendations of the DSMB during the ASN002AD-201 study that are applicable to the present OLE study will be applied, as needed.

5 STUDY POPULATION

5.1 Inclusion Criteria

For subjects who participated in the preceding ASN002AD-201 study and for which the Day 1 visit is performed on the same day as Week 12 visit or up to 2 weeks after, the following inclusion criteria will be applied at Day 1:

In order to be eligible to participate in this study, a subject must meet all of the following criteria **at Day 1 visit**, unless specified otherwise:

1. Subject with a history of moderate to severe atopic dermatitis who participated in the preceding ASN002AD-201 study, who completed at least the first 4 weeks of treatment without the use of prohibited treatments for AD, and completed the study visits up to Week 12.
2. Subject must be a candidate for prolonged open label ASN002 treatment according to the investigator's judgment.
3. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
4. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to continue using a highly effective contraceptive method until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

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

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 of the preceding ASN002AD-201 study and will continue to be abstinent from penile-vaginal intercourse throughout the OLE study. 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.

   Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

   Note: A woman of nonchildbearing potential is 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 (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory

levels). FSH testing not required if already performed in the preceding study (data is available on file) and confirmed nonchildbearing potential.

5. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #4, from Day 1 until at least 90 days after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives method listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 of the preceding ASN002AD-201 study until at least 90 days after the last study product administration of the present study.
6. Female of childbearing potential has had a negative urine pregnancy test at Day 1.
7. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
8. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

For subjects who participated in the preceding ASN002AD-101 study and for subjects who participated in the preceding ASN002AD-201 study but are enrolled more than 2 weeks after their Week 12 visit, the following inclusion criteria will be applied at the Screening and Day 1 visits:

In order to be eligible to participate in this study, a subject must meet all of the following criteria **at the Screening and Day 1 visits**, unless specified otherwise:

1. Subject with a history of moderate to severe atopic dermatitis who:
    a. participated in ASN002AD-101 study

       OR

    b. participated in ASN002AD-201 study, completed at least the first 4 weeks without the use of prohibited treatments for AD, and completed the study visits up to Week 12 (subjects who started prohibited systemic medication and who had the study product discontinued in ASN002AD-201 study are allowed to enroll in the OLE study but not earlier than 12 weeks after Day 1 of the ASN002AD-201 study).
2. For subjects who participated in the preceding ASN002AD-101 study only: Subject has an EASI score ≥ 16 at Day 1.
3. For subjects who participated in the preceding ASN002AD-101 study only: Subject has moderate to severe atopic dermatitis at Day 1, as defined by an IGA ≥ 3.
4. For subjects who participated in the preceding ASN002AD-101 study only: Subject has atopic dermatitis covering ≥ 10% of the BSA on Day 1.
5. Subject must be a candidate for prolonged open label ASN002 treatment according to the investigator's judgment.
6. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
7. Subject has been using an emollient (except those containing urea) daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient daily throughout the study.

Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

8. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject 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 study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

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

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. 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.

   Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.

   Note: A woman of nonchildbearing potential is 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 (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels). FSH testing not required if already performed in the preceding study (data is available on file) and confirmed nonchildbearing potential.

9. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #8, from Day 1 until at least 90 days after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives method listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 until at least 90 days after the last study product administration.
10. Female of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
11. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
12. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

For subjects who participated in the preceding ASN002AD-201 study and for which the Day 1 visit is performed on the same day as Week 12 visit or up to 2 weeks after, the following exclusion criteria will be applied at Day 1:

A subject who meets any of the following criteria **at the Day 1 visit**, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has any clinically significant medical condition or physical/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.
8. Subject has a 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
9. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
10. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
11. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.
12. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
13. Subject is known to have immune deficiency or is immunocompromised.
14. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
15. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
16. Subject has a known history of diverticulitis.
17. Subject has uncontrolled diabetes.

18. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
19. Subject has used dupilumab within 12 weeks prior to Day 1.
20. Subject has used doxepin within 1 week prior to Day 1.
21. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
22. Subject has used topical products containing urea within 1 week prior to Day 1.
23. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
24. Subject has used oral corticosteroids for the treatment of AD within 2 weeks prior to Day 1.
25. Subject has used systemic treatments (other than biologics and oral corticosteroids) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
26. Subject has received any marketed or investigational biological agent targeting the immune system or that could have an effect on the immune system within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
27. Subject is currently receiving any other systemic medication for AD.
28. Subject is currently receiving a nonbiological investigational product, other than ASN002, or device or has received one within 4 weeks prior to Day 1.
29. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
30. Subject had prior treatment with a systemic SYK or JAK inhibitor, other than ASN002, for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
31. Subject was withdrawn from the preceding study for which ASN002 has been stopped for safety reasons.
32. Subject has a known hypersensitivity to ASN002 or its excipients.
33. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
34. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO or subject is an employee of the sponsor.
35. Subject is institutionalized because of legal or regulatory order.
36. Subject is a placebo responder at Week 12 based on EASI75 in preceding study ASN002AD-201. Subject will be allowed to enter the OLE only if a flare occurs within 2 months following Week 12 visit of the preceding study.

For subjects who participated in the preceding ASN002AD-101 study and for subjects who participated in the preceding ASN002AD-201 study but are enrolled more than 2 weeks after their Week 12 visit, the following exclusion criteria will be applied at the Screening and Day 1 visits:

A subject who meets any of the following criteria **at the Screening and Day 1 visits**, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or QTc F $\geq$ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeat assessment. For subjects with QTcF$\geq$450 msec on initial ECG, the mean of the two QTc F assessments will determine eligibility.
8. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.
9. Subject has a 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
10. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
11. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
12. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.
13. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
14. Subject is known to have immune deficiency or is immunocompromised.
15. If not performed within 1 year prior to Screening visit:

Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at the Screening visit.

16. Presence of any of the following laboratory abnormalities at the Screening visit:
    a. Hemoglobin < 11 g/dL;
    b. White blood cell (WBC) < 3.0 x 10^3 /μL;
    c. Platelet count < 125 x 10^3 /μL;
    d. Neutrophils < 1.8 x 10^3 /μL;
    e. Lymphocytes < 1.0 x 10^3 /μL;
    f. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 x the upper limit of normal (ULN);
    g. Total bilirubin > 1.2 x ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome);
    h. Creatinine > ULN.
17. Subjects has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure >160 mm Hg or diastolic BP >95 mm Hg, confirmed by one repeat assessment.
18. If not performed within 1 year prior to Screening visit:
    Subject has a known active tuberculosis or a positive tuberculosis (TB) infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent TB (with negative chest x-ray findings for active TB).
19. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
20. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
21. Subject has a known history of diverticulitis.
22. Subject has uncontrolled diabetes.
23. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
24. Subject has used dupilumab within 12 weeks prior to Day 1.
25. Subject has used doxepin within 1 week prior to Day 1.
26. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
27. Subject has used topical products containing urea within 1 week prior to Day 1.

28. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
29. Subject has used oral corticosteroids for the treatment of AD within 2 weeks prior to Day 1.
30. Subject has used systemic treatments (other than biologics and oral corticosteroids) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
31. Subject has received any marketed or investigational biological agent targeting the immune system or that could have an effect on the immune system within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
32. Subject is currently receiving any other systemic medication for AD.
33. Subject is currently receiving a nonbiological investigational product, other than ASN002, or device or has received one within 4 weeks prior to Day 1.
34. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
35. Subject had prior treatment with a systemic SYK or JAK inhibitor, other than ASN002, for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
36. Subject was withdrawn from the preceding study for which ASN002 has been stopped for safety reasons.
37. Subject has a known hypersensitivity to ASN002 or its excipients.
38. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
39. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO or subject is an employee of the sponsor.
40. Subject is institutionalized because of legal or regulatory order.
41. Subject is a placebo responder at Week 12 based on EASI75 in preceding study ASN002AD-201. Subject will be allowed to enter the OLE only if a flare occurs within 2 months following Week 12 visit of the preceding study.

5.3 Discontinuation and Lost to Follow-Up

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject 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 one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

5.3.1 Discontinuation

Subjects who discontinue the study after the first dose will be asked, if they agree, to come for a last assessment (ET visit).

Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a serious adverse event (SAE), the study product is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The attending physician requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another therapeutic agent may be discontinued as detailed in Section 6.4.2.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the study.
- The subject may withdraw from the study for any other reason, including withdrawal of consent.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical trial site, inform both the subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.
- The subject is not receiving benefit from the study drug. If, at any time during the study, either the Investigator or the subject determines there is no clinical or symptomatic benefit from receiving continued treatment with the study drug, the Investigator must discuss alternative treatment options that are available to the subject.

5.3.2 Lost to Follow-Up

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

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

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial, but are not subsequently randomly assigned to the study products. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the Screening visit, including signature of a new consent form, will be performed.

6 TREATMENT

6.1 Study Products Administered

This study involves 3 different doses of ASN002 (40 mg, 60 mg, and 80 mg) orally administered once daily. ASN002 will be available in 20-mg strength tablets. All study products will be provided by the sponsor.

All study products will be administered orally once daily at approximately every 24 hours, as assigned, for up to 24 months. Subjects will be asked to take the study product on an empty stomach (2 hours before and 2 hours after a meal) with approximately 240 mL of water. On visit days, the study products will be administered at the study site. The date and time of the drug administration will be collected only on visit days at the study site. The subject should be instructed to take the study product at approximately the same time of the day.

Further details regarding the study products can be found in Table 2.

Table 2. Study Products

	Study Products		
Product name	**ASN002**	**ASN002**	**ASN002**
Dosage form	Tablet	Tablet	Tablet
Unit dose strength(s)	20 mg	20 mg	20 mg
Dosage level(s)	40 mg	60 mg	80 mg
Number of tablets per dose level	2 tablets	3 tablets	4 tablets
Route of Administration	Oral	Oral	Oral
Dosing instructions	Once a day	Once a day	Once a day
Source of procurement	Asana BioSciences, LLC	Asana BioSciences, LLC	Asana BioSciences, LLC

The contents of the label will be in accordance with all applicable regulatory requirements.

6.1.1 Missed or Vomited Doses

Should the subject forget to take the study product, she/he should take the study product as soon as she/he remembers up to 6 hours after the planned dosing time. Thereafter, the forgotten dose should not be taken and the next dose should be taken as per the originally planned schedule. Vomited doses should not be retaken.

6.1.2 Duration of Treatment

The maximum treatment duration per subject is up to 104 weeks (24 months).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation/Storage/Handling

All study products must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study product may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

The study product will be dispensed by the study site to the subject at the visits specified in Table 1. Subjects are to return all study product (used and unused) to the study site. The tablets will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents. Each subject will be instructed on the importance of returning study product at the next study visit and on taking the product as prescribed. If a subject does not return study product, he or she will be instructed to return it as soon as possible.

6.2.2 Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. After verification of the study product accountability by the sponsor or designee, used product will be stored safely until destruction/return. Any study product accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

All study 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 ICH 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 study products are provided in the study manual.

6.3 Randomization

At the study site, each eligible subject will be assigned a subject identifier number that will be used on all subject documentation. The subject identifier number will contain the site number and the subject number and will be assigned in numerical order based on chronological order of entering in the study (e.g., 002-010 for the 10^{th} subject who entered in the study at the Site #002).

Approximately 256 subjects will be randomized to receive either ASN002 40 mg, 60 mg, or 80 mg.

Randomization will occur at Day 1 visit. The randomization list will be generated using a validated software. 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 subjects by connecting to the IWRS.

Subjects from the preceding ASN002AD-101 study will be randomized in a 1:1:1 ratio to receive either ASN002 40 mg, 60 mg, or 80 mg, regardless of the treatment received or the response observed in the ASN002AD-101 study.

Subjects from the preceding ASN002AD-201 study will be randomized according to the rules described in Table 3. The treatment assignment was designed to maintain the blind of the ASN002AD-201 study that will be conducted in parallel to the OLE study, except for the placebo responders who will be unblinded for the ASN002AD-201 study as they are prevented from entering directly in the OLE study.

