[redacted]

Statistical Analysis Plan

Study Title:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ASN002 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS**
Protocol Number and Version:	**ASN002AD-201 V3.0 (Canada/US) dated 07 February 2019**
Protocol Number and Version:	**ASN002AD-201 V2.2 (Germany only) dated 15 October 2018**
Product:	**ASN002**
Sponsor:	**Asana BioSciences, LLC** [redacted]
Date:	**12-Aug-2019**
Version:	**Final 2.0**
Prepared by:	[redacted]

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
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Final V2.0	12-Aug-2019	PPD [redacted]	Added text excluding site 027 from all analyses. Updated the denominator used for discontinued subjects.

SIGNATURE PAGE

AUTHOR(S):

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APPROVALS:

Name	Signature	Title	Date (DD-MMM-YYYY)
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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
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BMI	body mass index
BSA	Body Surface Area
bpm	beats per minute
CI	confidence interval
CMH	Cochran Mantel Hansel
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
ITT	intent-to-treat (population)
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
MMRM	mixed model repeated measures
msec	millisecond
NRS	Numeric Rating Scale
OC	observed case
PD	pharmacodynamic
POEM	Patient Oriented Eczema Measure
PP	per-protocol (population)
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-201. The analyses described in the SAP are based upon the protocol Version 3.0 (Canada US) dated 7-Feb-2019 and the protocol Version 2.2 (Germany only) dated 15-Oct-2018.

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.

2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	Efficacy endpoint:
To evaluate the efficacy of ASN002 in subjects with moderate to severe atopic dermatitis (AD)	• Change from baseline in Eczema Area and Severity Index (EASI) score at Week 12
Secondary	Efficacy endpoints:
To evaluate the efficacy of ASN002 in subjects with moderate to severe AD	• Change from baseline in EASI score at Weeks 2, 4, and 8 • Percent change from baseline in EASI score at Weeks 2, 4, 8, and 12 • Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at Weeks 2, 4, 8, and 12 • Time to achieve EASI50, EASI75, and EASI90 relative to baseline.

OBJECTIVES	ENDPOINTS
	• 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 Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at Weeks 2, 4, 8, and 12Change and percent change from baseline in SCORing Atopic Dermatitis (SCORAD) (total score, sleep score, pruritus score) at Weeks 2, 4, 8, and 12 • Change from baseline in 5-D Pruritus Scale at Weeks 2, 4, 8, and 12 • Change and percent change from baseline in single daily timepoint pruritus Numeric Rating Scale (NRS) at Week 1 (Day 2 up to Day 7) • Change and percent change from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 • Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 • Time to achieve at least 4-point reduction from baseline in NRS. • Change and percent change from baseline in Body Surface Area (BSA) involved with AD at Weeks 2, 4, 8, and 12 • Change from baseline in Patient Oriented Eczema Measure (POEM) at Weeks 2, 4, 8, and 12 • Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 2, 4, 8, and 12
	Safety endpoints:
To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe AD	• Number of Treatment Emergent Adverse Events (TEAEs) • Number of drug-related TEAEs • Proportion of subjects withdrawing from worsening AD at Weeks 2, 4, 8, and 12 • Changes in vital signs, ECG, and safety laboratory tests • Abnormal physical examinations
	Pharmacokinetic endpoints:

OBJECTIVES	ENDPOINTS
To evaluate the PK profile of ASN002 in subjects with moderate to severe AD	• Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment
Exploratory	Exploratory endpoints:
To assess population PK of ASN002 in AD subjects via a population PK analysis approach	• Characterization of population PK parameters via nonlinear mixed-effects modeling
To evaluate PD and biomarkers for evidence of drug activity in subjects with moderate to severe AD	• Change from baseline in expression levels and kinase activity of key disease pathways in skin biopsies, such as Th2 and other T helper cell axes • Changes from baseline in cellular infiltrates of T-cells and dendritic cells • Changes from baseline in epidermal hyperplasia measures (epidermal thickness, ki67, and K16 expression) • Changes from baseline in mRNA and protein expression of differentiation markers • Changes in inflammatory measures in peripheral blood using proteomics
To explore the relationships between PK exposure and clinical measurement (e.g., biomarker, efficacy and safety) as appropriate	• Changes from baseline in clinical safety, efficacy and biomarker measurements in relationship to PK exposure

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.

