PPD

Statistical Analysis Plan

Study Title:	**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 Number and Version:	**ASN002AD-202 V6.0 dated 01 October 2019**
Product:	**ASN002**
Sponsor:	**Asana BioSciences, LLC** PPD
Date:	**22 April 2020**
Version:	**Final 1.0**
Prepared by:	PPD

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Final V1.0	22-Apr-2020	PPD [redacted]	Initial version

SIGNATURE PAGE

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This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

TABLE OF CONTENT

ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
BMI	body mass index
CHE	chronic hand eczema
CRO	contract research organization
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HECSI	hand eczema severity index
HIV	human immunodeficiency virus
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mTLSS	modified Total Lesion Symptom Score
PGA	Physician's Global Assessment
PaGA	Patient Global Assessment
PK	pharmacokinetic
PP	per-protocol
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
USA	United States of America
VAS	visual analog scale
vIGA	validated Investigator Global Assessment
WPAI-SHP	work productivity and activity impairment specific health problem

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Asana BioSciences, LLC clinical protocol ASN002AD-202. The analyses described in the SAP are based upon the protocol Version 6.0 dated 01-Oct-2019.

This SAP has been developed prior to database lock, final unblinding, and final analyses. All final analyses will be performed after the clinical trial data are entered into the database, any discrepancies in the data are resolved, the database is locked, and following the signature of the SAP.

Statistical analyses related to, Pharmacodynamic(PD) data, population pharmacokinetic (PK)/PD biomarkers and skin microbiome analysis are not covered in this SAP and will be described in a separate document.

2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	Efficacy endpoint:
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)	• Percent change from baseline in hand mTLSS at Week 16
Secondary	Efficacy endpoints:
To evaluate the efficacy of ASN002 in subjects with moderate to severe CHE.	• Change from baseline in hand mTLSS at Weeks 4, 8, 12, 16 • Percent change from baseline in hand mTLSS at Weeks 4, 8, and 12 • 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 and 16 • Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12 and 16 • Change from baseline in hand PGA at Weeks 4, 8, 12 and 16

OBJECTIVES	ENDPOINTS
	• Change and percent change from baseline in Hand Eczema Severity Index (HECSI) at Weeks 4, 8, 12 and 16 • Time to response relative to baseline (based on hand PGA) • Actual hand Patient Global Assessment (PaGA) at Weeks 4, 8, 12 and 16 • Change from baseline in hand Dermatology Life Quality Index (DLQI) at Weeks 2, 4, 8, 12 and 16 • Change and percent change from baseline in pain visual analog scale (VAS) at Weeks 4, 8, 12 and 16
	Safety endpoints:
To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe CHE	• 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 from baseline in vital signs • Change from baseline in ECG • Change from baseline in safety laboratory tests
	Pharmacokinetic endpoints:
To quantify the plasma concentrations of ASN002 in subjects with moderate to severe CHE	• Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment.
Exploratory	Exploratory endpoints:
To evaluate pharmacodynamic (PD), biomarkers and skin microbiome analysis for evidence of drug activity in subjects with moderate to severe CHE	• Change from baseline in PD, biomarkers and skin microbiome analysis at Weeks 4 and 16.

OBJECTIVES	ENDPOINTS
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 explore the efficacy of ASN002 in subjects with moderate to severe CHE in Part B (after week 16)	• Change from baseline in hand mTLSS in Part B • Percent change from baseline in hand mTLSS in Part B • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0), almost clear (1) or mild (2) in hand PGA in Part B • Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) in Part B • Change from baseline in hand PGA in Part B • Change and percent change from baseline in HECSI in Part B • Actual hand PaGA in Part B • Change from baseline in hand DLQI in Part B • Change and percent change from baseline in pain VAS in Part B
To evaluate the effect of ASN002 on work productivity in subjects with moderate to severe CHE	Change from baseline Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire for hands at all visits with assessments scheduled from Weeks 4 to Week 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 all visits with assessments scheduled from Weeks 4 to Week 32

OBJECTIVES	ENDPOINTS
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 all visits with assessments scheduled from Weeks 4 to Week 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 all visits with assessments scheduled from Weeks 4 to Week 32 • Proportion of subjects achieving a foot PGA of clear (0) or almost clear (1) at all visits with assessments scheduled • Change from baseline in foot PGA at all visits with assessments scheduled from Weeks 4 to Week 32 • Change and percent change from baseline in Extent of Disease affected with foot eczema at all visits with assessments scheduled from Weeks 4 to Week 32 • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA at Weeks 4 and 16 • Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA at Weeks 4 and 16 • Change from baseline in vIGA at Weeks 4 and 16