Table 3: Dose assignment for subjects who participated in the preceding ASN002AD-201 study

Treatment/dose received in preceding ASN002AD-201 study	Response in preceding ASN002AD-201 study[1]	Dose to be received in the OLE		
		ASN002 40 mg	ASN002 60 mg	ASN002 80 mg
Placebo	Non-responder		X	X
	Responder	X		
ASN002 40 mg	Non-responder		X	X
	Responder	X		
ASN002 60 mg	Non-responder			X
	Responder	X	X	
ASN002 80 mg	Non-responder			X
	Responder	X	X	X

[1] Response in preceding ASN002AD-201 study based on EASI75 at Week 12 or last assessment before the start of a prohibited medication.

Dose adjustment will be permitted after evaluation of the subject's condition every 3 months. Based on the subject's response to the study treatment, the dose may be increased to the next highest dose if the subject and the investigator agree that this is needed to achieve the desired response. Dose reduction will not be permitted.

Further guidance and information can be obtained in the study manual.

6.3.1 Blinding

This is an open-label study. Subjects and investigators will be aware of the study product and dose administered.

6.3.2 Study Product Compliance

Study product compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning and by maintaining adequate study product dispensing and return records. Any deviation from the prescribed dosage regimen will be recorded in the source document and eCRF.

Subjects who are significantly noncompliant with treatment based on IP accountability will be counseled and could be discontinued from the study, at the discretion of the investigator, following consultation with the sponsor. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of study product in the same time frame, as judged by the investigator.

6.4 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products and antacids) taken within 4 weeks prior to the first study visit (Screening or Day 1) and throughout the study must be recorded.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the 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.

6.4.1 Permitted Therapies

Topical medicated treatment for atopic dermatitis including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach baths are permitted during the study. Topical corticosteroids of class 5, 6, and 7 according to the American classification are allowed without any time restriction throughout the study. Topical corticosteroids of class 1, 2, 3, and 4 according to the American classification are only permitted for 2 short periods of time during the study (maximum of 2 weeks each time).

Psoralen-UV-A (PUVA) treatment and any UV-B phototherapy (including tanning beds) or excimer laser are also permitted during the study.

Subjects must apply an emollient of their choice (except those containing urea) on their skin. The emollient use must be initiated at least 1 week prior to study Day 1 and subjects must continue using it daily throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF.

Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.

No other products except those listed above may be applied to the lesions during the study.

6.4.2 Prohibited Therapies or Procedures

Table 4 lists prohibited medications that are not to be used from the defined washout periods before the first administration of study product at the Day 1 visit through the last study visit.
Subjects who start prohibited medications or therapies as a treatment for AD or other reasons during the study may be withdrawn from study treatment. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 4. Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Any marketed or investigational biological agent targeting the immune system or that could have an effect on the immune system	12 weeks or 5 half-lives (whichever is longer
Dupilumab	12 weeks
Nonbiological investigational product, other than ASN002, or device	4 weeks
Live attenuated vaccine	4 weeks
Systemic treatments (other than biologics and oral corticosteroids) that could affect atopic dermatitis (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, injectable corticosteroids) Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed	4 weeks
Oral corticosteroids for the treatment of AD	2 weeks
Systemic antibiotics	2 weeks
Topical antibiotics	1 week
Topical products containing urea	1 week
Hydroxyzine and diphenhydramine	1 week
Doxepin	1 week

6.4.3 Concomitant Use of Drugs that may affect Gastric pH

The use of antacids and H2 antagonists should be considered in place of proton pump inhibitors. However, H2 antagonists and aluminum or magnesium containing antacids may only be taken within a 3-10-hour window following dosing with ASN002. Refer to Table 5 for a sample list of concomitant medications that may affect gastric pH.

Table 5. Examples of H2 antagonists and Proton Pump Inhibitors

Prohibited	Permitted	
Proton Pump Inhibitors	**H2 antagonists**	**Antacids**
Esomeprazole/ omeprazole	cimetidine	Aluminum-based antacids
lansoprazole	nizatidine	Magnesium-based antacids
pantoprazole	ranitidine	Calcium-based antacids
rabeprazole		
The examples provided are not an exhaustive list of possible drugs that may affect gastric pH. The investigator is responsible for assessing all concomitant medications that may have effects on gastric pH.		