This study is a randomized, double-blind, placebo-controlled, multicenter, Phase 2b study. Approximately 220 subjects with moderate to severe AD (as defined by a BSA involved with AD of ≥ 10%, an EASI ≥ 16, and an IGA ≥ 3 at Day 1) will be included in this study to complete the study with at least 160 evaluable subjects (all subjects which have completed an EASI score at week 12). Subjects will be men or women, aged 18 to 75 years, inclusive, at the time of consent.

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 (1:1:1:1) on Day 1 to receive ASN002 at 40 mg, 60 mg, or 80 mg, or placebo once daily for 12 weeks. The treatment period will be followed by a 4-week follow-up period for subjects not participating in the open label extension (OLE) study. For scheduled study visits, subjects will come to the study centers on seven occasions: screening, Day 1, Weeks 2, 4, 8, and 12, and Week 16/ ET for subjects not participating in the OLE study.

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

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

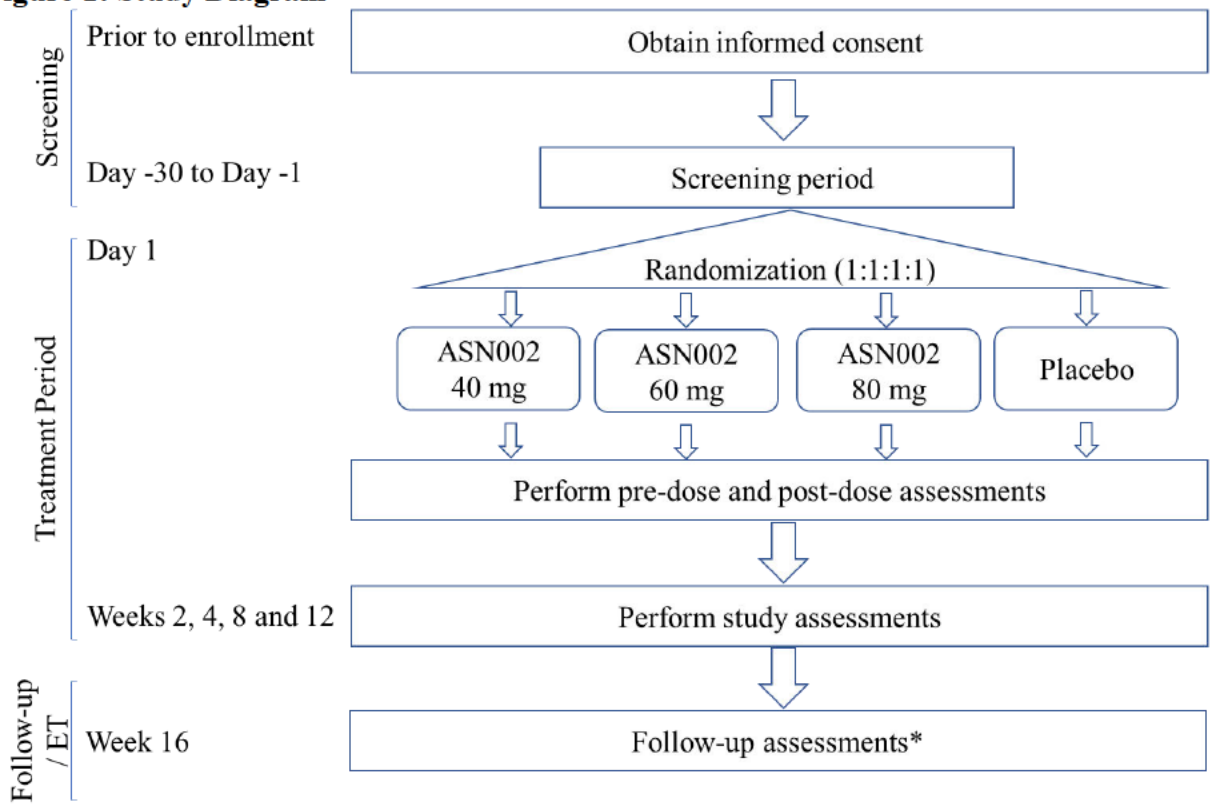
Pre- and post-dose PK blood samples will be collected from all subjects on a sparse sampling schedule at Day 1, and Weeks 2, 4, 8 and 12 (or ET visit, if applicable).