3 STUDY DESIGN

3.1 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

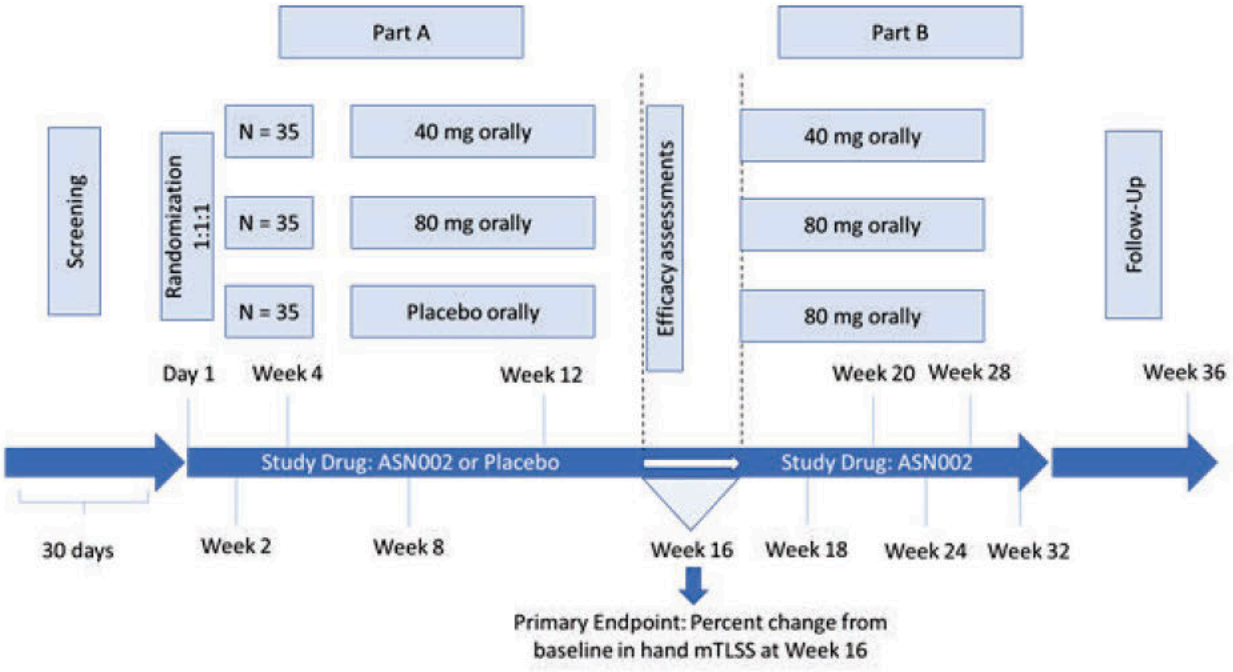
to Day -1), eligible subjects will be randomized (1:1:1) on Day 1 to receive ASN002 at 40 mg or 80 mg, or placebo once daily for 16 weeks (Part A). Randomization will be stratified for the biopsy collection and for the PGA score of '3' (moderate) or '4' (severe) per treatment group. Then, in Part B, 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).,

Figure 1: Study Diagram



3.2 Schedule of Events

Table 1 provides a description of the procedures planned at each visit.

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						

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
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
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 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
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 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

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

[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.

[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.

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

[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.

3.3 Treatment

The treatment groups are:

- 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)

3.4 Randomization, Replacement, and Unblinding Procedures

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 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

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.

3.5 Changes to the Analysis from the Protocol

Summary of physical examination will not be presented as specified in sections 8.4.2 and 8.4.3 of the protocol as results are not collected unless they appeared as Clinical significance, in which case they are entered as an AE.

Percent change from baseline in hand PGA and foot PGA at Weeks 4, 8, 12, 16, and 32 will not be present as specified in section 3 of the protocol.

Subgroup analysis by PGA strata at baseline (3 vs. 4) will be performed on the primary endpoint (percent change in mTLSS) and key secondary endpoint (proportion with reduction in PGA) as specified in sections 13.1 and 13.2.

Subgroup analysis by baseline description of CHE (hyperkeratotic, fingertip or pompholyx) will be performed on the primary endpoint (percent change in mTLSS) and key secondary endpoint (proportion with reduction in PGA) as specified in section 13.3 for exploratory purpose.

Validated Investigator Global Assessment (for subjects with AD only) will be analyzed as specified in Section 13.3 for exploratory purpose.

The pruritus score portion of the mTLSS will also be analyzed for exploratory purposes as described in Section 13.3.

All secondary efficacy endpoints will be up to Week 16 (Part A). All secondary efficacy endpoints data after week 16 (after the Placebo patients have crossed over to ASN002) will be considered exploratory efficacy endpoints and will be presented using descriptive statistics.

All exploratory efficacy endpoints specified in section 3 of the protocol, will be summarized by all visits with assessment scheduled from Weeks 4 to Week 32 as specified in section 13.3, instead at Weeks 4, 8, 12, 16, and 32.