6.4.4 Study Restrictions

Subject should be willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Efficacy Assessments

Clinical evaluations of atopic dermatitis 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, an effort will be made to have the same assessor perform all assessments on a given subject, whenever possible.

7.1.1 Eczema Area and Severity Index

The EASI will be assessed at the visits specified in Table 1 before the study product administration. It quantifies the severity of a subject's atopic dermatitis based on both lesion severity and the percentage of BSA affected. (18) 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 four 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. A detailed procedure of EASI score calculation is provided in Appendix A.

7.1.2 Investigator Global Assessment

The IGA disease severity will be assessed at the visits specified in Table 1 before the study product administration. The IGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity. A detailed description of the IGA scale is provided in Appendix B.

7.1.3 SCORing Atopic Dermatitis

The SCORAD will be measured at the visits specified in Table 1 before the study product administration. The SCORAD grading system was developed by the European Task Force on Atopic Dermatitis (1993) and has been a standard tool to assess AD severity in clinical studies in Europe (19, 20). Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be evaluated for the AD severity. The overall BSA affected by AD will be evaluated (from 0% to 100%) and included in the SCORAD scores (refer to Section 7.1.4). Loss of sleep and pruritus will be evaluated by subjects on a visual analog scale (0-10) and should be based on the average of the last three days/nights. The sum of these measures represents the SCORAD, which can range from 0 to 103. The detailed procedure of SCORAD score calculation is provided in Appendix C.

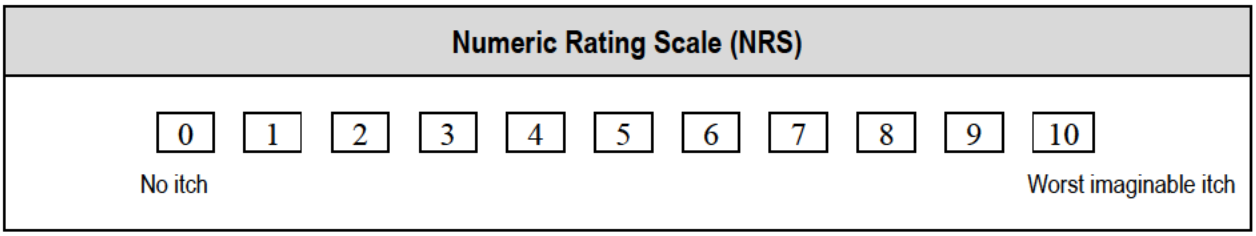
7.1.4 Body Surface Area

The overall BSA affected by AD will be evaluated (from 0% to 100%) at the visits specified in Table 1 before the study product administration. One subject's palm represents 1% of his or her total BSA. For all study visits except at screening, the BSA of involved skin will be measured with the SCORAD measurement (Section 7.1.3) and evaluated as a separate endpoint.

7.1.5 Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded at the visits specified in Table 1 using a numeric rating scale (NRS) (21). This will be evaluated by asking subjects to assign a numerical score representing the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The pruritus NRS is presented in Figure 2.

Figure 2: Pruritus Numeric Rating Scale



7.1.6 5-D Pruritus Scale

The 5-D Pruritus Scale will be evaluated at the visits specified in Table 1. 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. (22) Each question corresponds to 1 of the 5 dimensions of itch; subjects 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 is provided in Appendix D.

7.2 Quality-of-Life Assessments

7.2.1 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) will be assessed at the visits specified in Table 1. The POEM developed by Charman et.al. (23, 24) is a self-assessment of disease severity by the subject. The POEM has a maximum value of 28 based on the subject's response to seven questions scored from 0 to 4. A detailed description of the POEM assessment is provided in Appendix E.

7.2.2 Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI) will be assessed at the visits specified in Table 1. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. Its use has been described in more than 1,000 publications, including many

multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in Appendix F.

7.3 Safety Assessments

7.3.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), and body temperature (°C).

