A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ASN002 IN SUBJECTS WITH MODERATE TO SEVERE CHRONIC HAND ECZEMA REFRACTORY TO CORTICOSTEROID THERAPY

PROTOCOL ASN002AD-202

FINAL

VERSION 6.0
01 October2019

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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 26 Oct 2018	Initial version	N/A
2.0 / 01 Nov 2018	Correct discrepancies in the footnote of the Schedule of Events for collection of microbiome samples.	-Section 1.3, Table 1, Footnote i: Clarified that the skin microbiome samples at Week 4 and 16 will include a nonlesional and a lesional samples. Also clarified the foot sampling areas.
	Clarification of the tape stripping sampling.	-Section 1.3, Table 1, Footnote k, and section 8.5.3: clarified by changing the term "same sampling area" for "lesional area selected on Day 1". Also clarified the foot sampling areas.
	To clarify storage time and possible research on study samples.	-Section 10.5, to add information on the storage time allow and possible future research to be performed with the skin and blood samples collected.
2.1 / 08 Nov 2018	To clarify the evaluation procedure of the mTLSS	-Section 8.1.1 – It was clarified that the most affected side (palmar or dorsal) of the most affected hand will be identified on Day 1 and the same most affected side of the most affected hand will be evaluated throughout the study.
	To correct a typographical error	-Section 8.1.2 – Footnote [a] in Table 7 was revised to clarify the sentence and to be consistent with the literature reference.
	To correct a typographical error	-Table 8: past tense was corrected to future tense in the footnote of the table
3.0 / 21 Nov 2018	To add a primary contact medical monitor	-Cover Page: [redacted] was added to the Medical Monitors' contact list of the protocol.
	To clarify Inclusion Criterion #7 with regard to the double barrier methods of contraception	-Criterion #7 was modified in synopsis and Section 5.1 to clarify that a double barrier method is comprise of a male condom used simultaneously with a female barrier method in conjunction with spermicide.
	To revise Criterion #8 with regards to the timeframe of the	-Criterion #8 was modified in synopsis and Section 5.1 to require the use of contraceptives by male subjects for 90

	contraception requirements for male subjects	days (not 4 weeks) after the last study product administration (i.e. full spermatogenesis cycle). The 4 weeks was also modified to 90 days for the female partners of male subjects using a hormonal contraceptive method.
	To add an inclusion criterion for sperm donation	-Synopsis and Section 5.1: inclusion criterion #9 was added to prevent male subjects to donate sperm throughout the study starting at Day 1 and up to 90 days after the last study product administration.
	To increase the frequency of pregnancy testing throughout study	-Section 1.3 (Table 1): Urine pregnancy tests were added at the following visits: W2, W12, W18, W20 and W28 following recommendation from the FDA and Health Canada.
	To add a visit at W18 for a total number of 13 visits	-Synopsis, Section 1.2 (Figure 1), Section 1.3 (Table 1), Section 4.1: A visit was added at Week 18 to assess vital signs and for AEs monitoring. -Section 1.3 (Table 1, footer q); Section 6.1: a mention was added to specify that dosing on Week 18 will occur at home.
	To harmonize clinical laboratory testing and ECG assessments between Part A and Part B	-Section 1.3 (Table 1): A 'X' was added to W20 for ECG assessment and to W20 and W28 for clinical laboratory tests. Footnote corresponding to ECG was updated accordingly.
	To add a footnote related to the emollient use	-Section 1.3 (Table 1): footer was added to clarify that emollient use must start at least 1 week prior to Day 1.
4.0 / 04 February 2019	To revise the wording for the PaGA secondary efficacy endpoint as no change from baseline can be evaluated for the PaGA measurement.	-Synopsis and Section 3: wording was changed to "Actual PaGA measurements at Weeks 4, 8, 12, 16, 32" instead of "Change and percent change from baseline in hand Patient Global Assessment (PaGA) measurements at Weeks 4, 8, 12, 16, and 32".

	To correct a discrepancy in the footnote of the Schedule of Events for collection of biopsy samples.	-Section 1.3, Table 1, Footnote l: Clarified that biopsies should be collected adjacent to the tape stripping site.
	To revise the inclusion criterion related to body mass index (BMI) in order to increase subject eligibility by allowing a higher BMI.	-Synopsis and Section 5.1, inclusion criterion #6, BMI was revised to ≤ 38 kg/m^2.
	To clarify that the number of tape strips required per sampling site is an approximate.	-Section 8.5.3 Tape stripping: It was clarified that "*approximately*" 20 tape strips are required per sampling site.
	To correct discrepancies in the statistical analyses section	-Synopsis and Section 9.3.2 Efficacy Analyses: clarified that the primary efficacy endpoint is "*percent*" change-from-baseline in hand mTLSS at Week 16.
5.0 / 12 April 2019	To allow inclusion of subjects with moderate CHE, as defined by a hand PGA 3 or 4.	-Added mention of moderate CHE throughout the protocol, where applicable.
	To specify that the randomization will be stratified for the PGA score and update the statistical analysis accordingly.	-Synopsis and Section 6.3: Added mention of stratification for the PGA score of '3' (moderate) or '4' (severe). -Synopsis and Section 9.3.2: Added mention of the PGA scores as a stratification factor.
	To specify that inclusion of moderate CHE will be limited to 30% of total enrollment.	-Synopsis, Section 4.1 and Section 8.1.2: Added mention that Subjects with moderate CHE will be limited to 30% of total enrollment.
	To add the moderate potency topical corticosteroids and systemic corticosteroids in the list of refractory treatment for CHE.	-Cover page and Synopsis: Study title updated to remove mention specific to topical corticosteroid therapy. -Synopsis and Section 5.1: Inclusion criterion #3, updated to include moderate potency topical corticosteroids and systemic corticosteroids.

		-Section 6.4 and 6.4.1: updated to include moderate potency topical corticosteroids and systemic corticosteroids.
	To remove the sensitivity analyses for the primary efficacy endpoint.	-Section 9.3.1: Removed the following sentence: *Moreover, the analyses performed on observed case (i.e. without imputation of missing observations) will be done as sensitivity analyses.*
	Minor discrepancy corrected.	- Synopsis and Section 5.1: Added the abbreviation 'e.g' to inclusion criterion #7.
6.0 / 01 October 2019	To update a sponsor contact.	- Tittle Page: Updated the name of sponsor's associate director – clinical operations, to reflect that Jaimini Shah occupies this position for now on.
	To remove the upper limit of age as requested by the FDA, as CHE occurs in patients >75 years of age.	- Synopsis, Section 4.1, and Section 5.1 (Inclusion Criterion #1): Updated to include subjects aged 18 years or older in the study.
	To allow recruitment of up to 30 additional subjects, because of the high dropout rate observed in the study. This will ensure the statistical power of the primary analysis is maintained by having at least 75 subjects completing the 16 weeks of treatment.	- Synopsis and Section 4.1: Updated to allow inclusion of approximately 105 subjects in the study. - Section 1.2 (study diagram): Updated the number of subjects to 35 for each group. - Synopsis and Section 9.1: Added the following sentence to the sample size considerations: *Assuming between 25-30% dropout rates, up to 35 patients per group will be included in this study.*
	To correct the number of study centers participating in this study.	- Synopsis and Section 4.1: Updated the number of study centers participating in this study from 15-20 to 20-25.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), 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), 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 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 before the changes are implemented to the study. All changes to the consent form will be IRB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Sponsor: PPD

01-OCT-2019
Date (DD-MMM-YYYY)

Scientific Affairs: PPD

01-OCT-2019
Date (DD-MMM-YYYY)

Study Statistician: PPD

02-OCT-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, and applicable 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
AUC	area under concentration-time curve
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CHE	chronic hand eczema
CK	creatine kinase
C_{max}	maximum observed concentration
CRO	contract research organization
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HECSI	hand eczema severity index
Hgb	hemoglobin
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IRB	institutional review board
LDH	lactate dehydrogenase
LMW	low molecular weight
Mapi	Mapi Life Sciences
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent-to-treat
mTLSS	modified Total Lesion Symptom Score
MPV	mean platelet volume
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter (medication)
PGA	Physician's Global Assessment
PaGA	Patient Global Assessment
PK	pharmacokinetic
PLT	platelets
PP	per-protocol
PPD	purified protein derivative
PUVA	psoralen-UV-A
RBC	red blood cell (count)
REB	research ethics board
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SD	standard deviation
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USA	United States of America
VAS	visual analog scale
vIGA	validated Investigator Global Assessment
VTE	venous thromboembolic event
WBC	white blood cell (count)
WOCBP	women of childbearing potential
WPAI-SHP	work productivity and activity impairment specific health problem

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 Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of ASN002 in Subjects with Moderate to Severe Chronic Hand Eczema Refractory to Corticosteroid Therapy.

Phase of Development:

Phase 2

Study Centers:

Approximately 20-25 study centers located in the United States and Canada will participate in this study.

Number of Subjects (planned):

Approximately 105 subjects will be included in this study.

Duration of Study:

The maximum study duration per subject is up to 40 weeks (including up to 30 days for the screening period, followed by a 32-week treatment period, and up to 4 weeks for the follow-up period).

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.

Investigational Product, Dosage, and Mode of Administration:

ASN002 40 mg, 80 mg or placebo will be orally administered once daily during the treatment period. ASN002 will be available in 20-mg strength tablets.

Subjects will be randomized in a 1:1:1 ratio to one of the following treatment regimens:

- Part A: ASN002 40 mg (16-week treatment); Part B: ASN002 40 mg (16-week treatment)
- Part A: ASN002 80 mg (16-week treatment); Part B: ASN002 80 mg (16-week treatment)
- Part A: Placebo (16-week treatment); Part B: ASN002 80 mg (16-week treatment)

Subjects who were assigned to regimen starting with a placebo in Part A (first 16 weeks) of the study will receive the highest dose of ASN002 (80 mg) for the rest of the treatment period (up to 32 weeks of treatment). Subjects who were assigned to ASN002 in the first part of the study will continue on the assigned treatment dose during the second part of the study up 32 weeks of treatment.

The blind will be maintained until the primary efficacy analyses are locked for Part A and all safety data for Part A has been cleaned and monitored. The CRO team and the sponsor will be unblinded after the database lock of Part A and safety data review, but the sites, investigators and subjects will remain blinded throughout the study. Randomization will be stratified for the biopsy collection and for the PGA score of '3' (moderate) or '4' (severe).