In section 9.3.2 of the protocol, Holm's step-down procedure adjustment was proposed to adjust for the two comparisons of interest (40mg vs. Placebo and 80mg vs. Placebo). It is well known that the Hochberg method is optimal than Holm's adjustment. Therefore, Hochberg adjustment will be used for the multiple dose/treatment comparisons. The decision for this changed was made before the unblinding. Since this change would not affect the conduct of the trial in any sense, no protocol amendment was made to account for this change.

4 POPULATIONS FOR ANALYSIS

4.1 Modified Intent-to-Treat Population

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.

4.2 Per-Protocol Population

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 at Week 16. All subjects will be analyzed according to the treatment group that they actually received during Part A.

The protocol deviations will be presented in a listing and summarized by category. Upon sponsor's review, the listing will also include a flag indicating whether each deviation is considered important or not. Important deviations will be interpreted as major and will result in excluding the related subject from the Per-Protocol Population. This exercise will be done prior to the database lock, on blinded data.

4.3 Safety Population

The safety population will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment that they actually received in Part A.

4.4 Pharmacokinetic Population

The Pharmacokinetic (PK) population will include all subjects who received at least one dose of ASN002 and have plasma concentration data.

4.5 Pharmacodynamic Population

The Pharmacodynamic (PD) population will include all subjects who received at least one dose of the study product and have at least one assessment of PD parameters

5 GENERAL CONSIDERATIONS

Formats and layouts of tables, listings, and figures (TLF) will be provided in a separate document (output general layout is described in Appendix 1).

5.1 Sample Size

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.

5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last non-missing assessment prior to or on the first study treatment application date (including unscheduled assessments) in Part A. If the last non-missing assessment is performed on the same date as the first study treatment and time is not available, the assessment will be considered as baseline, except for adverse events (AEs) and medications starting on the first study treatment dose date which will be considered post-baseline.

5.3 Reference Start Date and Analysis Day

Analysis day will be calculated from the first study treatment date and will be used to show start/end day of assessments or events.

For dates on or after the first treatment date, Analysis Day = Date – First Study Treatment Date + 1

For dates before the first treatment date, Analysis Day = Date – First Study Treatment Date

In the situation where the assessment/event date is partial or missing, analysis day will be missing.

5.4 Windowing Conventions

No Statistical Windows have been proposed for this study:

5.5 Descriptive Statistics

All continuous variables will be summarized by presenting the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented as frequencies and percentages. Summary tables will be presented by treatment and visit, when applicable.

Change from baseline will be calculated as:

Assessment value at post-baseline visit X – baseline value.

Percent change from baseline will be calculated as:

(Assessment value at post-baseline visit X – baseline value) / baseline value × 100.

5.6 Statistical Tests

Unless otherwise specified, all statistical tests will be two-sided and will be performed with a significance level of 0.05. Confidence intervals (CIs) will be two-sided with 95% coverage.

5.7 Handling of Retests, Unscheduled Visits, and Early Termination Data

When retests measurements are done, the retest measurement will be considered for the summary analysis. All data from retest visits will be listed.

For Safety Data, unscheduled measurements will not be summarized in by-visit summary tables or figures. However, data from unscheduled visits will be listed.
Early Termination (ET) visit assessments will be summarized as a separate visit in by-visit outputs.

5.8 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6 STATISTICAL CONSIDERATIONS

6.1 Adjustments for Covariates

Baseline value for the absolute change from baseline of continuous efficacy parameters will be included as a covariate in the statistical models.

6.2 Handling of Dropouts or Missing data

See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications and adverse events.

For safety analyses, no imputation of the data will be done and analyses will be conducted on the observed cases (OC). In Part A efficacy analyses will be performed using Mixed Model Repeated Measures (MMRM) analyses as primary analyses to account for missing observations (See section13.1).

For subjects starting prohibited medications as listed in section 6.4.3 of the protocol, all efficacy data captured after the start of prohibited medication will be considered missing for the analysis of those parameters. A sensitivity analysis on the primary endpoint mTLSS will be done including all efficacy data for these subjects (before and after the prohibited medication).

6.3 Interim Analysis and Data Monitoring

No Interim analysis has been planned for this study.

The final analyses on efficacy parameters will be done once all patients have finalized their week 16 assessments. All data will be cleaned up to week 16, a database lock of Part A will be performed and final efficacy results will be provided. The efficacy summaries will be updated for additional visits once the Part-B visits are completed; these Part B summaries will be considered exploratory.

6.4 Multicenter Studies

No by center analysis has been planned for this study.

6.5 Multiple Comparisons/Multiplicity

For the primary endpoint of change-from-baseline in hand mTLSS at Week 16, a Hochberg adjustment will be performed to test the two comparisons of interest (40mg vs. Placebo and 80mg vs. Placebo).