The weight (kg) and BMI will be recorded at the visits specified in Table 1. The height collected at the Screening visit of the preceding study will be used in the present study and does not need to be collected again. The same value for the height will be used for BMI calculation at each visit.

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

7.3.2 Physical Examination

The following sites/systems will at least be included in the physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except atopic dermatitis)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

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 will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

7.3.3 Brief Physical Examination

The following sites/systems will at least be included in the brief physical examination that will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except atopic dermatitis)
- Respiratory
- Cardiovascular
- Abdominal

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 will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

7.3.4 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The tests will include urinalysis, hematology with differential, a standard chemistry panel (chemistry includes liver function tests and cholesterol), and serum pregnancy test (screening) for women of childbearing potential (WOCBP), as applicable. At the visit specified in Table 1, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). The specific tests in these panels are listed in Table 6.

Table 6: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, PLT, RBC, reticulocyte count, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, calcium, carbon dioxide, chloride, creatinine (enzymatic), CPK, GGT, glucose random, LDH, lipid panel (HDL, LDL, total cholesterol and triglycerides (non-fasting)), phosphorus, potassium, sodium, total bilirubin, TBIL (direct bilirubin reflex if elevated), urea (BUN), uric acid, CRP, total protein
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen and microscopic analysis (as required)
Urine pregnancy test	For females of childbearing potential (at each visit, except screening)
Laboratory tests required at screening only	β-hCG for females of childbearing potential (only for subjects performing the Screening visit). FSH levels for women who have had a cessation of menses for at least 12 months without an alternative medical cause. FSH testing not required if already performed in the preceding study (data is available on file) and confirmed nonchildbearing potential. Tuberculosis test (PPD or QuantiFERON-TB Gold), if not performed within 1 year prior to screening visit. Serology (HBV (HBsAg, anti-HBc), HCV, HIV), if not performed within 1 year prior to screening visit.

ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = Creatine phosphokinase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl-transferase; HBsAg = hepatitis B surface antigens; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HDL = high-density lipoproteins; Hgb = hemoglobin; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PLT = platelets; PPD = purified protein derivative; RBC = red blood cell (count); WBC = white blood cell (count).

Subjects who do not qualify to participate in the study due to a screening laboratory value abnormality can repeat the test once within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a subject from study participation. Any significant change will be reported as an AE.

7.3.5 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Clinically significant findings in the ECG should exclude a subject from study participation (as deemed appropriate by the investigator). Any significant change will be reported as an AE.

7.4 Pharmacokinetic Assessment

Blood samples will be collected for ASN002 exposure assessment on the study visits and time points indicated in the Schedule of Events in Table 1. The actual date and time of each blood sample collection will be recorded. Approximately 4 mL of blood will be collected for each time point.

Details about the collection, processing, handling, storage and shipping of blood samples will be provided in the laboratory manual.

The PK concentration data from this study will be combined with the data from other ASN002 clinical trials for population PK assessment. The population PK analysis plan and the results derived from the analysis are beyond the scope of this study and, thus, will be addressed separately.

PK-efficacy and PK-safety relationships may be explored. The results from these analyses may be reported separately.

7.5Adverse Events and Serious Adverse Events

7.5.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject 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 study product, whether or not considered related to the study product. AEs and SAEs will be collected from the time of informed consent signature until the final visit / contact.

7.5.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product in the present study but appeared following treatment, 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).

7.5.3 Definition of Serious Adverse Event

A serious adverse event 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 subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

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 subject or may require intervention to prevent one 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.

7.5.4 Classification of an Adverse Event

7.5.4.1 Relationship to Study Product

The investigator will establish causality of the AE to the experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The degree of "relatedness" of the AE to the study 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 study medication.

Possibly related indicates that a direct cause and effect relationship between study 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 study medication.

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

The statement "**reasonable possibility for relationship**" meaning 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 investigators may also change their opinion for causality after follow-up information and may provide a follow-up SAE report with the revised causality assessment.

7.5.4.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.

- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.

- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

7.5.4.3 Expectedness

The expectedness of each SAE in relation to the study product will be determined in consultation with the Sponsor when necessary.