At selected study centers, in a subset of approximately 68 subjects who consent, PD blood samples will be collected pre-dose on Day 1 and Week 12 (or ET visit, if applicable). PD samples will be obtained from the same subjects who consent to biopsy collection. An additional PD blood sample will be collected at Week 4 in subjects who also consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, three or four skin biopsies will be collected during this study. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected at Day 1, and one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 12 (or ET visit, if applicable). In addition, one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, medical photographs of the area of worst AD involvement will be taken to illustrate any visible clinical change.

Figure 1: Study Diagram



*The follow-up assessments at Week 16 will be for subjects who completed the study and declined to participate in the OLE study.

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[12]
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Window (days)	-30 to -1		±1	±2	±2	±2	±2
Informed consent	X						
Demographics	X						
Medical and surgical history	X	X					
Inclusion-exclusion criteria	X	X					
Pregnancy test[1]	X	X	X	X	X	X	X
Physical examination	X	X		X[3]		X	X[3]
Vital signs[2]	X	X	X	X	X	X	X
ECG[5]	X	X		X		X	X[4]
Clinical laboratory tests (hematology, chemistry, and urinalysis)	X	X		X		X	X
Serology (HIV, HBV, HCV)	X						
Tuberculosis evaluation[6]	X						
BSA	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X
SCORAD		X	X	X	X	X	X
Pruritus NRS		X	X	X	X	X	X
5-D pruritus scale		X	X	X	X	X	X
DLQI		X	X	X	X	X	X
POEM		X	X	X	X	X	X
Skin biopsies collection[7]		X		X[9]		X	X[4]
Blood sampling for PD analyses[8]		X		X[9]		X	X[4]
Blood sampling for PK evaluation		X[10]	X[11]	X[10]	X[11]	X[11]	X[4,11]
Randomization		X					
Study product administration at study center		X	X	X	X		
Study product administration daily[13]		X----------				----------X	
Emollient use		X----------					----------X
Daily subject diary[14]		X ----------					----------X

Study Visits	Screening	Treatment Period					Follow-up / ET[12]
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Window (days)	-30 to -1		±1	±2	±2	±2	±2
Dispensing of study product		X		X	X		
Collecting of study product				X	X	X	X[4]
Study product accountability/ compliance			X	X	X	X	X[4]
Verification of subject diary		X	X	X	X	X	X
Photograph AD area[15]		X		X		X	X
Concomitant medication	X	X	X	X	X	X	X
Adverse events evaluation	X	X	X	X	X	X	X

BSA=body surface area; 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; NRS=numeric rating scale; PD=pharmacodynamic; PK=pharmacokinetics; POEM=Patient-Oriented Eczema Measure; SCORAD=SCORing Atopic Dermatitis.

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

[2] 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.

[3] Brief physical examinations.

[4] Only at ET

[5] ECG will be recorded at 0 (pre-dose, within 1 hour of dosing), 1 (± 30 min), and 3 (± 1 hour) hours post-dose on Day 1 and Week 4. ECG will be recorded only once at screening, Week 12, and ET visits.