Under Hochberg procedure, the comparison proceeds stepwise from the largest p-value to the smallest p-value to compare the kth largest p-value with $0.05/k$, which is the significance level corresponding to the kth largest p-value. The first time a p-value is less than the corresponding significance level, the testing stops and the significance is claimed for the current comparison and subsequent ones that produce smaller p-values than the current one. If all p-values are larger than or equal to the corresponding significance level, none of the doses are statistically different from placebo.

No adjustments will be made to account for multiplicity in secondary endpoints and multiple assessments through time in the same subjects. P-values presented for these endpoints will be nominal p-values.

6.6 Examination of Subgroups

Subgroup analysis by PGA = 3 (moderate) or 4 (severe) will be performed for the primary efficacy endpoint (percent change from baseline in mTLSS) and key secondary endpoints (proportion of patients with reduction in PGA) including inferential statistics as described in section 13.1 and 13.2.

6.7 Analysis Presentation

Subjects will be presented in columns according to their treatment assignment in Part A. In the tables presenting Part B data or combined Part A and Part B data, placebo subjects from Part A

crossed over to ASN002 80 mg will be presented in the placebo/ASN002 80mg column. See Appendix 1 for presentation of treatment groups.

7 STUDY SUBJECTS

7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. Subject disposition will be presented separately for part A and part B. The number of subjects screened and subjects rescreened will be presented. Screen failures and the reason for screen failure will be presented for all screened subjects except for those who were rescreened and did not fail the second screening. Moreover, the number of subject randomized included in each population will be presented. Study completion status and the reason for study discontinuation will also be presented. Number of subjects using prohibited therapy on study up to Week 16 are also presented. The percentage of subjects with screen failures will be calculated using the number of subjects screened as denominator. The percentage of screen failure by reasons will be calculated using the number of screen failures as denominator. Otherwise percentages will be calculated using the number of subjects randomized as denominator. Number of days in the study will be calculated as follows and will be summarized:

Number of days in study = Date of completion/discontinuation – First dose date +1

A listing of subject's disposition will be provided. Information on first screening for subjects who were rescreened, including the rescreened subject identifier, will be presented under the first screening subject identifier. A listing of subject's randomization information and a listing of subjects included in each of the study populations will also be provided.

7.2 Protocol Deviations

The number of events and the number and percentage of subjects with at least one major protocol deviation will be summarized by deviation category and treatment group using the safety population. A listing of all major protocol deviations will also be provided.

The protocol deviations in the study will be evaluated on a case to case basis and will be categorized as major or minor. A major protocol deviation is defined as any deviation that may affect the efficacy outcome or subject safety or subject's right. Subjects having major protocol deviation will be finalized prior to the data base lock.

Following are some potential major protocol deviations.

- Violation of major Inclusion /Exclusion Criteria Assessment
- Treatment compliance of <80% or >120%
- Violation of assessment of efficacy parameter
- Violation of visit scheduling.

A subject will be considered non-compliant for the overall study treatment if the subject is non-compliant in Part A.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized with descriptive statistics using the safety population. The list of demographics and baseline characteristics to be summarized will include:

- Age (years) – calculated relative to date of consent
- Age (categorical) - <65 and >=65
- Self-Reported Gender
- Ethnicity
- Race
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline BMI (kg/m^2)
- Baseline Extent of Disease (%)
- Baseline hand mTLSS total score
- Baseline hand PGA Score
- Baseline HECSI

- Baseline hand DLQI
- Baseline pain VAS
- Baseline BSA (%) in AD patients
- Baseline vIGA for AD patients
- Biopsy collection Status

A listing of all demographics and baseline characteristics will be provided.

9 SURGICAL AND MEDICAL HISTORY

Medical and surgical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0

Surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) using the safety population. A subject who experienced the same surgical and medical history event multiple times will be counted only once for the corresponding PT. Similarly, if a subject experienced multiple surgical and medical history events within the same SOC, the subject will be counted only once for that SOC. Surgical and medical history events will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

A listing of all surgical and medical history events will be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), March 2018 B3.

Prior medications are defined as any medications started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medications taken from the first study treatment dose throughout the end of the study including those started prior to the first study treatment date and continued past that date. See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications.

Incidence of prior medications will be tabulated by Anatomical Therapeutic Chemical Classification System (ATC) level 3, and PT using the safety population. Incidence of concomitant medications will be tabulated in the same way but presented separately for Part A and Part B using

the safety population. Concomitant medications for Part A are defined as any medications taken after the first dose of treatment and on or before or at week 16 visit, including those that started prior to the first dose of treatment date and continued past that date. Concomitant medications for Part B are defined as any medications taken after week 16, including those started prior to week 16 and continued past that date. A subject with the same medication taken multiple times will be counted only once for the corresponding PT. Similarly, if a subject has taken more than one medication within the same ATC level, then the subject will be counted only once for that ATC.

A listing of all prior and concomitant medications will be provided.