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Objectives:

Primary:

- To evaluate the efficacy of ASN002 in subjects with moderate to severe chronic hand eczema (CHE), based on hand modified Total Lesion Symptom Score (mTLSS)

Secondary:

- To evaluate the efficacy of ASN002 in subjects with moderate to severe CHE, based on hand Physician's Global Assessment (PGA)
- To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe CHE
- To quantify the plasma concentrations of ASN002 in subjects with moderate to severe CHE

Exploratory:

- To evaluate pharmacodynamic (PD), biomarkers and skin microbiome analysis for evidence of drug activity in subjects with moderate to severe CHE
- To assess population PK of ASN002 in subjects with moderate to severe CHE via a population PK analysis approach
- To explore the relationships between PK exposure and clinical measurement (e.g., biomarker, efficacy and safety) as appropriate in subjects with moderate to severe CHE
- To evaluate the effect of ASN002 on work productivity in subjects with moderate to severe CHE
- To evaluate the efficacy of ASN002 on foot eczema in subjects with moderate to severe CHE

Endpoints:

Primary Endpoint:

- Percent change from baseline in hand mTLSS at Week 16

Secondary Endpoints:

Secondary efficacy endpoints include:

- Change from baseline in hand mTLSS at Weeks 4, 8, 12, 16, and 32
- Percent change from baseline in hand mTLSS at Weeks 4, 8, 12, and 32
- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0), almost clear (1) or mild (2) in hand PGA at Weeks 4, 8, 12, 16, and 32
- Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16, and 32
- Change and percent change from baseline in hand PGA at Weeks 4, 8, 12, 16, and 32
- Change and percent change from baseline in Hand Eczema Severity Index (HECSI) at Weeks 4, 8, 12, 16, and 32
- Time to response relative to baseline (based on hand PGA)

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- Actual PaGA measurements at Weeks 4, 8, 12, 16, 32
- Change from baseline in hand Dermatology Life Quality Index (DLQI) at Weeks 2, 4, 8, 12, 16, and 32
- Change and percent change from baseline in pain visual analog scale (VAS) at Weeks 4, 8, 12, 16, and 32

Secondary safety endpoints include:

- Number of treatment-emergent adverse events (TEAEs)
- Number of drug-related TEAEs
- Proportion of subjects withdrawing for worsening of their CHE at Weeks 4, 8, 12, and 16
- Changes in vital signs, electrocardiogram (ECG), and safety laboratory tests

Secondary pharmacokinetic (PK) endpoint includes:

- Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment

Exploratory Endpoints:

Exploratory endpoints include:

- Change from baseline in PD, biomarkers and skin microbiome analysis at Weeks 4 and 16
- Characterization of population PK parameters via nonlinear mixed-effects modeling
- Evaluate clinical safety, efficacy and biomarker measurements in relationship to PK exposure
- Change and percent change from baseline in Extent of Disease affected with moderate to severe CHE at Weeks 4, 8, 12, 16, and 32
- Change from baseline Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire for hands at Weeks 4, 8, 12, 16, and 32
- Change and percent change from baseline in foot mTLSS at Weeks 4, 8, 12, 16, and 32
- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0), almost clear (1) or mild (2) in foot PGA at Weeks 4, 8, 12, 16, and 32
- Proportion of subjects achieving a foot PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16 and 32
- Change and percent change from baseline in foot PGA at Weeks 4, 8, 12, 16, and 32
- Change and percent change from baseline in Extent of Disease affected with foot eczema at Weeks 4, 8, 12, 16, and 32

Study Design:

This study will be performed at approximately 20-25 study centers located in the United States and Canada.

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Approximately 105 subjects with moderate to severe CHE (as defined by a hand PGA 3 or 4 at Day 1) will be included in this randomized, double-blind, placebo-controlled, multicenter, Phase 2 study. Subjects will be men or women, 18 years of age or older, at the time of consent. Subjects with moderate CHE will be limited to 30% of total enrollment.

Each subject should read and sign an informed consent form prior to any screening procedures being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1:1) on Day 1 to receive ASN002 at 40 mg or 80 mg, or placebo once daily for 16 weeks (Part A). Then, in Part B, subjects who were assigned to placebo in the first part of the study will receive the highest dose of ASN002 (i.e. 80 mg) for the rest of the treatment period (up to Week 32). The subjects who were assigned ASN002 in the first part of the study will continue on the same assigned treatment dose during the second part of the study (Week 16 to Week 32). The total treatment period of 32 weeks will be followed by a 4-week follow-up period. For scheduled study visits, subjects will come to the study centers on 13 occasions: screening; Day 1; Weeks 2, 4, 8, 12, 16, 18, 20, 24, 28 and 32 (end of treatment visit); and Week 36 (follow-up visit)/early termination (ET).

Efficacy will be assessed using mTLSS, PGA, HECSI, pain VAS and Extent of Disease. In addition, a 6-grade PaGA scale will be used. Quality of life will be evaluated using DLQI. Impact on work productivity and activity will be studied using the WPAI-SHP questionnaire.

Safety will be assessed by collecting AEs, recording vital signs, performing physical examination and 12-lead ECG, and evaluating clinical laboratory tests.

Pre- and post-dose PK blood samples will be collected from all subjects on a sparse sampling schedule on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, and 32 (or ET visit, if applicable).

At selected study centers, in a subset of approximately 36 subjects who consent, PD blood samples will be collected pre-dose on Day 1 and Week 16 (or ET visit, if applicable and if it occurs prior to Week 16). PD samples will be obtained from the same subjects who consent to biopsy collection. An additional PD blood sample will be collected at Week 4 in subjects who also consent to four skin biopsies.

At selected study centers, in a subset of approximately 36 subjects who consent, three or four skin biopsies will be collected during this study. Two 2.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected from the palmar aspect of the hand at Day 1, and one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 16 (or ET visit, if applicable and if it occurs prior to Week 16). In addition, one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

For all subjects, on Day 1, and Weeks 4 and 16 (or ET visit, if applicable and if it occurs prior to Week 16), skin samples from the hands and feet (if feet involvement on Day 1) will be collected using tape stripping technique. On those same visits, skin microbiome samples will be collected from the worst hand eczema lesion and worst foot eczema lesion (if applicable).

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Inclusion/Exclusion Criteria:

Inclusion criteria:

1. Male or female subject, 18 years of age or older, at the time of consent.
2. Subject has a history of moderate to severe CHE for at least 6 months prior to baseline. (information obtained from medical chart or subject's physician, or directly from the subject).
3. Subject has hand eczema refractory to moderate potency, high potency or ultra-high potency topical corticosteroids (defined in Table 3) or systemic corticosteroids (including oral or injectable corticosteroids) used in the past year (information obtained from medical chart or subject's physician, or directly from the subject). Refractory is defined by failure to achieve a status of clear, almost clear or mild CHE following at least a 2-week course of moderate potency, high potency or ultra-high potency topical corticosteroid or systemic corticosteroids (including oral or injectable corticosteroids).
4. Subject has moderate to severe CHE at Day 1, as defined by a hand PGA 3 or 4.
5. Subject has been using an emollient on their hands and feet (if foot eczema is present) (except those containing urea or salicylic acid) every day at the same frequency for at least 1 week prior to Day 1 and agrees to continue using that same emollient, daily and at the same frequency, throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time on their hands and feet.
6. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
7. For female subject 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 (e.g. 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 (e.g. male condom with cervical cap, male condom with diaphragm, or male condom with 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: A female subject of nonchildbearing potential is as follows:

   a. Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy);
   b. Female subject 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).
8. For male subject 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 #7, from Day 1

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until at least 90 days after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptive methods 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 by the male subject.

9. Male subjects must not donate sperm from Day 1 until at least 90 days after the last study product administration.
10. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test on 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:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has known allergic contact dermatitis of the hands or hands and feet and is unable to avoid exposure to the causative allergen.
3. Only for subjects with a history of atopic dermatitis (clinically confirmed diagnosis according to Hanifin and Rajka criteria (APPENDIX C)): the atopic dermatitis is covering > 15% of the BSA at baseline (Day 1) (excluding hands and feet).
4. Only for subjects with a history of atopic dermatitis (clinically confirmed diagnosis according to Hanifin and Rajka criteria (APPENDIX C)): subject had a flare in his atopic dermatitis in the last 4 weeks prior to the screening visit.
5. Subject has active skin infections of the hands and/or feet.
6. Subject has a history or has current active psoriasis.
7. 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
8. 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.
9. 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.
10. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Note: 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.
11. 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.

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12. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or a QTcF ≥ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeated assessment. For subjects with a QTcF ≥ 450 msec on initial ECG, the mean of the two QTcF values will determine eligibility.
13. Subject has a history of congestive heart failure of class III or IV as per the New York Heart Association (NYHA) classification.
14. Subject has a history of recurrent venous thromboembolic event (VTE) (≥ 2 episodes in the past).
15. 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.
16. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
17. Subject is known to have immune deficiency or is immunocompromised.
18. 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.
19. 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 < 0.9 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.
20. Subject has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure > 160 mmHg or diastolic BP > 95 mmHg, confirmed by one repeat assessment.
21. Subject has a known active tuberculosis (TB) or a positive 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 Bacillus 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).
22. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
23. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
24. Subject has a known history of diverticulitis.

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25. Subject has uncontrolled diabetes.
26. 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.
27. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
28. Subject has used dupilumab within 12 weeks prior to Day 1.
29. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
30. 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.
31. Subject has used alitretinoin, isotretinoin, acitretin or other systemic retinoids within 4 weeks before Day 1, or has not completely recovered from its side effects.
32. Subject has used systemic treatments (other than biologics) that could have an impact on CHE less than 4 weeks prior to Day 1 (e.g. methotrexate, cyclosporin), systemic steroids (including oral or injectable corticosteroids), or systemic immunosuppressants

    Note: Intranasal corticosteroids, eye or ear drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
33. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
34. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
35. Subject has had an excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
36. Subject has used any topical treatments that could have an impact on CHE within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, topical retinoids, crisaborole, calcineurin inhibitors, tars, bleach, bleach baths, antimicrobials, medical devices.
37. Subject has used systemic antibiotics within 2 weeks prior to Day 1.
38. Subject has used topical antibiotics within 2 weeks prior to Day 1.
39. Subject has used topical products containing urea or salicylic acid within 1 week prior to Day 1.
40. Subject has used ASN002 prior to Day 1.
41. Subject had prior treatment with a systemic SYK or JAK inhibitor 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.
42. Subject has a known hypersensitivity to ASN002 or its excipients.
43. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
44. 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.

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45. Subject is institutionalized because of legal or regulatory order.
46. Only for subjects consenting to biopsies:
    a. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics or their components;
    b. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites;
    c. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Note: Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

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.

Efficacy Analyses:

The primary efficacy endpoint will be analyzed using a repeated measures analysis of covariance on percent change-from-baseline variable to compare the time profile between treatments where the visit will be the time factor; and the stratification factor PGA score, treatment group, and interaction term for treatment-by-visit will be the fixed effects and the baseline value will be the covariate. An unstructured variance-covariance matrix will be used.