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

[7]Optional, only for a subset of approximately 68 subjects who consent: two 4.5-mm skin biopsies at Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one at Week 12/ET (from lesional skin). Subjects consenting to biopsies collection must also consent to PD samples. Biopsies should be collected prior to study product administration.

[8] Optional, only for a subset of approximately 68 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 collection. PD samples should be collected prior to study product administration.

[9] An additional skin biopsy from lesional skin and PD sample will be collected at Week 4 for subjects who consent to four biopsies.

[10] PK samples will be collected at 0 (pre-dose), 1 (± 30 min), 3 (± 30 min), and 6 (between 5 to 12 hours post-dose) hours post-dose. The dosing time for the previous day should be recorded accurately.

[11] 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 and Week 12, only one PK sample will be collected.

[12] Follow-up visit for subjects not participating in the OLE study. Subjects who have their study product discontinued due to the start of a prohibited medication for the treatment of AD or for any other safety reasons will be asked to come back for an additional follow-up visit about 4 weeks after the study product discontinuation (in addition to the ET visit)..

[13] Study products will be taken at home daily for 12 weeks, except on study visit days when the study products will be administered on site. No drug administration will be given at Week 12 visit as part of the present study.

[14] Pruritus NRS, emollient use, time of study products administration, and fasting conditions will be recorded daily for 12 weeks in a subject diary. Pruritus NRS and emollient use will be recorded daily in a diary up to Week 16

Study Visits	Screening	Treatment Period					Follow-up / ET[12]
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Window (days)	-30 to -1		±1	±2	±2	±2	±2

visit for subjects not entering in the OLE study. Compliance to diary entry, including emollient use, will be verified by the site at every visit.

[15] Optional, only for a subset of approximately 68 subjects who consent. Photographs should be performed prior to drug administration and biopsy collection (for subjects consenting to biopsies).

3.3 Treatment

The treatment groups are:

- ASN002 40 mg (in 20-mg strength tablets) orally administered once a day for 12 weeks
- ASN002 60 mg (in 20-mg strength tablets) orally administered once a day for 12 weeks
- ASN002 80 mg (in 20-mg strength tablets) orally administered once a day for 12 weeks
- Placebo orally administered once a day for 12 weeks

3.4 Randomization, Replacement, and Unblinding Procedures

Approximately 220 subjects will be randomized in a 1:1:1:1 ratio to receive either ASN002 40 mg, 60 mg, or 80 mg, or placebo, in order to complete the study with 160 evaluable subjects.

Randomization will occur prior to first dosing, at Day 1 visit. The randomization list will be generated using a validated software. Randomization will be stratified by baseline disease severity at Day 1 ([EASI = 16.0-21.2] vs. [EASI = 21.3-29.9] vs. [EASI = ≥ 30.0]) and biopsy collection. The master randomization list will be kept secured until the study blind is broken at the end of study. 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 investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until after the conclusion of the study.

Safety oversight will be under the direction of an independent DSMB, who will remain unblinded during the study.

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 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.

The subject for whom the blind has been broken will be discontinued from the study and undergo the ET procedures.

Subjects who did not complete the study for reasons other than safety, or have demonstrated significant noncompliance to study treatments based on IP accountability (defined as a subject who received <80% or >120% of the scheduled doses during the study treatment period) will be evaluated by the principal investigator or designee at each visit and may potentially be replaced. If a subject drops out during the first 4-week period, the subject may be replaced at the sponsor's discretion.

3.5 Changes to the Analysis from the Protocol

Section 8.3.2 of the protocol mentions the inclusion of stratification factors as fixed effects in the statistical model. The biopsy collection stratification factor was included for an operational purpose only (to have samples for biopsy in the four treatment groups), therefore this variable was not included in any of the statistical models. In addition, for the primary endpoint EASI, the baseline value will not be included as covariate in the statistical model, since it is already included as stratification factor (baseline disease severity) and to include both variables would create a problem of multicollinearity.