11 Study Treatment Exposure and Treatment Compliance

A summary of exposure will be presented using the safety population for each treatment group and will include descriptive statistics of the number of days treated for each treatment group. For each treatment, compliance will be calculated as follow:

$$\frac{\text{Number of doses taken}}{\text{Number of days between the last dose date and the first dose date} +1} \times 100$$

Descriptive statistics for compliance will be presented for each treatment group. Frequency distribution will also be presented for the following categories: < 80%, [80% - 120%] and > 120%.

Exposure and compliance will be displayed in a listing of study treatment administration.

12 Pharmacokinetic Analysis

Due to the sparse PK data collected from individual subjects, non-compartmental analysis will not be performed.

Descriptive statistics of the concentration data will be summarized based on nominal timepoints per dose level and will be presented in a table using the PK population. PK concentration data, including actual sampling time, will be provided in a listing. Concentration-time profiles (mean and individual) will be presented in figures.

For computation of mean plasma concentrations, data that are below the limit of quantification (BLQ) will be set to zero. However, BLQ data between two non-BLQ concentrations will be set to missing.

The analysis plan for population PK, PK/PD and population PK/PD analyses will be addressed elsewhere, and the results will be reported separately from the clinical study report.

13 EFFICACY ANALYSIS

13.1 Primary Efficacy Endpoint

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 2. 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). The score will be set to missing in case of at least one missing value.

For exploratory purposes, a separate mTLSS will be evaluated for the feet for subjects 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.

Additionally, the pruritus score portion of the mTLSS will also be analyzed for exploratory purposes.

Table 2. 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.	

Descriptive statistics on hand mTLSS value will be presented by visit for each treatment group. Change from baseline and percentage change from baseline will be also summarized.

Primary Endpoint 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. The primary efficacy analysis will be done using the mITT population and the PP population will be used as a supportive analysis.

A mixed effect model for repeated measures (MMRM) will be used to model the percent change from baseline in hand mTLSS. The model will include the stratification factor PGA score at baseline, if baseline PGA score is not highly correlates with baseline mTLSS score, treatment, visit and treatment-by-visit interaction as fixed effects and baseline hand mTLSS as a covariate. Primary comparison between Placebo and Treatment groups will be for Week 16 using contrasts. The unstructured (UN) variance-covariance matrix will initially be assumed. If the model does not converge using the UN covariance structure, the autoregressive (order 1) AR(1) structure will be used. If the AR(1) structure also does not converge, other covariance structures deemed appropriate to fit the data will be used. .

Distribution of residuals will be visually examined to determine whether substantial departures from normality and homogeneity of variance are apparent. If the data are inconsistent with the assumption of normality, either a normalizing transformation to the primary endpoint will be applied or a nonparametric analysis will be performed.

The same analysis will be performed on the per-protocol population.

Overall type 1 error control

For the primary endpoint of percent change-from-baseline in hand mTLSS at Week 16, a Hochberg step-up procedure adjustment will be done to test the two comparisons of interest (40mg vs. Placebo and 80mg vs. Placebo) as detailed in Section 6.5.

Sensitivity Analysis:

Additional sensitivity analyses will be performed for the primary endpoint - percent change from baseline in mTLSS using MMRM model described above and including all efficacy hand mTLSS data for these subjects (before and after the prohibited medication).

Subgroup Analysis:

Subgroup analysis by PGA strata will also be presented for the primary endpoint -percent change from baseline in mTLSS. MMRM model will be used with treatment, visit and treatment-by-visit interaction as fixed effects, and baseline hand mTLSS as a covariate and primary comparison will be performed at Week 16.

13.2 Secondary Endpoints

Hand modified Total Lesion Symptom Score (mTLSS)

mTLSS will also be analyzed as follows:

- Change from baseline in hand mTLSS score at Weeks 4, 8,12 and 16
- Percent change from baseline in hand mTLSS at Weeks 4, 8, 12

Hand Physician Global Assessment (PGA) score

The PGA is a global assessment of the current state of the disease. 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 3.

Table 3. 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.

Hand PGA score will be analyzed as follows:

- 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 and 16.
- Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12 and 16.
- Change from baseline in hand PGA at Weeks 4, 8, 12 and 16.
- Time to response defined as achieving an assessment of clear (0), or almost clear (1) in hand PGA.

Subgroup analysis by PGA strata at baseline (3 vs 4) will be done on the following endpoints:

- Proportion of subjects achieving a hand PGA of clear (0) or almost clear (1) at Weeks 4, 8, 12 and 16.
- 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 and 16.
- Change from baseline in hand PGA at Weeks 4, 8, 12 and 16.

Hand Eczema Severity Index (HECSI)

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. The score will be set to missing in case of at least one missing value.

