[redacted]

Statistical Analysis Plan

Study Title:	**A PHASE 2, MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF ASN002 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS**
Protocol Number and Version:	**ASN002AD-201-EXT V2.0 (Canada/US) dated 07 February 2019**
Protocol Number and Version:	**ASN002AD-201-EXT V2.0 (Germany only) dated 07 February 2019**
Product:	**ASN002**
Sponsor:	**Asana BioSciences, LLC** [redacted]
Date:	**25-Feb-2020**
Version:	**Final 1.0**
Prepared by:	[redacted]

[redacted]	**STATISTICAL ANALYSIS PLAN, Version Final 1.0**
Protocol Number: ASN002AD-201-EXT V2.0	Sponsor: Asana BioSciences, LLC

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Original V1.0	25-Feb-2020	PPD [redacted]	Initial version

SIGNATURE PAGE

AUTHOR(S):

Name	Signature	Title	Date (DD-MMM-YYYY)
PPD [redacted]		[redacted]	25 FEB 2020

APPROVALS:

Name	Signature	Title	Date (DD-MMM-YYYY)
PPD [redacted]		[redacted]	2-26-2020
		[redacted]	26 Feb 2020
		[redacted]	26 FEB 2020

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
ATC	anatomical therapeutic chemical
BMI	body mass index
BSA	Body Surface Area
bpm	beats per minute
CRF	case report form
CRO	contract research organization
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
ET	early termination
HR	heart rate
IGA	Investigator's Global Assessment
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond
NRS	Numeric Rating Scale
OC	Observed Cases
POEM	Patient Oriented Eczema Measure
PK	pharmacokinetic
PT	preferred term
QTcF	Fridericia's correction formula for QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system®
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TLF	tables, listings, and figures
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Asana BioSciences, LLC clinical protocol ASN002AD-201EXT. The analyses described in the SAP are based upon the protocol Version 3.0 (Canada US) dated 16-Aug-2019 and the protocol Version 3.0 (Germany only) dated 16-Aug-2019.

This SAP has been developed prior to database lock, 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.

Analyses related to pharmacokinetic parameters are not covered in this SAP and will be described in a separate document.

2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the long-term safety and tolerability of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies (ASN002AD-101 and ASN002AD-201)	Primary safety endpoint:
	• Number and rate (events per 100 patient-years) of treatment-emergent adverse events (TEAEs)
	Secondary safety endpoints:
	• Number and rate (events per 100 patient-years) of drug-related TEAEs • Proportion of subjects withdrawing from worsening AD at each visit • Changes in vital signs, physical examinations, electrocardiogram (ECG), and safety laboratory tests
Secondary	
To evaluate the long-term efficacy of ASN002 in subjects with moderate to severe AD who have participated in one of the preceding studies	Secondary efficacy endpoints:
	• Change and percent change from baseline in Eczema Area and Severity Index (EASI) score at each visit • Proportion of subjects achieving at least a 50% reduction from baseline in EASI (EASI50) at each visit

OBJECTIVES	ENDPOINTS
(ASN002AD-101 and ASN002AD-201)	• Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at each visit • Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at each visit • Time to achieve EASI50, EASI75, and EASI90 relative to baseline only in subjects who received the placebo in the previous study • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator's Global Assessment (IGA) at each visit • Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at each visit • Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit • Change from baseline in SCORing Atopic Dermatitis (SCORAD) at each visit • Change from baseline in 5-D Pruritus Scale at each visit • Change and percent change from baseline in pruritus Numeric Rating Scale (NRS) at each visit • Proportion of subjects achieving at least a 4-point reduction from baseline in pruritus NRS at each visit • Change and percent change from baseline in Body Surface Area (BSA) involved with AD at each visit • Change from baseline in Patient-Oriented Eczema Measure (POEM) at each visit • Change from baseline in Dermatology Life Quality Index (DLQI) at each visit • Number and percentage of subjects with dose increase after randomization in the present study • Time to first AD flare
To evaluate the effect of dose reduction at randomization in responder subjects with moderate to severe AD treated with ASN002 at 60 mg or 80 mg in study ASN002AD-201	• Proportion of subjects maintaining EASI75 in responder subjects in ASN002AD-201 randomized to a reduced dose of ASN002 in ASN002AD-201-EXT