For categorical efficacy endpoints involving proportions of PGA (e.g. the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in PGA at Week 16), a Cochran Mantel Hansel test (CMH) controlling for PGA score at baseline will be performed.

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.

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. This analysis may be combined with PK concentrations from other clinical trials in healthy and AD subjects as appropriate.

PD Analyses:

Biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group and overall using descriptive statistics.

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PK/PD Analyses:

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

Primary statistical analysis:

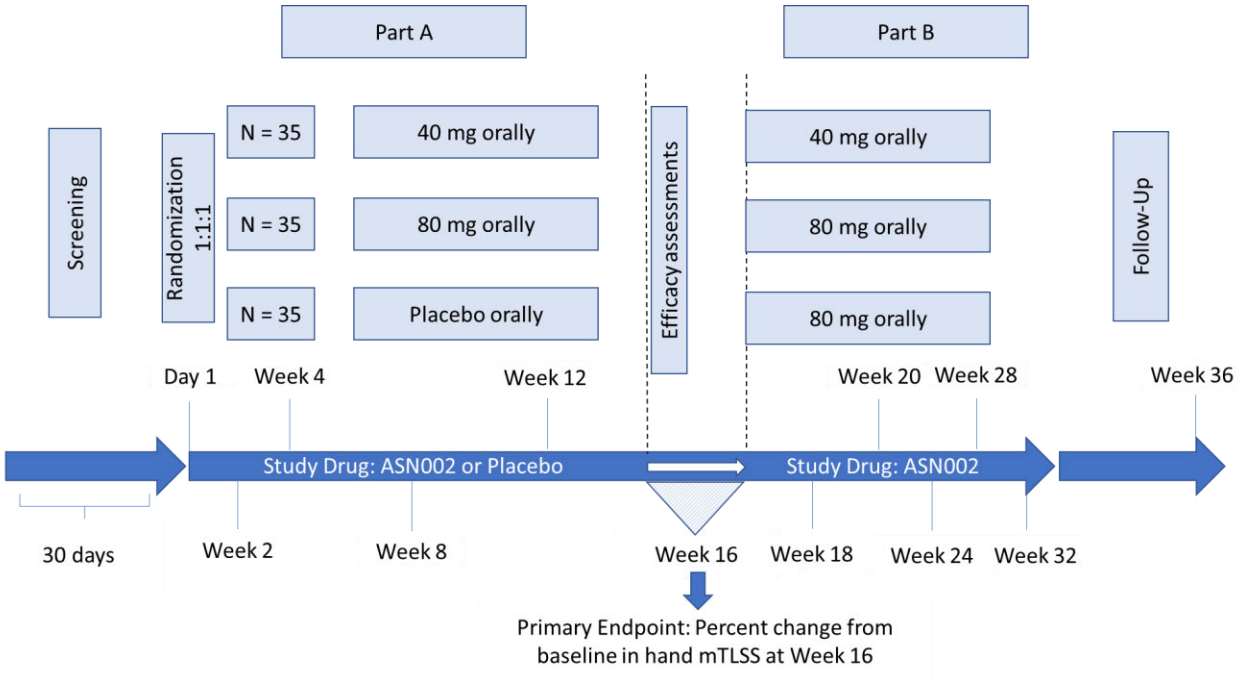
Unblinded primary efficacy analyses will be performed after Week 16 is completed for all subjects. The CRO team and the sponsor will be unblinded after the database lock of Part A for the efficacy assessments, and a cleaning and monitoring of all safety data collected in Part A. The sites, investigators and subjects will remain blinded throughout the study.

Sample Size Consideration:

Assuming a common standard deviation of 39% for the % change-from-baseline mTLSS, a difference of 25% and 35% between the 40 mg dose vs. placebo and the 80 mg dose vs. placebo, respectively, alpha of 5% (two-sided), 25 patients per group would insure an 80% power to obtain a statistically significant treatment effect (using the general F test in an analysis of variance). Assuming between 25-30% dropout rates, up to 35 patients per group will be included in this study.

1.2Study Diagram

Figure 1: Study Diagram



1.3Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit. The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

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 product administration. If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

- Patient reported outcomes and PaGA
- Vital signs
- 12-lead ECG
- Blood draw for PK evaluations (time window vs drug administration detailed in footer of Table 1) and/or safety blood draw

Note: The timing of the assessments should allow the blood draw to occur within the allowed window of the nominal time.

Table 1. Schedule of Events

Study Visits	Screening	Treatment Period											Follow-up / ET
		Part A						Part B					
Day (D); Week (W)		**D1**	**W2 (D15)**	**W4 (D29)**	**W8 (D57)**	**W12 (D85)**	**W16 (D113)**	**W18 (D127)**	**W20 (D141)**	**W24 (D169)**	**W28 (D197)**	**W32 (D225) EOT [a]**	**W36 (D253) EOS**
Window (days)	-30 to -1		±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2
Informed consent	X												
Demographics	X												
Medical and surgical history	X	X											
Patch testing history	X	X											
Inclusion-exclusion criteria	X	X											
Pregnancy test[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X[c]		X			X[c]		X	X[c]
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[e]	X	X		X	X		X		X	X		X	X[f]
Clinical laboratory tests (hematology, chemistry, and urinalysis)	X	X		X	X	X	X		X	X	X	X	X
Serology (HIV, HBV, HCV)	X												
Tuberculosis evaluation[g]	X												
BSA (excluding hands and feet) (subjects with AD only)	X	X											
vIGA (excluding hands and feet) (subjects with AD only)		X		X			X						
Diagnostic Criteria for Atopic Dermatitis (subjects with AD only)	X												
Presence or absence of foot eczema	X	X											
Extent of Disease[h]		X	X	X	X	X	X		X	X	X	X	X
HECSI		X	X	X	X	X	X		X	X	X	X	X
mTLSS[h]		X	X	X	X	X	X		X	X	X	X	X
PGA[h]	X	X	X	X	X	X	X		X	X	X	X	X
PaGA		X	X	X	X	X	X		X	X	X	X	X
DLQI		X	X	X	X	X	X		X	X	X	X	X

Study Visits	**Screening**	**Treatment Period**											**Follow-up / ET**
		Part A						**Part B**					
Day (D); Week (W)		**D1**	**W2 (D15)**	**W4 (D29)**	**W8 (D57)**	**W12 (D85)**	**W16 (D113)**	**W18 (D127)**	**W20 (D141)**	**W24 (D169)**	**W28 (D197)**	**W32 (D225) EOT [a]**	**W36 (D253) EOS**
Window (days)	-30 to -1		±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2
WPAI-SHP		X	X	X	X	X	X		X	X	X	X	X
Pain Visual Analog Scale		X	X	X	X	X	X		X	X	X	X	X
Skin microbiome analysis [worst hand (palmar aspect, when possible) involved with eczema (and plantar aspect (when possible) of foot, if foot involvement)][i]		X		X			X						X[j]
Tape strips collection [from hand (and foot if applicable][k]		X		X			X						X[j]
Skin biopsies collection[l]		X		X[m]			X						X[j]
Blood sampling for PD analyses[n]		X		X[m]			X						X[j]
Blood sampling for PK evaluation		X[o]	X[p]	X[o]	X[p]	X[p]	X[p]		X[p]	X[p]	X[p]	X[p]	X[f,p]
Randomization		X											
Study product administration at study center		X	X	X	X	X	X		X	X	X	X	
Study product administration daily[q]		X----------X											
Emollient use on hands and feet (if foot eczema)[r]		X----------X											
Dispensing of study product		X		X	X	X	X[s]		X	X	X		
Study product collection/accountability/ compliance[t]			X[u]	X	X	X	X		X	X	X	X	X[f]
Photograph of both aspects (palmar and dorsal) of both hands[v]		X			X		X			X		X	X
Concomitant medication	X	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	X

BSA=Body Surface Area; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ET=early termination; HBV=hepatitis B virus; HCV=hepatitis C virus; HECSI=hand eczema severity index; HIV=human immunodeficiency virus; mTLSS=modified Total Lesion

Study Visits	Screening	Treatment Period											Follow-up / ET
		Part A						Part B					
Day (D); Week (W)		D1	W2 (D15)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113)	W18 (D127)	W20 (D141)	W24 (D169)	W28 (D197)	W32 (D225) EOT [a]	W36 (D253) EOS
Window (days)	-30 to -1		±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2

Symptom Score; PaGA=Patient Global Assessment; PD=pharmacodynamic; PGA=Physician's Global Assessment; PK=pharmacokinetics; VAS=visual analog scale; WPAI-SHP=Work Productivity and Activity Impairment – Specific Health Problem.

[a] The end of treatment (EOT) visit will occur on the first day of Week 32 (D 225) (+/- 2 days)).

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

[c] Brief physical examinations.

[d] Including height, weight and BMI. Height will be measured only at screening and the same value will be used for BMI calculation at other visits.

[e] ECG will be recorded at 0 (pre-dose, within 1 hour prior to dosing), 1 (± 30 min), and 3 (± 1 hour) hours post-dose on Day 1, Week 4, Week 16 and Week 20. ECG will be recorded only once at screening, Weeks 8, 24 and 32 and ET visit (if applicable).

[f] Only at ET

[g] If PPD is used, a second screening visit will be necessary.

[h] mTLSS, Extent of Disease and PGA to be assessed only for hands and feet, but evaluated separately.

[i] Microbiome samples will be collected for all subjects prior to tape stripping collection and skin biopsy (if applicable). Microbiome samples will be collected on Day 1, Week 4 and Week 16 (or ET visit, if applicable) (one from lesional skin (palmar aspect (when possible) of the worst hand) and one from adjacent nonlesional skin). At each visits samples should be collected from the same areas selected on Day 1. Microbiome samples should be collected prior to study product administration and after photographs, if applicable. If the subject has presence of foot eczema on Day 1, microbiome samples (lesional and non lesional) will be collected from the plantar aspect (when possible) of the worst foot.

[j] Only at ET, if ET visit is performed prior to Week 16.

[k] Skin tape stripping samples will be collected for all subjects as close as possible to the site of microbiome collection (preferably the same palmar lesion when possible) and of the skin biopsy (if applicable). Skin tape stripping samples will be collected on Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one at Week 4 and Week 16 (or ET visit, if applicable) (from same lesional area as Day 1). Tape stripping should be collected prior to study product administration and after photographs, if applicable. If the subject has presence of foot eczema on Day 1, skin tape stripping samples will also be collected from the foot (one from lesional skin and one from adjacent nonlesional skin) at Day 1 and one at Week 4 and Week 16 (or ET visit, if applicable) from same lesional skin as Day 1.

[l] Optional, only for a subset of approximately 36 subjects who consent: two 2.5-mm skin biopsies at Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one at Week 16 (or ET visit, if applicable) (from the same lesional skin as Day 1) and preferably from the same lesion as the one selected for the microbiome and tape stripping sampling. Biopsies are collected from the palmar aspect of the hand and should be collected adjacent to the tape stripping site. Subjects consenting to biopsies collection must also consent to PD samples. Biopsies should be collected prior to study product administration and after photographs, if applicable.