In section 8.3.2 of the protocol, Bonferroni adjustment was proposed to adjust for the multiple dose comparisons between ASN002 and placebo. It is well known that the Bonferroni adjustment is overly conservative. Therefore, Hochberg adjustment will be used for the multiple dose 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.

The section 8.3.3 of the protocol has planned for summary of physical exams using descriptive statistics presenting the value at each visit as well as the change from baseline. Since significantly

abnormal physical exams will be presented in the summary of AEs, only listings of physical exams will be presented.

The following endpoints are listed in the protocol:

1) 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 Weeks 2, 4, 8, and 12

2) Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 2, 4, 8, and 12

Since the study has an inclusion criterion of 3 and 4 on IGA, both endpoints will contain exactly the same set of subjects. For this reason, only the first endpoint listed above will be provided.

Data from site 027 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 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all randomized 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

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

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.

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 have at least one assessments 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

Using the following assumptions for the primary efficacy endpoint: a change-from-baseline in EASI at week 12 of at least -15 in the ASN002 dosing groups, a change-from-baseline of -8 in the placebo group, a common standard-deviation of 8, nominal alpha of 0.0167 for each comparison of interest, we would need 40 evaluable subjects per group in order to achieve a power of 92% on the primary efficacy endpoint.

Moreover, with 46 subjects per group, we would have 80% power to show a statistically significant difference between the higher dosing group and placebo in IGA responses (one of the key secondary efficacy endpoint), assuming a response of 37.5% vs. 11.1% in the higher dosing and placebo groups, respectively, using an alpha of 5%.

Thus, assuming about 15% dropout rate, 55 subjects per group will need to be enrolled in this trial for a total of 220 subjects in order to have a minimum of 46 subjects per group to evaluate efficacy with adequate power.

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). 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

Statistical Windows have been proposed for the efficacy endpoints of this study:

	D1 (Baseline)	W2	W4	W8	W12	W16
Day	1	14	28	56	84	112
Statistical Window	Latest pre-dose measurement	[D1 post dose (i.e. Day 2); day 20]	[Day 21 – Day 34]	[Day 35 – D62]	[D63-D87]	[D88-End of study]

If there is more than one assessment for a given timepoint and analysis visit, the assessment closest to the target day will be considered. If there is more than one assessment with the same target date, then the scheduled assessment result will be considered.

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 significant 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.

For efficacy data, unscheduled measurements and ET visit assessments will be re-mapped according to the windowing conventions in section 5.4.

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 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). All efficacy analyses will be performed using Mixed Model Repeated Measures (MMRM) analyses as primary analyses to take care of missing observations. (See section 12.1).

For subjects starting prohibited medications as listed in section 6.4.2 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 EASI will be done including all efficacy EASI data for these subjects (before and after the prohibited medication).

6.3 Interim Analysis and Data Monitoring

No interim analysis is planned for this study. However, unblinded safety data will be generated and reviewed by the DSMB during the study.

The final analyses on efficacy parameters will be done once all patients have finalized their week 12's assessment. All data will be cleaned up to week 12, a soft lock will be performed and final efficacy results will be provided. The efficacy summaries will be updated once the follow-up visit week 16 will be completed, but this will not affect or change any of the final efficacy results.

6.4 Multicenter Studies

To obtain a sufficient and better-balanced number of subjects among study sites, pooling of sites within each country will be applied. Sites without at least 10 subjects in the mITT population will be incorporated into pooled sites as described below. German sites will be pooled together, USA sites will be pooled together and Canadian sites will be pooled together.