7.5.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Before subject enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present at the time of consent signature will be considered as part of medical history and not reported as an AE (this includes AEs that are ongoing at the last completed study visit of the preceding study). However, if the study subject's condition deteriorates after the consent signature, it will be recorded as an AE.

If a subject experiences an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (e.g., screening procedure) will be recorded in the source document and eCRF from the time a subject consents to participate in the study until the end of participation in the study.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

Worsening of atopic dermatitis is captured by efficacy assessments and will not be recorded as an AE.

7.5.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

7.5.7 Serious Adverse Events Reporting

[redacted] will be responsible for the overall pharmacovigilance process for this study. All SAEs, related to the experimental treatment or not, occurring during the course of the study must be reported on an SAE form to [redacted] (see below) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends at the end of the follow-up period or if the subject begins an alternative therapy.

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

Safety Contact Information: PPD
E-mail: PPD
Fax: (PPD

[redacted] will inform the sponsor, the primary medical monitor, and CRO within 1 business day of awareness of a new SAE. [redacted] will process and evaluate all SAEs as soon as the reports are received. For each SAE received, [redacted] will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. [redacted] will manage the AE reporting, including suspected unexpected serious adverse reactions, in accordance with the applicable local regulations. SAEs will be reported to the IRB/EC as per local IRB/EC requirements.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

7.5.8 Pregnancy Reporting

If a female subject or a female partner of a male subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to [redacted] within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE

reporting). [redacted] will report all cases of pregnancy to the sponsor and CRO in a timely manner. Posttreatment follow-up should be done to ensure subject 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 [redacted] and CRO 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 subject treatment assignment may be unblinded if judged necessary by the investigator and/or medical monitor in consultation with the sponsor. Once the subject treatment assignment is unblinded, the subject for whom the blind has been broken will be discontinued from the study and undergo the ET procedures.

7.5.9 Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Study drug compliance (see Section 6.3.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 7.5.7, 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 Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

No formal sample size or power calculations were performed for this study. The sample size is based on the completion of the preceding ASN002AD-101 and ASN002AD-201 studies and the consenting for the extension.

8.2 Populations for Analyses

The Safety Population (SAF): This population will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment group that they actually received.

Efficacy evaluable: This population will include all subjects who received at least one dose of the study product, have evaluable baseline and one post-dose assessment for at least one efficacy parameter. All subjects will be analyzed according to the treatment group that they initially received.

The PK Population: This population will include all subjects who received at least one dose of ASN002 and have plasma concentration data.

8.3 Statistical Analyses

8.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of subjects, mean, SD, CV%, median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages.

The safety analysis will be done using the SAF population. The efficacy analysis will be done using the Efficacy Evaluable population. All efficacy analyses will be performed on observed case (i.e. without imputation of missing observations).

Additional details regarding the efficacy and safety variable definitions, analyses strategy, and techniques for handling missing values will be detailed in a SAP that will be prepared before the database is locked and any analyses are undertaken.

8.3.2 Safety Analyses

The treatment group for safety will be determined as the last dose received prior to the AEs or prior to the safety results. Thus, a subject may be assigned to more than one treatment group, depending on the safety results assessed. The safety summaries will be presented for 1) subjects who just started treatment (i.e. subjects from Phase 1b and subjects dosed on Placebo in Phase 2b)

and 2) for subjects who are continuing treatment (i.e. subjects treated with ASN002 in Phase 2b), separately. Additional safety analyses may be performed and will be described in the SAP.

All safety data, including AEs and SAEs will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, and the outcome. The focus in this protocol will be the prevalence of TEAEs and drug-related TEAEs.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class, Preferred Term, severity, seriousness, and relationship to study product. For the summary of AEs by severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, System Organ Class, Preferred Term, start date, stop date, intensity, outcome, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. SAEs will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing.

Results from laboratory analyses, vital signs, ECGs, and physical examinations will be tabulated by treatment and visit using descriptive statistics. The value at each visit as well as the change from baseline will be presented descriptively.

Concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

8.3.3 Efficacy Analyses

The efficacy endpoints will be summarized with descriptive statistics for each treatment group. All subjects will be analyzed according to the treatment group to which they were initially randomized at the start of the OLE study (regardless of dose increase after randomization during the study).