[m] An additional skin biopsy from same lesional skin as Day 1 (and adjacent from the tape stripping site) and PD sample will be collected at Week 4 for subjects who consent to four biopsies.

[n] Optional, only for a subset of approximately 36 subjects who consent: PD samples to be drawn as trough samples prior to study product administration. Subjects consenting to PD samples must also consent to biopsies. PD samples should be collected prior to study product administration.

Study Visits	Screening	Treatment Period											Follow-up / ET
		Part A						Part B					
Day (D); Week (W)		D1	W2 (D15)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113)	W18 (D127)	W20 (D141)	W24 (D169)	W28 (D197)	W32 (D225) EOT [a]	W36 (D253) EOS
Window (days)	-30 to -1		±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2

[o] PK samples will be collected at 0 (pre-dose), 2 (± 30 min)) hours post-dose and 6 hours post-dose (between 5 to 12 hours post-dose). The dosing time for the previous day should be recorded accurately.

[p] PK samples will be collected at 0 (pre-dose) and 2 (± 30 min) hours post-dose. The dosing time for the previous day should be recorded accurately. At ET visit (if applicable), only one PK sample will be collected.

[q] Study products will be taken at home daily for 32 weeks, except on study visit days when the study products will be administered on site. For visit Week 18, subjects will dose at home.

[r] Emollient use must be initiated at least 1 week prior to Day 1.

[s] On this visit, subject who were receiving placebo since Day 1, will start receive ASN002 80 mg until EOT visit.

[t] Subject should be instructed to always bring their medication to the site when there is a scheduled visit.

[u] On Week 2 visit, there will be no collection/dispensing, but subject will dose on site with the medication kit dispensed on Day 1.

[v] Optional, only for a subset of approximately 36 subjects who consent. Photographs should be performed prior to drug administration, biopsy (if applicable) and tape stripping and microbiome sample collection.

2 INTRODUCTION

2.1 Background

2.1.1 Chronic Hand Eczema

Chronic hand eczema (CHE) causes itching, pain, discomfort as well as embarrassment caused by the inconvenient location of the disease.[1] Severe CHE leads to disfiguring changes in hand appearance caused by the classic features of eczema, such as erythema, oedema, vesiculation/blistering, hyperkeratosis, fissures, pruritus and pain leading to considerable occupational, functional, social and psychological disabilities.[2] Yearly hand eczema (HE) is thought to present itself in 7%~12% in the general population in Northern Europe and could possibly be higher in the USA.[2] Among the sufferers of HE, 5-7 % are thought to develop severe CHE.[3] This condition is known to interfere greatly with daily activities and work assiduity of over 81% of the affected population. Severe CHE can seriously disturb a patient's daily life, leading to prolongated sick leave or even forcing a change in their career choice.[4] The most common type of HE comprise of irritant contact dermatitis, atopic hand eczema and allergic contact dermatitis.[4] Exposure to irritants or allergens such as nickel, cobalt, fragrance-mix, colophony and unspecified chemicals, water and detergents or dust and dry dirt could trigger the disease. Endogenous factors such as atopic dermatitis (AD) could also be a risk factor.[2,4,5]

Mild cases of CHE can be controlled with diligent use of emollients and topical corticosteroids combined with the avoidance of potential irritants, but severe CHE is debilitating as this prescribed regimen is usually inefficient.[2] A Swedish study disclosed that treatment for HE with topical steroids was reported by 51% of patients while emollients were used by 85%. Of the 1385 patients who answered the questionnaire, 81% experienced some kind of disturbance of their daily life considered to be caused by the HE. 69% of the patients had consulted a doctor and 21% had been on sick-leave at least once because of their HE.[4]

Severe CHE is characterized as hand eczema that shows a prolonged and relapsing course or is unresponsive to standard treatment using emollients and topical corticosteroids.[6] Among the sufferers of severe CHE, 2%~4% are unresponsive to standard treatment.[5] There are no approved systemic treatments for CHE in the US. Alitretinoin, a systemic retinoid, is approved in Canada and several countries for CHE but only half of treated patients will achieve a clear or almost clear status after 16 weeks of therapy.[2] Other systemic therapies such as cyclosporine are sometimes used off-label in severe, chronic, and refractory cases.[2,6]

There is a definite need for randomized controlled clinical trials of existing and new treatment options based on clearly diagnosed subtypes of hand eczema and their various severities.[7]

2.1.2 ASN002

ASN002 is an orally bioavailable, potent dual inhibitor of JAK and SYK kinases with 50% inhibitory concentrations (IC50 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 (IC50 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 the treatment of inflammatory disorders, such as CHE. In a Phase 1b study (ASN002AD-101), plasma concentrations of ASN002 were measured in subjects with AD following single and repeated once daily oral administration at 20, 40 and 80 mg. At steady state, Cmax and AUC were dose dependent with approximately 1.5-fold or less accumulation compared to those on Day 1, and the mean elimination t1/2 were 7.3-13.7 hours. At 80 mg, the mean Cmax and AUCtau 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 in that Phase 1b study. 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 clinical trial (ASN002AD-101), ASN002 has showed significant benefit for the treatment of AD, especially at 40 and 80 mg once-daily dosing regimens. It is hypothesized that the efficacy of ASN002 in AD will also be observed in CHE. This trial is therefore to investigate the benefit and risk of ASN002 in subjects with moderate to severe CHE for a 16-week treatment duration, followed by a 16-week treatment extension.

Current therapies for moderate to severe chronic hand eczema provide relief of symptoms for some but not all patients. There is definitely a need for new treatments in moderate to severe CHE in order to increase the existing options available to clinicians.

The primary objective of this study is to assess the efficacy of ASN002 in subjects with moderate to severe CHE. Safety and tolerability of ASN002 will also be evaluated as secondary endpoint as well as its PK profile. The doses to be administered in this study are 40 and 80 mg, which were found to be well tolerated and safe in a previous Phase 1b study. AEs observed in the Phase 1b study were of mild or moderate intensity following 80 mg dose. Once daily administration was chosen based on the data from the clinical studies in oncology subjects and healthy volunteers. PK analysis indicate sufficient systemic exposure for ASN002 efficacy and a half-life ($t_{1/2}$) 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 safe and well-tolerated at the doses to be administered in the present study.

In cancer subjects, ASN002 has been well tolerated. 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 have also been studied in a safety, tolerability, PK and food effect study in healthy subjects at doses up to 100 mg following a single oral administration. The most common AE in this study was headache. One serious adverse event (SAE), premature ventricular contractions, which were asymptomatic and mild, was experienced by one subject dosed with 50 mg ASN002 once. These 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 (AEs) observed in the Phase I study were mild or moderate at doses up to 80 mg. 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

It is anticipated that subjects will see an improvement in their moderate to severe CHE condition as a result of participating in this study, if they are randomized to active investigational product. Participation in this study may help generate future benefit for larger groups of patients with CHE.

2.2.3 Assessment of Risks and Benefits

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of CHE 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 efficacy of ASN002 in subjects with moderate to severe chronic hand eczema (CHE), based on hand modified Total Lesion Symptom Score (mTLSS)	Primary efficacy endpoint includes: • Percent change from baseline in hand mTLSS at Week 16
Secondary	
To evaluate the efficacy of ASN002 in subjects with moderate to severe CHE, based on hand Physician's Global Assessment (PGA)	Secondary efficacy endpoints include: • Change from baseline in hand mTLSS at Weeks 4, 8, 12, 16 and 32 • Percent change from baseline in hand mTLSS at Weeks 4, 8, 12, and 32 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0), almost clear (1) or mild (2) in hand PGA at Weeks 4, 8, 12, 16, and 32 • Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16, and 32 • Change and percent change from baseline in hand PGA at Weeks 4, 8, 12, 16, and 32 • Change and percent change from baseline in Hand Eczema Severity Index (HECSI) at Weeks 4, 8, 12, and 32 • Time to response relative to baseline (based on hand PGA) • Actual PaGA measurements at Weeks 4, 8, 12, 16, 32Change from baseline in hand DLQI at Weeks 2, 4, 8, 12, 16, and 32 • Change and percent change from baseline in pain visual analog scale (VAS) at Weeks 4, 8, 12, 16, and 32
To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe CHE	Secondary safety endpoints include: • Number of treatment-emergent adverse events (TEAEs) • Number of drug-related TEAEs • Proportion of subjects withdrawing for worsening of their CHE at Weeks 4, 8, 12, and 16 • Changes in vital signs, electrocardiogram (ECG), and safety laboratory tests

OBJECTIVES	ENDPOINTS
To quantify the plasma concentrations of ASN002 in subjects with moderate to severe CHE	Secondary PK endpoint includes: • Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment
Exploratory	
To evaluate pharmacodynamic (PD), biomarkers and microbiome for evidence of drug activity in subjects with moderate to severe CHE	Exploratory endpoints include: • Change from baseline in PD, biomarkers and skin microbiome analysis at Weeks 4 and 16
To assess population PK of ASN002 in subjects with moderate to severe CHE via a population PK analysis approach	• Characterization of population PK parameters via nonlinear mixed-effects modeling
To explore the relationships between PK exposure and clinical measurement (e.g., biomarker, efficacy and safety) as appropriate in subjects with moderate to severe CHE	• Evaluate clinical safety, efficacy and biomarker measurements in relationship to PK exposure
To evaluate the effect of ASN002 on work productivity in subjects with moderate to severe CHE	• Change from baseline in Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire at Weeks 4, 8, 12, 16, and 32
To evaluate the efficacy of ASN002 in subjects with moderate to severe CHE based on hand Extent of Disease	• Change and percent change from baseline in Extent of Disease affected with moderate to severe CHE at Weeks 4, 8, 12, 16, and 32
To evaluate the efficacy of ASN002 on foot eczema in subjects with moderate to severe CHE	• Change and percent change from baseline in foot mTLSS at Weeks 4, 8, 12, 16, and 32 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0), almost clear (1) or mild (2) in foot PGA at Weeks 4, 8, 12, 16, and 32 • Proportion of subjects achieving a foot PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12, 16 and 32 • Change and percent change from baseline in foot PGA at Weeks 4, 8, 12, 16, and 32 • Change and percent change from baseline in Extent of Disease affected with foot eczema at Weeks 4, 8, 12, 16, and 32

4 STUDY DESIGN

4.1 Overall Design

This study will be performed at approximately 20-25 study centers located in the United States and Canada.

Approximately 105 subjects with moderate to severe CHE (as defined by a hand PGA 3 or 4 at Day 1) will be included in this randomized, double-blind, placebo-controlled, multicenter, Phase 2 study. Subjects will be men or women, 18 years of age or older, at the time of consent. Subjects with moderate CHE will be limited to 30% of total enrollment.