Sites in USA or Canada (for each country separately):

1) Sites with less than 10 subjects in the mITT will be pooled within a country:

    a. Sites with less than 10 subjects will be ordered from lowest to highest in terms of number of mITT subjects. In case of ties, the ordering for tied sites will be determined according to the site identification number (from smallest to largest).

    b. Sites will be combined beginning at the smallest until the resulting pooled site contains at least 10 mITT subjects. The sites pooled in this way will be considered as a single site in the statistical analyses.

    c. The process described above will resume for the remaining sites not meeting the criterion of at least 10 mITT subjects. If the final set of pooled sites does not meet the criterion of at least 10 mITT subjects, the final set will be pooled with the preceding pooled site.

    d. If there is only one site with less than 10 mITT subjects, then this site will be combined with the site with the second lowest number of subjects. As above, in the

case of ties, the ordering for tied sites will be determined according to the site identification number (from smallest to largest).

In the case where less than 10 mITT subjects are available in one country, the subjects from both countries will be pooled.

Sites in Germany

1) Sites with less than 10 subjects will be ordered from lowest to highest in terms of number of mITT subjects. In case of ties, the ordering for tied sites will be determined according to the site identification number (from smallest to largest).
2) Sites will be combined beginning at the smallest until the resulting pooled site contains at least 10 mITT subjects. The sites pooled in this way will be considered as a single site in the statistical analyses.
3) The process described above will resume for the remaining sites not meeting the criterion of at least 10 mITT subjects. If the final set of pooled sites does not meet the criterion of at least 10 mITT subjects, the final set will be pooled with the preceding pooled site.
4) If there is only one site with less than 10 mITT subjects, then this site will be combined with the site with the second lowest number of subjects. As above, in the case of ties, the ordering for tied sites will be determined according to the site identification number (from smallest to largest).

6.5 Multiple Comparisons/Multiplicity

For the primary endpoint of change-from-baseline in EASI at Week 12, a Hochberg adjustment will be performed to test the three comparisons of interest (40mg vs. Placebo, 60mg 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 and exploratory 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

The effect of EASI score at baseline (disease severity) on the treatment effect will be examined for the change-from-baseline EASI, %change-from-baseline EASI, and % subjects with at least a 50%, 75% and 90% reduction in EASI, % subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA, % subjects achieving at least a 2-grade reduction from baseline in IGA.

The change and percent change from baseline in single daily timepoint pruritus NRS at Week 1 (Day 2 up to Day 7) and the change and percent change from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 as well as the % subjects achieving at least a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 will be presented in the subgroup of subjects with baseline NRS ≥ 4.

Moreover, inferential statistical analysis will be done at Week 12 for change-from-baseline and %change-from-baseline EASI. Details on the inferential statistical analysis are presented under section 12.1 Primary Efficacy Endpoint.

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 and subjects rescreened will be presented. Screen failures will be presented for all screened subjects except for those who were rescreened and did not fail the second screening. 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. Number of subjects using therapy on study up to Week 12 and the number of subjects continuing into the open label extension are also 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. 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.

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 SCORAD
- Baseline DLQI

- Baseline POEM

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 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. 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:

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

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%.

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

12 EFFICACY ANALYSIS

12.1 Primary Efficacy Endpoint

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.

Primary Endpoint Analysis

The primary efficacy endpoint is change from baseline in EASI score at Week 12. 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 change from baseline in EASI score between treatments. The model will include treatment, visit, stratification factor (baseline disease severity, [EASI = 16.0-21.2] vs. [EASI =21.3-29.9] vs. [EASI = ≥ 30.0), and treatment-by-visit interaction as fixed effects. The unstructured (UN) variance-covariance matrix and Kenward Roger degrees of freedom will be used.

Information for stratification factor will be taken from the Electronic Data Capture (EDC) database, and not the IWRS for primary analysis.

<u>Sensitivity Analyses</u>

An analysis of variance (ANOVA) will be performed, where the absolute change from baseline in EASI score at Week 12 will be the dependent variable, the treatment group and stratification factor (baseline disease severity) will be fixed effects. A supportive analysis with pooled site and pooled

site-by-treatment interaction included as fixed factors in addition to the other factors listed above will be performed in order to study the impact of pooled site on efficacy. If the pooled site-by-treatment interaction is not statistically significant, it will be removed from the model.