A detailed description of the HECSI scoring system is shown in

HECSI **will be analyzed as follows:**

- Change and percent change from baseline in Hand Eczema Severity Index (HECSI) at Weeks 4, 8, 12 and 16.

Table 4.

HECSI will be analyzed as follows:

- Change and percent change from baseline in Hand Eczema Severity Index (HECSI) at Weeks 4, 8, 12 and 16.

Table 4. 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 xEx +	Sum xEx +	Sum xEx +	Sum xEx +	Sum xEx

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.

Patient Global Assessment (PaGA)

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 5. Patient Global Assessment2,10

Cleared or Almost Cleared	□
Marked improvement (at least 75% clear)	□

Moderate improvement (at least 50% clearing)	□
Mild improvement (at least 25% clearing)	□
No change	□
Worsening	□

PaGA will be analyzed as follows:

- Actual hand Patient Global Assessment (PaGA) at Weeks 4, 8, 12 and 16.

below, which best matches their perception of treatment effect. Since PaGA was assessed at baseline as well all subjects were asked to grade their baseline visit score as 0 = no change at baseline.

Table 5. Patient Global Assessment[2,10]

Cleared or Almost Cleared	□
Marked improvement (at least 75% clear)	□
Moderate improvement (at least 50% clearing)	□
Mild improvement (at least 25% clearing)	□
No change	□
Worsening	□

PaGA will be analyzed as follows:

- Actual hand Patient Global Assessment (PaGA) at Weeks 4, 8, 12 and 16.

Dermatology Life Quality Index (DLQI)

Dermatology Life Quality Index Questionnaire (DLQI) is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The DLQI total score is defined as the sum of the 10 item scales, ranging from 0 to 30. If missing answers or mistakes, the following rules will be followed:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
4. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If it is answered 'no', but the second half is left incomplete, the score will remain 0.

DLQI will be analyzed as follows:

- Change from baseline in hand Dermatology Life Quality Index (DLQI) at Weeks 2, 4, 8, 12, and 16.

Pain visual analog scale (VAS)

Pain intensity of the CHE will be recorded at the visits specified in Table 1using 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

Pain VAS will be analyzed as follows:

- Change and percent change from baseline in pain visual analog scale (VAS) at Weeks 4, 8, 12 and 16.

Secondary Endpoint Analyses

The key secondary analysis will be based on the data from Part A with the exception of Time to PGA response analysis. MMRM as described for the primary efficacy analyses (Section 13.1) will be used to analyze the change and/or percent change in hand mTLSS, HECSI, DLQI and pain VAS for weeks 4, 8, 12 and 16 (Part A). Analyses will be based on the mITT population and supported by the PP population.

For categorical efficacy endpoints involving proportions hand PGA, a Cochran Mantel Hansel test (CMH) stratified by baseline PGA will be presented by visit for Part A. Analyses will be based on the mITT population for all secondary parameters and supported by the PP population. Missing data at any post-baseline assessment will be imputed as a non-responder.

Actual values of PaGA will summarized descriptively using frequency and percentage.

Time to response relative to baseline (based on hand PGA) will be compared between treatments using the Kaplan Meier method. A subject will be considered censored if he has not met the event of interest at the end of the study or if the subject is lost to follow up at last observation. Those subjects will be censored at their last available hand PGA assessment.

Descriptive statistics will be presented for all secondary endpoints by visit and treatment group and sorted by Part A.

All endpoints relative Part B for the above assessments are considered exploratory only and will be summarized descriptively by initial treatment group and overall.

13.3 Exploratory Endpoints

Chronic Eczema Subtype Analysis

Subgroup analysis using descriptive statistics by baseline description of CHE (hyperkeratotic, fingertip or pompholyx) will be performed using the primary endpoint - percent change in mTLSS.

Subgroup analysis using descriptive statistics by baseline description of CHE will also be performed for the PGA response outcome as defined in Section 13.2.

Pruritus NRS section of hand mTLSS

The pruritus/pain parameter score of the hand mTLSS questionnaire will be analyzed using descriptive statistics.

Work Productivity and Activity Impairment Measure: Specific Health Problem

The work productivity and activity impairment: specific health problem (WPAI:SHP) measure will be assessed at the visits specified in Table 1, and evaluated for 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 WPAI-SHP allows us to calculate four scores (multiply by 100 for percent):

Percent work time missed due to CHE: Q2/(Q2a+Q4)

Percent impairment while working due to CHE: Q5/10

Percent overall work impairment due to CHE: Q2/(Q2+Q3) + {(1-(Q2)/(Q2+Q3)) x Q5/10

Percent activity impairment due to CHE: Q6/10

Where variables Q1-Q6 are the questions from WPAI-SHP:

Questions:
1 = currently employed
2 = hours missed due to CHE
3 = hours missed other reasons
4 = hours actually worked
5 = degree CHE affected productivity while working
6 = degree CHE affected regular activities

WPAI-SHP scores will be analyzed as follows:

- Change from baseline in Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire at all visits with assessments scheduled from Weeks 4 to Week 32 for each domain
- Proportion of patients with 20% or higher impairment in Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire at all visits with assessments scheduled from Weeks 4 to Week 32 for each domain

Extent of Disease

Extent of disease 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%.