Each subject should read and sign an informed consent form prior to any screening procedures being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1:1) on Day 1 to receive ASN002 at 40 mg or 80 mg, or placebo once daily for 16 weeks (Part A). Then, in Part B, subjects who were assigned to placebo in the first part of the study will receive the highest dose of ASN002 (i.e. 80 mg) for the rest of the treatment period (up to Week 32). The subjects who were assigned ASN002 in the first part of the study will continue on the same assigned treatment dose during the second part of the study (Week 16 to Week 32). The total treatment period of 32 weeks will be followed by a 4-week follow-up period. For scheduled study visits, subjects will come to the study centers on 13 occasions: screening; Day 1; Weeks 2, 4, 8, 12, 16, 18, 20, 24, 28 and 32; and Week 36 (follow-up visit)/early termination (ET).

Efficacy will be assessed using mTLSS, PGA, HECSI, pain VAS and Extent of Disease. In addition, a 6-grade PaGA scale will be used. Quality of life will be evaluated using DLQI. Impact on work productivity and activity will be studied using the WPAI-SHP questionnaire.

Safety will be assessed by collecting AEs, recording vital signs, performing physical examination and 12-lead ECG, and evaluating clinical laboratory tests.

Pre- and post-dose PK blood samples will be collected from all subjects on a sparse sampling schedule on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, and 32 (or ET visit, if applicable).

At selected study centers, in a subset of approximately 36 subjects who consent, PD blood samples will be collected pre-dose on Day 1 and Week 16 (or ET visit, if applicable and if it occurs prior to Week 16). PD samples will be obtained from the same subjects who consent to biopsy collection. An additional PD blood samples will be collected at Week 4 in subjects who also consent to four skin biopsies.

At selected study centers, in a subset of approximately 36 subjects who consent, three or four skin biopsies will be collected during this study. Two 2.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected from the palmar aspect of the hand at Day 1, and one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 16 (or ET visit, if

applicable and if it occurs prior to Week 16). In addition, one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

For all subjects, on Day 1, and Weeks 4 and 16 (or ET visit, if applicable and if it occurs prior to Week 16), skin samples from of the hand and foot (if subject has presence of foot eczema on Day 1) will be collected using tape stripping technique. During the same visits, skin microbiome samples will be collected from the worst eczema lesion of the hand (palmar aspect, when possible) and worst eczema lesion of the foot (plantar aspect, when possible) (if subject has presence of foot eczema on Day 1). The microbiome sampling must be collected prior to tape stripping and biopsies.

Preferably, all skin sampling (microbiome samples, tape strips and biopsies) should be collected from the same lesion.

At selected study centers, in a subset of approximately 36 subjects who consent, medical photographs of both aspects (palmar and dorsal) of both hands will be taken.

4.2Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy of ASN002 study products compared to a placebo in subjects with moderate to severe chronic hand eczema, and to evaluate the safety and tolerability of ASN002 study product in subjects with moderate to severe chronic hand eczema.

The study will be randomized to ensure random allocation of subjects to treatment arms to reduce bias. Because efficacy assessments of moderate to severe chronic hand eczema have a high degree of subjectivity, the study will be double-blinded. The highest degree of subjects and assessor blinding should be sought to achieve credible inference. It is also important to have a placebo control in a Phase 2 study to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied.

4.3End 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 temporarily or permanently discontinued based on the investigator's judgment and preferably

following a discussion with the medical monitor 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 subject'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 interruption or discontinuation of study medication and the reasons for it must be recorded in the case report form.

No dose reductions or modifications are permitted.

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 > 0.2 x 10^3 /μL but < 0.5 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 who 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.

5 STUDY POPULATION

5.1 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. Male or female subject, 18 years of age or older, at the time of consent.
2. Subject has a history of moderate to severe CHE for at least 6 months prior to baseline. (information obtained from medical chart or subject's physician, or directly from the subject).
3. Subject has hand eczema refractory to moderate potency, high potency or ultra-high potency topical corticosteroids (defined in Table 3) or systemic corticosteroids (including oral or injectable corticosteroids) used in the past year (information obtained from medical chart or subject's physician, or directly from the subject). Refractory is defined by failure to achieve a status of clear, almost clear or mild CHE following at least a 2-week course of moderate potency, high potency or ultra-high potency topical corticosteroid or systemic corticosteroids (including oral or injectable corticosteroids).
4. Subject has moderate to severe CHE at Day 1, as defined by a hand PGA 3 or 4.
5. Subject has been using an emollient on their hands and feet (if foot eczema is present) (except those containing urea or salicylic acid) every day at the same frequency for at least 1 week prior to Day 1 and agrees to continue using that same emollient, daily and at the same frequency, throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time on their hands and feet.
6. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
7. For female subject 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 (e.g. 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 (e.g. male condom with cervical cap, male condom with diaphragm, or male condom with 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: A female subject of nonchildbearing potential is as follows:

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

b. Female subject 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).

8. For male subject 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 #7, 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 contraceptive methods 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 by the male subject.
9. Male subjects must not donate sperm from Day 1 until at least 90 days after the last study product administration.
10. Female subject of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test on 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

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 known allergic contact dermatitis of the hands or hands and feet and is unable to avoid exposure to the causative allergen.
3. Only for subjects with a history of atopic dermatitis (clinically confirmed diagnosis according to Hanifin and Rajka criteria (APPENDIX C)): the atopic dermatitis is covering > 15% of the BSA at baseline (Day 1) (excluding hands and feet)
4. Only for subjects with a history of atopic dermatitis (clinically confirmed diagnosis according to Hanifin and Rajka criteria (APPENDIX C)): subject had a flare in his atopic dermatitis in the last 4 weeks prior to the screening visit.
5. Subject has active skin infections of the hands and/or feet.

6. Subject has a history or has current active psoriasis.
7. 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
8. 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.
9. 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.
10. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Note: 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.
11. 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.
12. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or a QTcF ≥ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeated assessment. For subjects with a QTcF ≥ 450 msec on initial ECG, the mean of the two QTcF values will determine eligibility.
13. Subject has a history of congestive heart failure of class III or IV as per the New York Heart Association (NYHA) classification.
14. Subject has a history of recurrent venous thromboembolic event (VTE) (≥ 2 episodes in the past).
15. 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.
16. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
17. Subject is known to have immune deficiency or is immunocompromised.
18. 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.
19. 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 < 0.9 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.

20. Subject has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure > 160 mmHg or diastolic BP > 95 mmHg, confirmed by one repeat assessment.

21. Subject has a known active tuberculosis (TB) or a positive 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 Bacillus 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).

22. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.

23. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.

24. Subject has a known history of diverticulitis.

25. Subject has uncontrolled diabetes.

26. 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.

27. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.

28. Subject has used dupilumab within 12 weeks prior to Day 1.

29. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.

30. 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.

31. Subject has used alitretinoin, isotretinoin, acitretin or other systemic retinoids within 4 weeks before Day 1, or has not completely recovered from its side effects.

32. Subject has used systemic treatments (other than biologics) that could have an impact on CHE less than 4 weeks prior to Day 1 (e.g. methotrexate, cyclosporin), systemic steroids (including oral or injectable corticosteroids), or systemic immunosuppressants

    Note: Intranasal corticosteroids, eye or ear drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.

33. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.

34. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
35. Subject has had an excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
36. Subject has used any topical treatments that could have an impact on CHE within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, topical retinoids, crisaborole, calcineurin inhibitors, tars, bleach, bleach baths, antimicrobials, medical devices.
37. Subject has used systemic antibiotics within 2 weeks prior to Day 1.
38. Subject has used topical antibiotics within 2 weeks prior to Day 1.
39. Subject has used topical products containing urea or salicylic acid within 1 week prior to Day 1.
40. Subject has used ASN002 prior to Day 1.
41. Subject had prior treatment with a systemic SYK or JAK inhibitor 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.
42. Subject has a known hypersensitivity to ASN002 or its excipients.
43. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
44. 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.
45. Subject is institutionalized because of legal or regulatory order.
46. Only for subjects consenting to biopsies:
    a. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics or their components;
    b. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites;
    c. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Note: Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

5.3 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 treatment. 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.

Subjects who do not qualify to participate in the study due to a vital sign or screening laboratory value abnormality can repeat the test once within the original screening time window without resulting in screen failure, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

6 TREATMENT

6.1 Study Treatment Administered

This study involves two different doses of ASN002 (40 mg and 80 mg) both orally administered once daily compared to a placebo in Part A (first 16 weeks of treatment). Then, only active products (ASN002 40 mg and 80 mg) will be administered in Part B. ASN002 will be available in 20-mg strength tablets. All study products will be provided by the sponsor. All study products will be self-administered orally, at home or at the clinic on clinic visit days.

Study products administration will occur daily for 32 weeks at approximately every 24 hours, 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 center, except at Week 18. The date and time of the drug administration and fasting conditions will be collected by the study site on the visit days. When dosing at home, the subject will be instructed to take the study product at approximately the same time of the day and compliance will be self-reported during each study visits.

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

Table 2. Study Products

	Study Products		
Product name	**ASN002**	**ASN002**	**Placebo (Part A only)**
Dosage form	Tablet	Tablet	Tablet
Dosage level(s)	40 mg	80 mg	N/A
Unit dose strength(s)	20 mg	20 mg	N/A
Number of tablets per dose level	2 active and 2 placebo	4 active	4 placebo
Route of administration	Oral	Oral	Oral
Dosing instructions	Once a day with approximately 240 mL of water	Once a day with approximately 240 mL of water	Once a day with approximately 240 mL of water
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 32 weeks.

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(s) may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

Study product(s) 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. At the conclusion of the study, all used and unused investigational products and all medication containers will be returned to the sponsor unless the sponsor has approved other arrangements. 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 investigational site, each screened subject will be assigned a subject identifier number during screening 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 at the screening visit based on chronological order of screening dates (e.g., 02-010 for the 10^{th} subject screened at the Site #02).

Subjects will be randomized in a 1:1:1 ratio to one of the following treatment regimens:

- Part A: ASN002 40 mg (16-week treatment); Part B: ASN002 40 mg (16-week treatment)
- Part A: ASN002 80 mg (16-week treatment); Part B: ASN002 80 mg (16-week treatment)
- Part A: Placebo (16-week treatment); Part B: ASN002 80 mg (16-week treatment)

Subjects assigned to regimen starting with a placebo in Part A (first 16 weeks) of the study will receive the highest dose of ASN002 (i.e. 80 mg) for the rest of the treatment period (up to Week 32). Subjects who were assigned to ASN002 in the first part of the study will continue on the assigned treatment dose during the second part of the study up 32 weeks of treatment.