An additional sensitivity analysis will be carried out on the change from baseline in EASI score at Week 12 where data from site 029 is excluded.

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, a nonparametric analysis of variance will be performed.

Additional sensitivity analyses will be performed using the stratification factor as per IWRS database in the primary efficacy MMRM model described above and including all efficacy EASI data for these subjects (before and after the prohibited medication).

Subgroup Analyses

An analysis of variance (ANOVA) will be performed, where the absolute change from baseline or the percent change from baseline in EASI score at Week 12 will be the dependent variable, the treatment group and stratification factor as per EDC (baseline disease severity, [EASI = 16.0-21.2] vs. [EASI =21.3-29.9] vs. [EASI = ≥ 30.0) and treatment-by-stratification factor will be fixed effects. Treatment effect per stratification factor subgroup will be presented as well as associated p-values.

12.2 Secondary Endpoints

Eczema Area and Severity Index (EASI):

EASI score (as a secondary endpoint) will be assessed as:

- Change from baseline in EASI score at Weeks 2, 4, and 8
- Percent change from baseline in EASI score at Weeks 2, 4, 8, and 12
- Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at Weeks 2, 4, 8, and 12.
- Proportion of subjects with at least a 75% reduction from baseline in EASI (EASI75) at Weeks 2, 4, 8, and 12.
- Proportion of subjects with at least a 90% reduction from baseline in EASI (EASI90) at Weeks 2, 4, 8, and 12.
- Time to EASI50, EASI75 and EASI90 relative to baseline.

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 Weeks 2, 4, 8, and 12.
- Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at Weeks 2, 4, 8, and 12.

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 Weeks 2, 4, 8, and 12.

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.

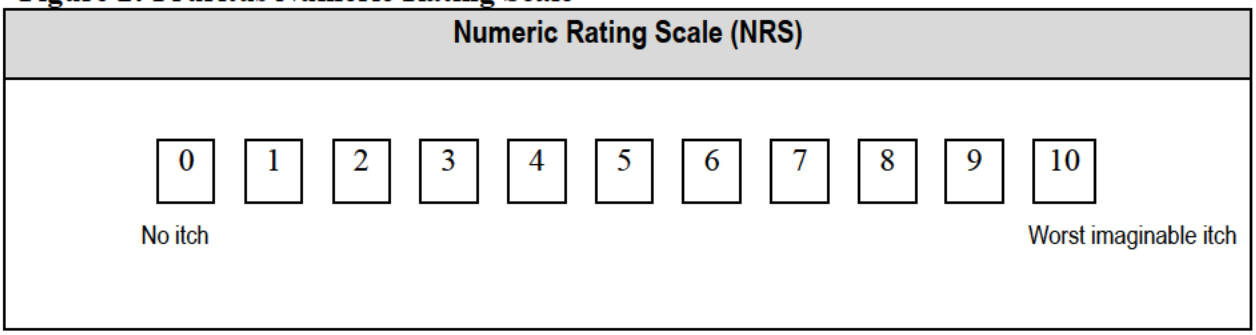
SCORAD will be assessed as

- the change from baseline in total SCORAD score, sleep and pruritus sub-scores at Weeks 2, 4, 8, and 12.
- The percent change from baseline in total SCORAD score, sleep and pruritus sub-scores at Weeks 2, 4, 8, and 12.

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. Assessments within 7 days prior to each of the Week 2, 4, 8, and 12 visits, and on Days 2 to 7 of the Week 1 visit, will be used for the calculation of the weekly average of pruritus NRS.

Figure 2: Pruritus Numeric Rating Scale



The pruritus numeric rating scale will be assessed as:

- Change and percent change from baseline in single daily timepoint NRS at Week 1 (i.e. Day 2, Day 3, up to Day 7).
- Change and percent change from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12.
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12.