OBJECTIVES	ENDPOINTS
To evaluate the effect of dose increase at randomization in non-responder subjects with moderate to severe AD treated with ASN002 at 40 mg or 60 mg in study ASN002AD-201	• Proportion of subjects achieving EASI75 in non-responder subjects in ASN002AD-201 randomized to an increased dose of ASN002 in ASN002AD-201-EXT
To assess population PK of ASN002 in AD subjects via a population PK analysis approach (Not covered in this SAP)	Secondary PK endpoint: • Measurement of plasma concentrations of ASN002
Exploratory	
To explore the relationships between PK exposure and clinical measurement (e.g., efficacy and safety) as appropriate (Not covered in this SAP)	• Characterization of population PK parameters via nonlinear mixed-effects modeling • Characterization of the relationship between PK exposure and efficacy and safety parameters

3 STUDY DESIGN

3.1 Overall Design

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

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

Approximately 256 subjects with AD who participated in one of the preceding studies on ASN002 (ASN002AD-101 and ASN002AD-201) will be included in this study. Subjects will be eligible to enter the OLE study if they (1) participated in ASN002AD-101 study OR (2) participated in

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

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

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

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

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

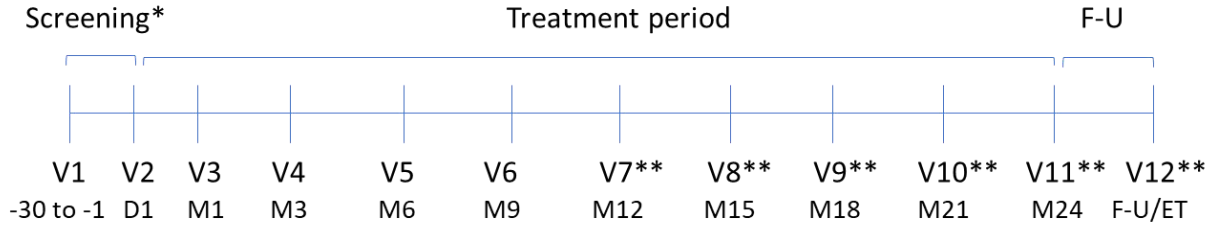
For scheduled study visits, subjects will come to the study center up to 12 occasions: Screening; Day 1; Months 1, 3, 6, 9, 12, 15, 18, 21, 24, and Follow-up/Early Termination (ET). For subjects who participated in the preceding ASN002AD-201 study and are enrolled in the OLE study within 2 weeks after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

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

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

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

Figure 1: Study Diagram



D=Day; ET=Early Termination; F-U=Follow-up; M=Month; V= Visit

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

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

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

Study Visits	**Screening[1]**	**Baseline[1]**	**Treatment Period**									**Follow-up/ET**
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7***	**V8***	**V9***	**V10***	**V11***	**V12***
Month (M)			**M1**	**M3**	**M6**	**M9**	**M12**	**M15**	**M18**	**M21**	**M24**	
Week (W)		**D1**	**W4**	**W13**	**W26**	**W39**	**W52**	**W65**	**W78**	**W91**	**W104**	**W54 or W106**
Day (D)			**D29**	**D92**	**D183**	**D274**	**D365**	**D456**	**D547**	**D638**	**D729**	**D743**
Window (days)	-30 to -1		±7	±7	±7	±7	±7	±7	±7	±7	±7	±2
EASI	X	X	X	X	X	X	X	X	X	X	X	
SCORAD		X	X	X	X	X	X	X	X	X	X	
Pruritus NRS		X	X	X	X	X	X	X	X	X	X	
5-D pruritus scale		X	X	X	X	X	X	X	X	X	X	
DLQI		X	X	X	X	X	X	X	X	X	X	
POEM		X	X	X	X	X	X	X	X	X	X	
Randomization		X										
Study product administration at study center		X	X	X	X	X	X	X	X	X		
Study product administration daily[10]		X----------									X	
Blood sampling for PK evaluation[11]		X	X	X	X		X					
Dispensing of study product		X	X	X	X	X	X	X	X	X		
Collection of study product			X	X	X	X	X	X	X	X	X	
Study product accountability/ compliance		X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

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

BSA=body surface area; D=day; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; ET=early termination; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IGA=Investigator Global Assessment; M=month; NRS=numeric rating scale; PK=pharmacokinetics; POEM=Patient-Oriented Eczema Measure; SCORAD=SCORing Atopic Dermatitis; V=visit.