Randomization will occur prior to first dosing, at Day 1 visit. The randomization list will be generated using a validated software. Randomization will be stratified for the biopsy collection and for the PGA score of '3' (moderate) or '4' (severe) per treatment group. The master randomization list will be kept secured until the study blind is broken. 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.

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

6.3.1 Blinding

This study will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to, the contract research organization (CRO), or the sponsor's study team until database lock of Part A is completed and all safety data has been cleaned and monitored. Investigators, subjects and clinical staff will remain blinded throughout the study.

After Part A, the database will be locked for efficacy assessments in order to evaluate the primary efficacy endpoint of the study (percent change from baseline in hand mTLSS at Week 16). After the first lock, the sponsor and CRO will be unblinded, but the sites, investigators and subjects, will remain blinded to the dose administered. During Part B, the blind (i.e. 40 mg or 80 mg dose) will be maintained until the database lock of Part A, however, since the placebo-controlled part of the study will have been finalized, with assessment of the primary endpoint and safety done after Part A, Part B will be considered as supportive only. A second lock will be done after Part B in order to produce the supportive secondary endpoint results for safety and efficacy.

The safety data from Part A will be cleaned and monitored prior to the unblinding of the sponsor and CRO personnel. This process will not involve EDC database lock and interim statistics but rather unblinded look of the available data. The sponsor and CRO personnel will remain blinded until the last patients of the study complete Week 16 assessments, and data is cleaned and monitored.

Blinding codes should only be broken in emergency situations for reasons of subject safety. If unblinding the treatment assignment for a subject is necessary due to a medical emergency (an unexpected SAE per product's safety profile) and other significant medical situations such as pregnancy, the investigator can make the decision to unblind the treatment assignment if knowing the treatment assignment will help treatment decision of the particular AE. When the blind for a subject has been broken, the reason must be fully documented in the source document and electronic case report form (eCRF). Whenever possible, the investigator should contact the sponsor or its designee before breaking the blind. If the blind is broken, the investigator should promptly inform the medical monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

Emergency unblinding details are provided in the study manual.

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

6.3.2 Study Treatment 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.

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.

6.4Concomitant Therapy

All medications (including over-the-counter (OTC) drugs, vitamins, herbal/natural products and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded.

All past and current medication taken by subject to treat CHE (all medication used) and refractory moderate potency, high potency and ultra-high potency topical corticosteroids as well as refractory systemic corticosteroids (including oral or injectable corticosteroids) will be documented as medication history for CHE. The duration of the treatment and the reason for discontinuation will be documented.

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 Comparative Potencies of Topical Corticosteroids

Ultra-high potency, high potency and moderate potency topical corticosteroids as well as systemic corticosteroids (including oral or injectable corticosteroids) used for CHE must be documented as per section 6.4. A list of moderate potency, high potency and ultra-high potency topical corticosteroids is described in Table 3.

Table 3 is also intended to be used as a guide for documenting past medication history of the subjects on study.

Table 3. Comparative Potencies[a] of Topical Corticosteroids[8]

Potency	Class	Topical Corticosteroid	Formulation
Ultra-High	I	Betamethasone dipropionate glycol	0.05% Cream, Ointment, Lotion
		Clobetasol 17-propionate	0.05% Cream, Foam, Ointment, Lotion, Shampoo, Solution
		Halobetasol propionate	0.05% Ointment
High	II	Amcinonide	0.1% Ointment
		Betamethasone dipropionate	0.05% Ointment
		Desoximetasone	0.25% Cream, Ointment, 0.05% Gel
		Fluocinonide	0.05% Cream, Ointment, gel
		Halobetasol propionate	0.05% Cream
	III	Amcinonide	0.1% Cream, Lotion
		Betamethasone dipropionate	0.025% Cream, 0.05% Cream, Lotion
		Betamethasone valerate	0.1% Ointment, 0.1% Transdermal Patch
		Mometasone furoate	0.1% Ointment
Moderate	IV	Beclomethasone dipropionate	0.025% Cream
		Clobetasone 17-butyrate	0.05% Cream
		Desoximetasone	0.05% Cream
		Diflucortolone valerate	0.1% Cream, Ointment
		Fluocinolone acetonide	0.025% Ointment
		Hydrocortisone 17-valerate	0.2% Ointment
		Mometasone furoate	0.1% Cream, Lotion
		Triamcinolone acetonide	0.1% Cream, Ointment
	V	Betamethasone valerate	0.05%, 0.1% Cream, Lotion
		Fluocinolone acetonide	0.01% Shampoo, Solution

		Hydrocortisone 17-valerate	0.2% Cream
		Prednicarbate	0.1% Cream, Ointment
Low	VI	Desonide	0.05% Cream, Ointment, Lotion
	VII	Hydrocortisone	0.5%, 1%, 2.5% Cream, Ointment, Lotion, Solution
		Hydrocortisone acetate	0.5%, 1% Cream
[a]Potency categories are intended to be used as guidelines only. Clinical effectiveness is dependent on many factors other than relative potency of the chemical entity. Potency rankings and terminology may differ from one publication to another. This table is adapted from the system generally used in the United States and from the World Health Organization (WHO) Anatomical Therapeutic Classification system. Assignment of each steroid to a particular potency category is based on literature review and is not necessarily the same potency category chosen for that topical corticosteroid in other publications using these systems.			

6.4.2 Permitted Therapies

6.4.2.1 Emollients

Subjects must apply an emollient of their choice (except those containing urea or salicylic acid) on their hands and feet (if foot eczema is present at screening). The emollient use must be initiated at least 1 week prior to Day 1 and subjects must continue using it at the same frequency throughout the study until the follow-up visit at Week 36. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

Every effort should be made to keep the same emollient throughout the study. The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study. Emollient use will be followed at each visit.

6.4.2.2 Other Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed. Eye drops containing corticosteroids are allowed.
- Low-dose aspirin
- Use of sunscreen products are permitted when sun exposure cannot be avoided, but sunscreen products are prohibited on hands and feet on the day of a scheduled visit prior to the scheduled visit time (protective apparel is strongly suggested).

6.4.3 Prohibited Therapies or Procedures

Table 4 lists prohibited medications are not to be used from the defined washout periods before the first administration of study treatment at the Day 1 visit through the last study visit.

The discretionary use of concomitant treatments or therapies for CHE is prohibited between Day 1 and Week 8 visit. However, after the Week 8 visit, should subjects experience an exacerbation of their CHE that requires, in the opinion of the investigator, the use of a prohibited topical therapy, the following approach should be followed:

1. The investigator needs to discuss the case with the medical monitor in order to obtain permission to use a prohibited medication.
2. Subjects who start prohibited topical medications as a treatment for CHE within the first 8 weeks of the study will be discontinued from the study product (ASN002 or placebo) and will perform the ET visit at the time of discontinuation.
3. Subjects who start prohibited topical medications as a treatment for CHE after the first 8 weeks of the study may continue all the study assessments up to the last study visit. Skin biopsies will not be performed after the start of a topical medication.
4. Subjects who start any other prohibited medications or therapies for other reasons may be withdrawn from the study, at the investigator's discretion in agreement with the medical monitor and the sponsor.

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	12 weeks or 5 half-lives (whichever is longer)
Dupilumab	12 weeks
Nonbiological investigational product or device	4 weeks
Live attenuated vaccine	4 weeks
Alitretinoin, isotretinoin, acitretin or other systemic retinoids	4 weeks
Systemic treatments (other than biologics) that could affect CHE (e.g., calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids) Note: Intranasal corticosteroids, eye or ear drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or has used tanning booths	4 weeks
Topical treatments that could have an impact on CHE including, but not limited to, topical corticosteroids, topical retinoids, crisaborole, calcineurin inhibitors, tars, bleach, bleach baths, antimicrobials, medical devices.	2 weeks
For subjects consenting to biopsies only: anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed) Note: Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.	2 weeks
Systemic antibiotics	2 weeks
Topical antibiotics Note: Use of topical antibiotics on biopsy site only is allowed.	2 weeks
Topical products containing urea or salicylic acid	1 week

6.4.4 Concomitant Use of Drugs that may affect Gastric pH

The use of antacids and H2 antagonists must be considered in place of proton pump inhibitors in subjects receiving ASN002. 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.		

6.4.5 Study Restrictions

Subject should be willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products (but not on hand and feet on a visit day prior to scheduled visit time) and protective apparel are recommended when exposure cannot be avoided.

For subjects with a known allergic contact dermatitis, the subject must avoid the causative allergen throughout the study.

7 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.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 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 are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up.

Subjects who did not complete the study for reasons other than safety, or have demonstrated significant noncompliance to study treatments based on IP accountability (define as subject who received < 80% or > 120% of the scheduled doses during the study treatment period) will be evaluated by the principal investigator or designee at each visit and may potentially be replaced.

Subjects who discontinue may be replaced at discretion of the sponsor.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a 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 that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- 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.
- Other: 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.

7.2 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.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

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

8.1.1 Modified Total Lesion Symptom Score

The modified Total Lesion Symptom Score (mTLSS) will be assessed at the visits specified in Table 1. The mTLSS is an assessment of the severity of each of the following: erythema, scaling, lichenification/hyperkeratosis, vesicles, oedema, fissures and pruritus/pain. Each of these are rated using the 4-point severity scale described in Table 6. Scores will be assigned for the most affected side (palmar or dorsal) of the most affected hand identified on Day 1. The same most affected side (palmar or dorsal) of the most affected hand will be followed throughout the study. These ratings are then added to create a total mTLSS calculated as the sum of assigned individual scores with a maximum value of 21 (most severe disease) and a minimum of 0 (no disease).[2,5]

For exploratory purposes, a separate mTLSS will be evaluated for the feet for subject for which the presence of foot eczema will be documented at the screening and Day 1 visits. Scores will be assigned for the most affected side (plantar or dorsal) of the most affected foot.

Table 6. Modified Total Lesion Symptom Score

Parameter	Description of Severity[a]
Erythema	0 = Absent 1 = Faint erythema 2 = Prominent redness 3 = Deep intense red colour
Scaling	0 = Absent 1 = Slight flaking over limited areas, mostly fine scales 2 = Flaking over widespread area(s), coarser scales 3 = Desquamation covering over 30% of the hand, with coarse thick scales
Lichenification /hyperkeratosis	0 = Absent 1 = Mild thickening with exaggerated skin lines over limited areas 2 = Palpable thickening over widespread area(s) 3 = Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesicles	0 = Absent 1 = Scattered vesicles affecting up to 10% of hand, without erosion 2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation 3 = High density of vesicles extending over large area(s), or with erosion or excoriation
Oedema	0 = Absent 1 = Dermal swelling over less than 10% of hands 2 = Definite dermal swelling over more than 10% of hand 3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent 1 = Cracked skin affecting a small area of the hand 2 = Cracked skin affecting multiple areas of the hand and causing pain 3 = One or more deep fissures and causing bleeding or severe pain
Pruritus /pain	0 = Absent 1 = Occasional, slight discomfort a few times per day 2 = Intermittent, causing discomfort frequently during the day 3 = Persistent or interfering with sleep
[a] 0 = absent; 1 = mild; 2 = moderate; 3 = severe.	