- Time to a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS.

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 Weeks 2, 4, 8, and 12.

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 Weeks 2, 4, 8, and 12.

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 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 Weeks 2, 4, 8, and 12.

Secondary Endpoint Analyses

The same methods (MMRM and ANOVA) as described for the primary efficacy analyses (Section 12.1) will be performed to analyze the change and percent change in EASI.

Similar methods (MMRM and ANCOVA) as described for the primary efficacy analyses (Section 12.1) will be performed to analyze the change and percent change in NRS, SCORAD (MMRM and ANCOVA for total score; MMRM only for sleep and pruritus sub-scores) and BSA, and the change in 5D-Pruritus Scale (change from baseline only), POEM (change from baseline only) and DLQI (change from baseline only), with the addition of the baseline score as covariate in the models. Analyses will be based on the mITT population for all secondary parameters.

For categorical efficacy endpoints involving proportions of IGA, EASI and NRS (e.g. the 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 week 12), a Cochran Mantel Hansel test (CMH) controlling for the stratification variable (baseline disease severity) will be performed. For subgroup analyses at each level of baseline severity, a Chi-squared test will be performed. Analyses will be based on the mITT population for all secondary parameters and also on PP population for IGA.

As a sensitivity analysis for IGA, the Cochran Mantel Hansel test (CMH) controlling for the stratification variable (baseline disease severity) will be performed, excluding the subjects for whom the IGA form was initially used to capture the vIGA assessment at baseline. This sensitivity analysis will be performed on the mITT and PP populations.

Additional exploratory analyses may be performed to further understand the impact, if the results of the sensitivity analyses excluding the subjects for whom the IGA form was initially used to capture the vIGA assessment at baseline reveal inconsistencies with the results including those subjects.

The time to achieve the 50%, 75%, or 90% reduction in EASI relative to baseline and the time to achieve a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS will be compared between treatments using the Kaplan Meier method. A subject will be considered as censored if he has not met the event of interest at the end of the study (Week 12 visit) or if the subject is lost to follow up at last observation. Those subjects will be censored at their last available EASI (or NRS) assessment.

Information for stratification factors will be taken from the EDC database, and not the IWRS for all secondary endpoint analyses.

Descriptive statistics will be presented on all secondary endpoints by visit and treatment group.

13 SAFETY ANALYSIS

All safety analyses will be conducted using the safety population.

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 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 relevance and of clinical interest.

TEAE of clinical relevance are:

- Neutropenia
- Lymphopenia
- Eosinopenia
- CPK elevation
- Headache
- Nausea
- Nasopharyngitis
- Diarrhea
- Vomiting

TEAE of clinical interest are:

- Thrombosis (deep venous thrombosis, pulmonary embolism, and arterial thrombosis)
- Anemia
- Arthralgia

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 experience 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 experience 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 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 TEAE of clinical relevance and TEAE of clinical interest will be summarized by SOC and PT within SOC.

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, only the worst case (greatest reported relationship) will be reported.

Proportion of subjects withdrawing from worsening AD will be summarized at Weeks 2, 4, 8, and 12. Furthermore, the time to onset, duration and time to onset greater than or less than 4 weeks of the most frequent TEAEs, defined as the 1% most prevalent TEAEs, will 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 discontinuation, and all most frequent TEAEs 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.

Shift tables from baseline to each post-baseline visits and to each timepoint 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.

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.

Shift tables from baseline to each post-baseline visits and to each timepoint 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

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.

Shift tables from baseline to each post-baseline visits describing shifts to abnormality will be provided for both investigator and cardiologist 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. Results captured by ERT will be presented in the summary tables and listings.

14 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.

The concentration data from this study will be used for population PK analysis and PK/PD analysis. The analysis plan for population PK and PK/PD analysis will be addressed elsewhere.

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 ≥ 0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001"; p-values greater than 0.9999 will be reported as ">0.9999".

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:

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

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.