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

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

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

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

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

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

[6] Brief physical examinations.

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

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

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

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

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

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

3.3 Treatment

The treatment groups are:

- ASN002 40 mg (in 20-mg strength tablets) orally administered once a day for up to 24 months
- ASN002 60 mg (in 20-mg strength tablets) orally administered once a day for up to 24 months
- ASN002 80 mg (in 20-mg strength tablets) orally administered once a day for up to 24 months

3.4 Randomization Procedures

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

Randomization will occur at Day 1 visit. The randomization list will be generated using a validated software. This list will be uploaded into an Interactive Web Response System (IWRS). The investigator or designee will be able to acquire a randomization number for eligible subjects by connecting to the IWRS.

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

Subjects from the preceding ASN002AD-201 study will be randomized according to the rules described in Table 2. The treatment assignment was designed to maintain the blind of the ASN002AD-201 study that will be conducted in parallel to the OLE study, except for the placebo responders who will be unblinded for the ASN002AD-201 study as they are prevented from entering directly in the OLE study.

Table 2: Dose assignment for subjects who participated in the preceding ASN002AD-201 study

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

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

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

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

Subjects who discontinue will not be replaced. This is an open-label study. Subjects and investigators will be aware of the study product and dose administered

3.5 Changes to the Analysis from the Protocol

- Due to early termination of the study, an abbreviated CSR will be written . All analyses will be descriptive in nature, no inferential statistical analyses will be carried out, and the following endpoints will not be analysed as part of this SAP. However, they may be analysed post-hoc and by-patient listings will be generated for all data collected for this study.
    - Rate (events per 100 patient-years) of TEAEs
    - Rate (events per 100 patient-years) of drug-related TEAEs
    - Time to achieve EASI50, EASI75, and EASI90 relative to baseline only in subjects who received the placebo in the previous study
    - Change from baseline in SCORAD at each visit

- Number and percentage of subjects with dose increase after randomization in the present study
- Time to first AD flare
- Proportion of subjects maintaining EASI75 in responder subjects in ASN002AD-201 randomized to a reduced dose of ASN002 in ASN002AD-201-EXT
- Proportion of subjects achieving EASI75 in non-responder subjects in ASN002AD-201 randomized to an increased dose of ASN002 in ASN002AD-201-EXT

- Data from site 127 has been deemed unreliable. For this reason, all data from this site will be excluded from all analysis for this study (both safety and efficacy).

4 POPULATIONS FOR ANALYSIS

4.1 Safety 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 that they actually received.

4.2 Efficacy Evaluable Population

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

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

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

5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last nonmissing assessment prior to or on the first study treatment dose (including unscheduled assessments). Therefore, for

subjects starting ASN002, baseline is defined as the last nonmissing assessment prior to or on the first dose date of the open label extension and for subjects continuing ASN002 it is the last nonmissing assessment prior to or on the first dose date of the preceding study. If the last nonmissing 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.

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

5.4 Windowing Conventions

No windowing convention is followed 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 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.

5.7 Software Version

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

6 STATISTICAL CONSIDERATIONS

6.1 Adjustments for Covariates

N/A

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.

No imputation of the data will be done and analyses will be conducted on the observed cases (OC).

6.3 Interim Analysis and Data Monitoring

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

6.4 Statistical Tests

N/A

7 STUDY SUBJECTS

7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened will be presented. Screen failures will be presented for all screened subjects Moreover, the number of subjects randomized included in each population will be presented. Study completion status and the reason for study discontinuation will also be presented. 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 – 1st dose date +1

A listing of subject's disposition will be provided. 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 that they initially received, using the safety population. A listing of all major protocol deviations will also be provided.

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 (< 65 years, ≥ 65 years) – calculated relative to date of consent
- Self-Reported Gender
- Ethnicity
- Race
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline BMI (kg/m^2)
- Baseline BSA (%)
- Baseline EASI total score
- Baseline IGA
- Baseline pruritus NRS
- Baseline 5-D pruritus scale

- Baseline SCORAD
- Baseline DLQI
- Baseline POEM

The subject's demographic data, including date of birth, height, race, and ethnicity collected at the baseline of the preceding study will be used in the present study and do not need to be collected again.