8.1.2 Physician's Global Assessment

The Physician's Global Assessment (PGA)[2,5] of disease severity will be assessed at the visits specified in Table 1. The PGA is a global assessment of the current state of the disease (moderate to severe CHE, hands only; subjects with moderate CHE will be limited to 30% of total enrollment). It is a 5-point scale of overall disease severity by rating the particular signs and symptoms of CHE (erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema, fissures and pruritus/pain). A detailed description of each PGA severity score is provided in Table 7.

For exploratory purposes, a separate PGA will be evaluated for the feet, for subject for which the presence of foot eczema will be documented at the screening and Day 1 visits.

Table 7. Physician's Global Assessment

PGA severity	Features	Intensity	Area involved[a]
Severe (4)	Erythema, scaling, hyperkeratosis/lichenification	At least one moderate or severe	> 30% of affected hand[b] surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one severe	
Moderate (3)	Erythema, scaling, hyperkeratosis/lichenification	At least one mild or moderate	10–30% of affected hand[b] surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one moderate	
Mild (2)	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10% of affected hand[b] surface
	Vesiculation, oedema, fissures, pruritus/pain	At least one mild	
Almost clear (1)	Erythema, scaling, hyperkeratosis/lichenification	At least one mild	Less than 10% of affected hand[b] surface
	Vesiculation, oedema, fissures, pruritus/pain	Absent	
Clear (0)	Erythema,scaling, hyperkeratosis/lichenification	Absent	Not detectable
	Vesiculation, oedema, fissures, pruritus/pain	Absent	

[a] Area involved does not apply to patients with mostly fingertips eczema. Affected hand surface refers to the surface area of the more severely affected side (palmar or dorsal) of the more affected hand.
[b] For PGA assessment on feet, % of feet surface is to be used.

8.1.3 Extent of Disease

Extent of disease[2,5] will be assessed at the visits specified in Table 1 and will be estimated by the physician as the percentage of hand area (palmar and dorsal) affected by eczema, both hands (both surface) cumulating 100%.[5]

Presence or absence of foot eczema will be assessed at the visits specified in Table 1 must be documented in the source document and eCRF. For exploratory purposes, a separate extent of the disease will be evaluated for the feet, for subject for which the presence of foot eczema will be documented at the visits specified in Table 1. Percentage will be estimated by the physician as the percentage of foot area (plantar and dorsal) affected by eczema, both feet (both surface) cumulating 100%.

8.1.4 Hand Eczema Severity Index

The HECSI[9] will be assessed at the visits specified in Table 1. The HECSI scoring system incorporates both the extent and the intensity of the disease. Each hand will be divided into five areas [fingertips, fingers (except the tips), palms, back of hands and wrists]. For each of these areas the intensity of the six following clinical signs: erythema, induration ⁄ papulation, vesicles, fissuring, scaling and oedema will be graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate and 3, severe. For each location (total of both hands) the affected area will be given a score from 0 to 4 (0, 0%; 1, 1–25%; 2, 26–50%; 3, 51–75% and 4, 76–100%) for the extent of clinical symptoms. Finally, the score given for the extent at each location will be multiplied by the total sum of the intensity of each clinical feature, and the total sum called the HECSI score will be calculated, varying from 0 to a maximum severity score of 360 points.[9] A detailed description of the HECSI scoring system is shown in Table 8.

Table 8. Hand Eczema Severity Index

Clinical Signs	Fingertips	Fingers (except tips)	Palm of Hands	Back of Hands	Wrists
Erythema (E)					
Infiltration / Papulation (I)					
Vesicles (V)					
Fissures (F)					
Scaling (S)					
Oedema (O)					
SUM (E + I + V + F + S + O)					
Extent (Ex)					
Total HECSI score =	Sum x Ex +	Sum x Ex +	Sum x Ex +	Sum x Ex +	Sum x Ex

Total HECSI score (min 0; max 360). For each location (**total of both hands**) the affected area will be given a score from 0 to 4 (0= 0%; 1= 1–25%; 2= 26–50%; 3= 51–75% and 4= 76–100%) for the extent of clinical symptoms. Finally, the score given for the extent for each location will be multiplied by the total sum of the intensity of each clinical feature (each contributing equally to the final score), and the total sum called the HECSI score will be calculated, varying from 0 to a maximum severity score of 360 points.

8.1.5 Patient Global Assessment

On the day of the visits specified in Table 1, using the PaGA chart, subjects will be asked by the investigator to grade their overall change from baseline in their CHE by selecting one of the following descriptions found in Table 9, which best matches their perception of treatment effect.

Table 9. Patient Global Assessment[2,10]

Cleared or Almost Cleared (at least 90% clearing of disease signs and symptoms compared to baseline)	☐
Marked improvement (at least 75% clear)	☐
Moderate improvement (at least 50% clearing)	☐
Mild improvement (at least 25% clearing)	☐
No change	☐
Worsening	☐

8.2 Skin Microbiome analysis

Collection of skin microbiome samples is a non-invasive procedure where a swab is passed along the lesional surface of the palmar aspect (when possible) of the hand with the worst eczema involvement, and another swab is passed along a nonlesional area of skin within 5 cm of the lesional area. Samples will be collected for all subjects from the same lesional and nonlesional areas at Day 1 and Weeks 4, 16 and ET visit (if applicable and occurs prior to Week 16). Skin microbiome must be collected prior to the tape stripping and biopsies.

It is preferred that the microbiome, tape strips and biopsies (if applicable) come from the same eczema lesion of the hand.

Skin microbiome sampling (lesional and non lesional) will also be performed from the plantar aspect (when possible) of the foot for the subject's with foot eczema documented on Day 1 (preferably same lesion as the one selected for the tape stripping, but adjacent to the tape stripping collection area).

The detailed procedure for collecting skin microbiome samples is provided in the Study Reference Manual.

8.3 Patient Reported Outcomes

8.3.1 Work Productivity and Activity Impairment Measure: Specific Health Problem

The work productivity and activity impairment: specific health problem (WPAI:SHP)[11] measure will be assessed at the visits specified in Table 1, and evaluated for moderate to severe CHE. It is a simple 6-question validated questionnaire that has been used for different health conditions and

customized by replacing the word PROBLEM of the questionnaire by the condition that is studied. Its use has been described in many publications, including many multinational studies. The customized questionnaire to CHE is provided in APPENDIX A.

8.3.2 Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI)[12] will be assessed for CHE 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 B.

8.3.3 Pain Visual Analog Scale

Pain intensity of the CHE will be recorded at the visits specified in Table 1 using a pain Visual Analog Scale (VAS). Pain intensity will be evaluated by asking subjects to place a line perpendicular to the VAS line at the point that represents their worst pain intensity over the last 24 hours.[13] The pain VAS, represented in Figure 2, is a scale from 0 to 10, where 0 indicates no pain and 10 indicate the worst imaginable pain.[13]

Figure 2: Pain Visual Analog Scale

8.4 Safety Assessments

8.4.1 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).

Weight (kg) and height (cm) will be collected to calculate the BMI and will be recorded at the visits specified in Table 1. The height will only be recorded at the screening visit and the same value will be used for BMI calculation at other visits.

Subjects who do not qualify to participate in the study due to a screening vital sign value abnormality can repeat the test once within the original screening time window without resulting in screen failure, 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 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.

8.4.2 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 hand and foot eczema (if present at screening and baseline))
- 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.

8.4.3 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 hand and foot eczema (if present at screening and baseline))
- 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.

8.4.4 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 female subjects of childbearing potential. At the visit specified in Table 1, a urine pregnancy test will be performed for female subjects of childbearing potential (conducted at the investigator site). The specific tests in these panels are listed in Table 10.

Table 10. 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, Direct bilirubin (if total bilirubin is elevated), Indirect bilirubin (if total bilirubin is > 1.2 x ULN at Screening), 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 FSH levels for women who have had a cessation of menses for at least 12 months without an alternative medical cause Tuberculosis test (PPD or QuantiFERON-TB Gold) Serology (HBV (HBsAg, anti-HBc), HCV, HIV)

ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; 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); ULN = Upper Limit of Normal; 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 without resulting in screen failure, 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 clinically significant findings will be reported as an AE.

8.4.5 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 clinically significant findings will be reported as an AE.

8.5Pharmacokinetic and Pharmacodynamic Assessments

8.5.1 Pharmacokinetics Assessment in Blood

Blood samples will be collected for all subjects for PK analyses of ASN002 on visits and time points indicated in the schedule of events in Table 1. Measurement of plasma concentrations of ASN002 will be performed in all subjects receiving ASN002 treatment.

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.

Non-compartmental PK analysis will not be performed for this study.

Population PK analysis will be performed using nonlinear mixed-effects modeling approach with first-order conditional methods. This analysis may be combined with PK concentrations from other clinical trials in healthy and AD subjects as appropriate. The results from this analysis may be reported separately.

8.5.2 Skin Biopsies

At selected study centers, in a subset of approximately 36 subjects who consent to the procedure, three or four 2.5-mm skin punch biopsies will be collected at the visits specified in Table 1. Two 2.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected from the palmar aspect of the hand at Day 1, and one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 16 or ET visit (if applicable, and subject is ET prior to Week 16). In addition, one 2.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies. Lesional skin biopsies should be as close as possible from the area of the skin tape stripping and preferably from the same lesion.

It is preferred that the microbiome, tape strips and biopsies come from the same eczema lesion of the hand.

Biopsy samples will be obtained from the same subjects who consent to PD samples.

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary.

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

8.5.3 Tape stripping

For all subjects included on study, superficial skin cells will be collected using tape stripping at visits indicated in the schedule of events in Table 1 for gene expression analyses.

Skin tape stripping samples will be collected on Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one at Week 4 and Week 16 (or ET visit, if applicable) (from same lesional skin as Day 1). Lesional skin tape stripping samples will be collected for all subjects as close as possible to the site of the skin biopsy (if applicable) and preferably from the same lesion. For each sampled site, approximately 20 tape strips units will be placed and removed from the exact same site one after the other. Tape stripping should be collected prior to study product administration and after photographs, if applicable.

It is preferred that the microbiome, tape strips and biopsies (if applicable) come from the same eczema lesion of the hand.

Tape stripping will also be performed from the plantar aspect (when possible) of the foot for the subject's with foot eczema documented on Day 1 (one from lesional skin and one from adjacent nonlesional skin) at Day 1 and one at Week 4 and Week 16 (or ET visit, if applicable) from same lesional skin as Day 1. Foot skin tape stripping samples will be collected as close as possible to the site of the foot microbiome collection (preferably the same plantar lesion when possible).