Extend of Disease will be analyzed as follows:

- Change and percent change from baseline in Extent of Disease affected with moderate to severe CHE at all visits with assessments scheduled

Modified Total Lesion Symptom Score (mTLSS) Feet

For exploratory purposes, a separate mTLSS will be evaluated for the feet for subjects 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. Only subjects with foot involvement at baseline will be part of these analyses.

Foot mTLSS will be analyzed as follows:

- Change and percent change from baseline in foot mTLSS at all visits with assessments scheduled from Weeks 4 to Week 32

Physician's Global Assessment (PGA) Feet

For exploratory purposes, a separate PGA will be evaluated for the feet, for subjects for which the presence of foot eczema will be documented at the screening and Day 1 visits. Only subjects with foot involvement at baseline will be part of these analyses.

Foot PGA will be analyzed as follows:

- 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 all visits with assessments scheduled from Weeks 4 to Week 32
- Proportion of subjects achieving a foot PGA of clear (0) or almost clear (1) at all visits with assessments scheduled from Weeks 4 to Week 32
- Change from baseline in foot PGA at all visits with assessments scheduled from Weeks 4 to Week 32

Extent of Disease for Subjects Affected with Foot Eczema

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 subjects 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%. Only subjects with foot involvement at baseline will be part of these analyses.

Analyzes will be done as follows:

- Change and percent change from baseline in Extent of Disease affected with foot eczema at all visits with assessments scheduled from Weeks 4 to Week 32

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 **Error! Reference source not found.**, 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. The condition will be documented in the eCRF along with the vIGA scores recorded at the visits specified in Table 1.

Analyzes will be done using:

- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in vIGA at Weeks 4 and 16.
- Proportion of subjects achieving at least a 2-grade reduction from baseline in vIGA at Weeks 4 and 16.
- Change from baseline in vIGA at Weeks 4 and 16

Exploratory Analysis

Change and/or percent change in hand mTLSS by CHE subtype, pruritus score portion of mTLSS, WPAI-SHP, Extent of Disease, foot mTLSS and foot PGA will be presented using descriptive statistics by visit and initial treatment group for both parts of the study. Analyses will be based on the mITT population.

For categorical efficacy endpoints involving proportions based on foot PGA and vIGA, counts and percentages will be presented for each visit.

14 SAFETY ANALYSIS

All safety analyses will be conducted using the safety population and will be presented combined except adverse events, which will be presented separately for Part A and Part B. For both parts subjects will be presented by their initial treatment as assigned in Part A.

14.1 Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0.

Treatment emergent adverse event (TEAE) is any condition that was not present prior to treatment with the study product but appeared following first dose in Part A, 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). See Appendix 2 for handling of completely or partially missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent. AEs will be considered in Part A or Part B depending on the onset date – if the AE onset date was on or before week 16 the AE will be considered as a Part A AE. If the AE had an onset after week 16 the AE will be considered as a Part B AE. AEs emerged in part A and last into part B would be reported in both parts A and B and be noted in the part B report for these AEs which are reported twice.

An overall summary table of adverse events will be provided. The number of events and the number and percentage of subjects who experienced AE, TEAE, TEAE by greatest reported relationship, TEAE by relationship, TEAE by highest reported severity, TEAE by severity, related TEAE by highest reported severity, related TEAE by severity, serious AE, serious TEAE, serious TEAE by greatest relationship, TEAE and related TEAE leading to study drug discontinuation, TEAE and related TEAE leading to study discontinuation, TEAE and related TEAE leading to treatment interruption and AE leading to death will be presented as well as TEAE of clinical interest.

TEAE of clinical interest are:

- Thrombotic events

- Serious infection
- Malignancy and lymphoproliferative disorders
- Gastrointestinal perforation
- Hypersensitivity
- Anemia
- Neutropenia
- Lymphopenia
- Liver enzyme elevation
- CPK and lipid elevation

Unless otherwise specified, a subject experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a subject experiences multiple TEAEs within the same SOC, the subject will be counted only once for that SOC. TEAEs will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and relationship. A treatment-related TEAE is defined as any TEAE that is assessed by the investigator as probably or possibly related to study treatment. TEAE that is assessed as not related will be defined as not treatment-related. If a subject experiences more than one TEAE within different relationship categories within the same SOC/PT, only the worst case (greatest reported relationship) will be reported. A TEAE with an unknown relationship will be considered as treatment-related.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and severity (mild/moderate/severe). If a subject experiences more than one TEAE within different severity categories within the same SOC/PT, only the worst case (highest reported severity) will be reported. TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects with TEAEs will be summarized by SOC, PT, relationship, and severity (mild/moderate/severe). 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. TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects who experience serious TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experience serious TEAE will be summarized by SOC, PT, and relationship. If a subject experiences more than one serious TEAE within different relationship categories within the same SOC/PT, only the worst case (greatest reported relationship) will be reported.