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

9 SURGICAL AND MEDICAL HISTORY

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

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 B2.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medication taken after the first study treatment dose or taken 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 and concomitant medications will be tabulated by Anatomical Therapeutic Chemical Classification System, (ATC) level 2 and PT using the safety population. Subjects will be presented under the treatment group of the last dose received prior to the start of the medication. A subject with the same medication taken multiple times will be counted only once for the corresponding PT within a treatment group. 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 within a treatment group.

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 follows:

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

Number of doses taken is obtained from IP accountability and for unreturned kits, the number of doses taken is assumed to be zero. Descriptive statistics for the compliance will be presented for each treatment group. Frequency distribution will also be presented for the following categories: < 80%, [80% - 120%] and > 120%. A subject's exposure and compliance will be counted and presented within each dose level received.

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

12 EFFICACY ANALYSIS

As an abbreviated CSR will be provided due to early termination of the study, all efficacy analyses will be descriptive in nature.

12.1 Efficacy Endpoints

Eczema Area and Severity Index (EASI):

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

• 0 = none

• 1 = mild

• 2 = moderate

• 3 = severe

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

• 0 = no involvement

• 1 = <10%

• 2 = 10% to <30%

• 3 = 30% to <50%

• 4 = 50% to <70%

• 5 = 70% to <90%

• 6 = 90% to 100%

The EASI score is obtained by using the formula below:

EASI = 0.1 (Eh + Ih + Exh + Lh) Ah + 0.2 (Eu + Iu + Exu + Lu) Au + 0.3 (Et + It+ Ext + Lt) At + 0.4 (El + Il + Exl + Ll) Al

Where E, I, Ex, L, and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively. The score will be set to missing in case of at least one missing value.

Descriptive statistics on EASI total score will be presented by visit for each treatment group. Change from baseline and percentage change from baseline will be also summarized.

EASI score will be assessed as:

- Change from baseline in EASI score at each available study visit

- Percent change from baseline in EASI score at each available study visit
- Proportion of subjects achieving at least a 50% reduction from baseline in EASI (EASI50) at each available study visit
- Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at each available study visit
- Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI95) at each available study visit

Investigator Global Assessment (IGA):

The Investigator Global Assessment (IGA) is a site-administered clinician-reported global assessment of the current state of the disease. It is measured on a 5-grade scale from 0 to 4, where 0 = clear to 4 = severe.

IGA will be assessed as

- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA at each available study visit
- Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at each available study visit
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each available study visit

SCORing Atopic Dermatitis (SCORAD):

The Scoring Atopic Dermatitis (SCORAD) is built from six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) selected to evaluate the atopic dermatitis severity. The intensity of each item is graded using a 4-point scale (half steps not allowed)

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

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

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

Subjective items include loss of sleep and the intensity of pruritus. These are evaluated by having the subjects indicate on a 10.0-cm (0.0 – 10.0) visual analog scale (VAS)) the point corresponding to the average value for the last 3 days/nights. The combined maximum score of these two is 20.0.

The sum of the measures above represents the SCORAD, which can vary from 0 to 103. If the subjective scores of pruritus and loss of sleep are excluded, the SCORAD becomes objective SCORAD (score range 0.0-83.0). The score will be set to missing in case of at least one missing value.

A by-patient listing of SCORAD results will be provided.

Body Surface Area (BSA):

The overall body surface area (BSA) affected by atopic dermatitis is evaluated (from 0% to 100%).