Further instructions regarding collection, handling, storing and shipment of these samples will be provided in the laboratory manual.

8.5.4 Pharmacodynamics Assessments in Blood

At selected study centers, for a subset of approximately 36 subjects who consent to the procedure, blood samples will be collected for PD analysis on visits indicated in the schedule of events in Table 1. PD samples will be drawn as trough samples prior to the study product administration. PD samples will be obtained from the same subjects who consent to biopsy collection.

The actual date and time of each blood sample collection will be recorded. Approximately 8 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.

8.5.5 PK/PD Relationship Assessments

PK-efficacy, PK-safety and PK-biomarkers relationships will be explored using linear regression, loess plots, Hills functions, or logistic regression, as appropriate. The results from these analyses may be reported separately.

8.6Other Assessments

8.6.1 Medical Photography

At selected study centers, for a subset of approximately 36 subjects who consent to the procedure, medical photographs will be performed at the visits specified in Table 1. Medical photographs of both aspects (palmar and dorsal) of both hands will be taken to illustrate any visible clinical change. Photographs should be taken prior to drug administration, biopsies, tape stripping and microbiome sample collection. Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

Photographs will be identified and stored as instructed in the photography manual.

8.6.2 Body Surface Area (for subjects with AD only)

For subjects with AD only, their condition will be evaluated based on the diagnostic criteria for AD listed in APPENDIX C. The overall Body Surface Area (BSA) affected by AD will be evaluated (from 0% to 100%) at the visits specified in Table 1. One subject's palm with the palmar aspect of all fingers represents 1% of his or her total BSA. The BSA will be evaluated to verify each subject's eligibility using the same method as previously described, but excluding hands and feet. Subjects with a BSA (excluding hands and feet) of > 15 % at baseline (Day 1) will be excluded from the study. The condition will be documented in the eCRF along with the BSA values recorded at the visits specified in Table 1.

8.6.3 Validated Investigator Global Assessment (for subjects with AD only)

For subjects with AD only, disease severity (excluding hands and feet) will be assessed at the visits specified in Table 1, before the study product administration, using the validated Investigator Global Assessment scale for atopic dermatitis (vIGA-AD). The vIGA 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 vIGA scale is provided in APPENDIX D. The condition will be documented in the eCRF along with the vIGA scores recorded at the visits specified in Table 1.

8.7 Adverse Events and Serious Adverse Events

8.7.1 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.

8.7.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product 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).

8.7.3 Definition of Serious Adverse Event

A SAE 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.

8.7.4 Classification of an Adverse Event

8.7.4.1 Relationship to Study Treatment

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.

8.7.4.2 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.

8.7.4.3 Expectedness

The expectedness of each SAE in relation to the study product will be determined by [redacted], in consultation with the medical monitor and the sponsor when necessary.

8.7.5 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, date 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 prior to informed consent signature will be considered as part of medical history and not reported as an AE. 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 CHE is captured by efficacy assessments and will not be recorded as an AE.

8.7.6 Adverse Event Reporting

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

8.7.7 Serious Adverse Event Reporting

[redacted] will be the pharmacovigilance unit 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 the pharmacovigilance unit (see below contact information) 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: [redacted]

E-mail: PPD [redacted]

Fax: PPD [redacted]

The pharmacovigilance unit will inform the primary medical monitor, the sponsor, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and the medical monitor will evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the medical monitor if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. The pharmacovigilance unit will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

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.

8.7.8 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 the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the sponsor, and Innovaderm 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 the pharmacovigilance unit and Innovaderm 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.

8.7.9 Overdose

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

Any study product 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 8.7.7, SAEs Reporting, 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.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Assuming a common standard deviation of 39% for the percent change-from-baseline mTLSS, a difference of 25% and 35% between the 40 mg dose vs. placebo and the 80 mg dose vs. placebo, respectively, alpha of 5% (two-sided), 25 patients per group would insure an 80% power to obtain a statistically significant treatment effect (using the general F test in an analysis of variance). Assuming between 25-30% dropout rates, up to 35 patients per group will be included in this study.

9.2 Populations for Analyses

Efficacy will be evaluated on the basis of the modified intent-to-treat (mITT) analysis set. A supportive analysis will also be conducted on the per-protocol (PP) analysis set.

Modified Intent-to-Treat Population (mITT): 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 to which they were randomized. The mITT population will be used as the primary analysis population for efficacy.

The Per-Protocol Population (PP): This population will include all subjects who were randomized, who received at least one dose of study product, with no major protocol deviations, and who provided evaluable data for the primary endpoint. All subjects will be analyzed according to the treatment group that they actually received.

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.

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

The PD Population: This population will include all subjects who have at least one assessments of PD parameters

9.3 Statistical Analyses

9.3.1 General Approach

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

The primary efficacy analysis will be done using the mITT population and the PP population will be used as supportive analysis. All efficacy analyses will be performed using Mixed Model Repeated Measures (MMRM) analyses as primary analyses to take care of missing observations.

Additional details regarding the efficacy and safety variable definitions, analyses strategy, control of the overall type 1 error, statistical justification, and techniques for handling missing values (e.g. for subjects who started prohibited medications) will be detailed in a SAP that will be prepared before the database is locked and any analyses are undertaken.

9.3.2 Efficacy Analyses

The primary efficacy endpoint will be analyzed using a repeated measures analysis of covariance on percent change-from-baseline variable to compare the time profile between treatments where

the visit will be the time factor (up to Week 16); and the stratification factor PGA score, treatment group, and interaction term for treatment-by-visit will be the fixed effects and the baseline value will be the covariate. An unstructured variance-covariance matrix will be used. Additional interaction terms will also be included in supportive statistical models and will be detailed in the SAP.

A similar approach as for the primary endpoint will be done for all other continuous efficacy endpoints.

For categorical efficacy endpoints involving proportions of PGA (e.g. the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in PGA at week 16), a Cochran Mantel Hansel test (CMH) controlling for PGA at baseline will be performed.

Overall type 1 error control

For the primary endpoint of percent change-from-baseline in hand mTLSS at Week 16, a Holm's step-down procedure (1979)[14] adjustment will be done to test the two comparisons of interest (40mg vs. Placebo and 80mg vs. Placebo).

9.3.3 Safety Analyses

All safety data, including AEs and SAEs will be presented and tabulated according to 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 treatment-emergent adverse events (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. Serious adverse events 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, and ECGs 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 Drug Dictionary (WHO-DD) and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

9.3.4 Pharmacokinetic Analyses

ASN002 concentration data will be listed per subject and summarized descriptively per dose.

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.

9.3.5 Pharmacodynamic Analyses

A biomarker analysis will be performed on blood, tape stripping skin samples and biopsy samples collected to evaluate PD effects of ASN002 on inflammatory markers and cell populations. Biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group and overall using descriptive statistics.

9.3.6 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.

9.3.7 Planned Interim Analyses

No interim analysis is planned in this study. However, a primary efficacy analysis of the results up to Week 16 visit will be performed after a database lock of all efficacy data of Part A and the sponsor will have access to these unblinded results before the study is completed (Week 32). Safety data up to Week 16 will be cleaned and monitored prior to unblinding the sponsor. Analysis and reporting of the efficacy and safety data will be detailed in the SAP.

The analysis of the results comprised of Week 16 visit up to Week 32 visit will be considered as supportive for the secondary and exploratory objectives of the study.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 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.

10.2 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 a research ethics board (REB)/ institutional review board (IRB). 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.

10.3 Informed Consent Process

An Informed Consent Form describing in detail the study treatment, 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 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 REB/IRB. 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.

10.4 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, 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, Health Canada, and FDA.

10.5 Confidentiality and Privacy

Subject confidentiality and privacy are 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, 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, institutional policies, or sponsor requirements.

Skin and blood samples collected during this study will be stored in a secure storage space with adequate measures to protect confidentiality. Samples will be stored for up to, but no longer than, 15 years from the end of the main study after which time the samples will be destroyed. The samples will be given a code and neither Asana BioSciences LLC. nor its partners will know the subject's identity. The samples will not be sold to other people or companies. The samples may be used when developing new tests, procedures and commercial products.

10.6 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.

10.7 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 study site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, 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 study 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.

10.8 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 electronic data capture (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.

10.9 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 per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements.

10.10 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.

11 REFERENCES

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APPENDIX A: Work Productivity and Activity Impairment Questionnaire (WPAI-SHP:CHE)

Subject ID #: ___ ___ - ___ ___ ___	Subject Initials: ___ ___ ___
Visit: _____	Visit Date (dd-mmm-yyyy):_____
Section to be completed by site staff	

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP:CHE)

The following questions ask about the effect of your *CHRONIC HAND ECZEMA* on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your CHRONIC HAND ECZEMA? *Include hours you missed on sick days, times you went in late, left early, etc., because of your CHRONIC HAND ECZEMA. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your CHRONIC HAND ECZEMA affect your productivity <u>while you were working</u>?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If CHRONIC HAND ECZEMA affected your work only a little, choose a low number. Choose a high number if CHRONIC HAND ECZEMA affected your work a great deal.

   Consider only how much <u>CHRONIC HAND ECZEMA</u> affected productivity <u>while you were working</u>.

CHRONIC HAND ECZEMA had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	CHRONIC HAND ECZEMA completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your CHRONIC HAND ECZEMA affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If CHRONIC HAND ECZEMA affected your activities only a little, choose a low number. Choose a high number if CHRONIC HAND ECZEMA affected your activities a great deal.

   Consider only how much <u>CHRONIC HAND ECZEMA</u> affected your ability to do your regular daily activities, other than work at a job.

CHRONIC HAND ECZEMA had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	CHRONIC HAND ECZEMA completely prevented me from doing my daily activities

   CIRCLE A NUMBER

WPAI:SHP:CHE V2.0 (US English)
http://www.reillyassociates.net/WPAI_SHP.html

APPENDIX B: Dermatology Life Quality Index

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

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

Section to be completed by the site staff

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 **garden?**	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.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.

APPENDIX C: Diagnostic Criteria for Atopic Dermatitis

Clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[15] The criteria are as follows:

Major Criteria (must have at least three)

- Pruritus
- Typical morphology and distribution:
  - Adults: flexural lichenification or linearity
  - Children and infants: involvement of facial and extensor surfaces
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria (must have at least three)

- Xerosis
- Ichthyosis/keratosis pilaris/palmar hyperlinearity
- Immediate (Type 1) skin test reactivity
- Elevated serum IgE
- Early age at onset
- Tendency to skin infections (*Staphylococcus aureus*, herpes simplex)/impaired cellular immunity
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

APPENDIX D: 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.