Moreover, additional subgroup analyses will be described in the SAP (e.g. by responders and non-responders within each dosing group).

8.3.4 Pharmacokinetic Analyses

ASN002 concentration data will be listed per subject and summarized descriptively per dose based on nominal times.

Individual plasma concentration vs. actual time profiles for each subject and treatment, as well as the mean (±SD) plasma concentration vs. scheduled time profiles for each dose level, will be presented graphically.

8.3.5 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data, prior concomitant therapy, and of subject disposition will be presented. In addition, a list of subjects who discontinued from the study will be provided

Protocol deviations will be summarized by treatment and category.

8.3.6 Planned Interim Analysis

No formal interim analyses are planned for this OLE study, except for the review of safety data on regular basis.

9 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

9.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by an IRB/EC. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or CRO) before initiation of the study and also whenever subsequent modifications to the protocol are made.

9.3 Informed Consent Process

An Informed Consent Form describing in detail the study products, study procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/EC approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of

their medical care will not be adversely affected if they decline to participate in this study.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/EC. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

9.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study subjects and the IRB/EC, and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/EC, and applicable local regulations.

9.5 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On case report forms or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to the sponsor (e.g., subjects' written consent forms).

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the

IRB/EC, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/EC, institutional policies, or sponsor requirements.

9.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan.

9.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study product accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the IRB/EC, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

9.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be

classified into two separate categories: investigator's study files and subject clinical source documents.

The investigator must maintain source documents for each subject in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using [redacted], a web-based EDC and reporting system. This application will be set up for remote entry. [redacted] is the developer and owner of [redacted]. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

9.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be sent to the reviewing IRB/EC as per the IRB/EC requirements.

9.10 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 trial will be registered on ClinicalTrials.Gov prior to the first subject being dosed.

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APPENDIX A: Eczema Area and Severity Index

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale (half steps **are** allowed):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by atopic dermatitis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of atopic dermatitis involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10% to <30%
- 3 = 30% to <50%
- 4 = 50% to <70%
- 5 = 70% to <90%
- 6 = 90% to 100%

The EASI score is obtained by using the formula below:

$$\text{EASI} = 0.1\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.4\,(E_l + I_l + Ex_l + L_l)\,A_l$$

Where E, I, E*x*, L, and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

APPENDIX B: vIGA-AD™

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

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

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

APPENDIX C: Scoring Atopic Dermatitis - SCORAD

Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) are selected to evaluate the atopic dermatitis severity. The intensity of each item is graded using a 4-point scale (half steps **not** allowed):

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

The area chosen for grading must be representative (average intensity) for each item. The individual intensity ratings for each item will then be added (ranging from 0-18) and multiplied by 3.5, giving a maximal score of 63.

The overall BSA affected by atopic dermatitis is evaluated (from 0% to 100%) and divided by 5. One subject's palm represents 1% of his or her total BSA. The maximum is 20.

Subjective items include loss of sleep and the occurrence of pruritus. These are evaluated by asking subjects to indicate on the 10-cm scale (0-10) of the assessment form the point corresponding to the average value for the last 3 days/nights. The combined maximum score of these two is 20.

The sum of the measures above represents the SCORAD, which can vary from 0 to 103. If the subjective scores of pruritus and loss of sleep are excluded, the SCORAD becomes objective SCORAD (score range 0-83).

APPENDIX D: 5-D Pruritus Scale

5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX E: Patient-Oriented Eczema Measure

Subject ID #: ___ ___ - ___ ___ ___ Subject Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your skin been itchy because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

2. **Over the last week, on how many nights has your sleep been disturbed because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

3. **Over the last week, on how many days has your skin been bleeding because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

4. **Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

5. **Over the last week, on how many days has your skin been cracked because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

6. **Over the last week, on how many days has your skin been flaking off because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

7. **Over the last week, on how many days has your skin felt dry or rough because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

APPENDIX F: Dermatology Life Quality Index

Subject ID #: ___ ___ - ___ ___ ___ Subject Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □

Please check you have answered EVERY question. Thank you.