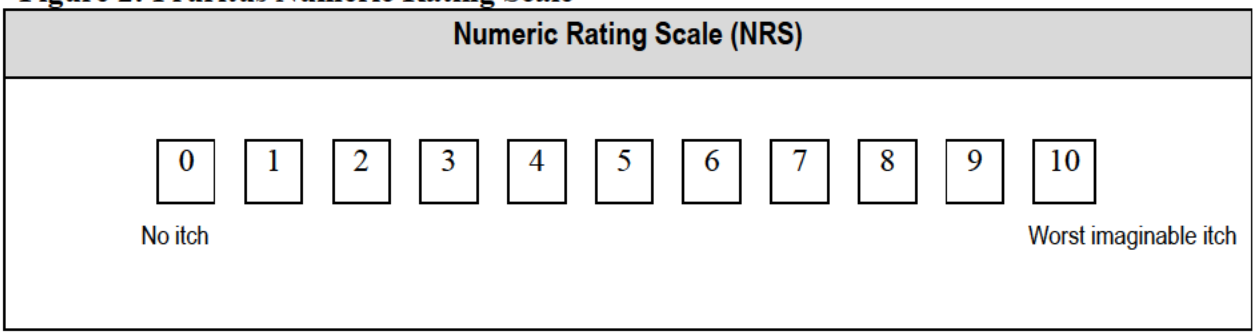
BSA will be assessed as

- the change and percent change from baseline in BSA involved with AD at each available study visit

Pruritus Numeric Rating Scale (NRS):

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

Figure 2: Pruritus Numeric Rating Scale



The pruritus numeric rating scale will be assessed as:

- Change and percent change from baseline in pruritus NRS at each available study visit

- Proportion of subjects achieving at least a 4-point reduction from baseline in pruritus NRS at each available study visit

5D-Pruritus Scale:

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

The scores of each of the five domains are achieved separately and then summed together to obtain a total 5-D score. 5-D scores can potentially range between 5 (no pruritus) and 25(most severe pruritus). The score will be set to missing in case where at least one of the five domain results is missing. Single-item domain scores (duration, degree and direction) are equal to the value in the response choice (range 1–5). The disability domain includes four items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands and work/school. The score for the disability domain is achieved by taking the highest score on any of the four items. For the distribution domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3– 5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5.

The 5D-Pruritus Scale will be assessed as

- the change from baseline in 5-D Pruritus Scale at each available study visit

Patient-Oriented Eczema Measure (POEM):

The Patient-Oriented Eczema Measure (POEM) is a self-assessment of disease severity by the subject. The POEM has a maximum value of 28 based on the subject's response to seven questions scored from 0 to 4. The score will be set to missing in case of at least one missing value.

POEM will be assessed as

- the change from baseline in POEM at each available study visit

Dermatology Life Quality Index Questionnaire (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 there are 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 assessed as

- the change from baseline in DLQI at each available study visit

13 SAFETY ANALYSIS

All safety analyses will be conducted using the safety population. The treatment group for safety will be determined as the last dose received prior to the AEs or prior to the safety results. For AEs occurring on the same day as a dose escalation, the AE will be presented under the preceding dose received. Thus, a subject may be assigned to more than one treatment group, depending on the safety results assessed. The safety summaries will be presented for 1) subjects who just started treatment (i.e. subjects from Phase 1b and subjects dosed on Placebo in Phase 2b) and 2) for subjects who are continuing treatment (i.e. subjects treated with ASN002 in Phase 2b), separately.

13.1 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 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). 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.

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 highest reported severity, related TEAE by highest reported severity, 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.

Unless otherwise specified, a subject experiencing the same TEAE multiple times will be counted only once for the corresponding PT within a treatment group. Similarly, if a subject experiences multiple TEAEs within the same SOC, the subject will be counted only once for that SOC within a treatment group. 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 experience more than one TEAE within different relationship categories within the same SOC/PT/treatment group, 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 experience more than one TEAE within different severity categories within the same SOC/PT/treatment group, 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 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 experience more than one TEAE within different relationship categories within the same SOC/PT/treatment group, only the worst case (greatest reported relationship) will be reported.

The proportion of subjects withdrawing from worsening AD will be summarized at each available study visit.

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

13.2 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.

Separate listings of all data for chemistry, hematology, urinalysis, and pregnancy tests 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.

13.3 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.

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

13.4 Physical Examination

Listings of abnormal physical examinations and all physical examination assessments will be provided

13.5 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.

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.

14 REFERENCES

15 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.

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 ASN002 category (Starting ASN002/Continuing ASN002), treatment group (latest dose prior to the event/assessment for safety), 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:

Study Treatment Full Names	Study Treatment Output Names
ASN002 40 mg	ASN002 40mg
ANS002 60 mg	ASN002 60mg
ASN002 80 mg	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.