Proportion of subjects withdrawing for worsening of their CHE will be summarized at Weeks 4, 8, 12, and 16. Summary of Most Frequent TEAE, defined as the 1% most prevalent TEAEs, will also be summarized.

Listings of all AEs, all AEs leading to death, all serious AEs, all TEAEs leading to study drug discontinuation, all TEAEs leading to study drug interruption all TEAEs leading to study discontinuation and all most frequent TEAEs will be provided.

14.2 Clinical Laboratory

Descriptive statistics will be presented for data related to chemistry, hematology and quantitative urinalysis. Change from baseline values will be presented for each post-baseline assessment. Frequencies and percentages for each result will be provided for qualitative urinalysis data.

Shift tables from baseline to each post-baseline visits describing shifts to abnormality will be provided as well. Only subjects with a baseline result and a result at the specified visit for the parameter will be considered.

Separate listings of all data for chemistry, hematology, urinalysis, serology and pregnancy test will be provided.

In addition, separate listings of data for chemistry, hematology, and urinalysis will be provided for each parameter where a subject had at least one abnormal result.

14.3 Vital Signs

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, pulse rate and body temperature). Change from baseline values will be presented for each post-baseline assessment.

Shift tables from baseline to each post-baseline visits describing shifts to abnormality will be provided as well. Only subjects with a baseline result and a result at the specified visit for the parameter will be considered.

A listing of all vital sign assessments will be provided. In addition, a listing will be provided for each parameter where a subject had at least one abnormal result.

14.4 Electrocardiogram (ECG)

Descriptive statistics will be presented for data related to ECGs (heart rate, RR interval, PR interval, QRS duration, QT interval and QTcF interval). Change from baseline values will be presented for each post-baseline assessment.

Shift tables from baseline to each post-baseline visit and to each timepoint describing shifts to abnormality will be provided for overall interpretation. Only subjects with a baseline result and a result at the specified visit will be considered.

A listing of ECG assessments will be provided. In addition, a listing will be provided for each parameter where a subject had at least one abnormal result.

15 REFERENCES

16 APPENDICES

Appendix 1: Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1 inch margins and 9 pt Courier New font.

The header section will comprise the sponsor's name, the protocol number, the delivery description, the data cut-off date (if applicable), the TLF number, the TLF title, the population, and the page number (Page X of Y). The footer section will include the TLF footnotes, the CRO's name, the date and time of the execution of the program, and the name of the program.

P-values ≥ 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999".

The mean, median, and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error, and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1". The denominator for each percentage will be the number of subjects within the population per treatment group unless otherwise specified.

Listings will be ordered by treatment group, subject number, date, and visit (where applicable). Imputed dates and imputed missing data will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

1. **Part A outputs:**

Study Treatment Full Names	Study Treatment Output Names
ASN002 40 mg	ASN002 40mg
ASN002 80 mg	ASN002 80mg
ASN002 40 mg and ASN002 80 mg	ASN002 Overall
Placebo	Placebo

2. **Part B outputs:**

Placebo patients from Part A cross over to ASN002 80 mg treatment during Part B. The treatment columns will be presented as ASN002 40 mg, ASN002 80 mg, Placebo crossed-over to ASN002 80 mg and combined ASN002 80 mg (ASN002 80 mg and Placebo crossed-over to ASN002 80 mg combined).

Study Treatment Full Names	Study Treatment Output Names
ASN002 40 mg	ASN002 40mg
ASN002 80 mg	ASN002 80mg
Placebo crossed-over to ASN002 80 mg	Placebo/ASN002 80mg
ASN002 80mg and Placebo crossed-over to ASN002 80 mg combined	Combined ASN002 80mg

3. **Combined Output for Part A and B:**

Placebo patients from Part A cross over to ASN002 80mg treatment during Part B.
For the analysis by treatment and visit, (ASN002 80mg and placebo/ASN002 80mg will be anchored by the first dose time) and presented as follows.

Study Treatment Full Names	Study Treatment Output Names
ASN002 40 mg	ASN002 40mg
ASN002 80 mg	ASN002 80mg
ASN002 40 mg and ASN002 80 mg	ASN002 Overall
Placebo	Placebo/ASN002 80mg
ASN002 80mg and Placebo crossed-over to ASN002 80 mg combined	Combined ASN002 80mg

Appendix 2: Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- Completely missing: Impute to the first study treatment date.
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event End Date Imputation

- Completely missing (and not flagged as "ongoing"): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.