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I confirm that I have reviewed this document and agree with the content.

APPROVALS	
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass index
BSA	Body Surface Area
CFB	Change From Baseline
CI	Confidence Interval
CDLQI	Children's Dermatology Life Quality Index
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GPP	Good Pharmacoepidemiology Practice
ICH	International Conference on Harmonization
LS	Least Squares
m-ITT	Modified Intent-to-Treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
Min	Minimum
MMRM	Mixed Effect Model Repeated Measures
N/A	Not Applicable
NA	Not Applicable
OR	Observational Research
PASS	Post Authorization Safety Study
PAES	Post Authorization Efficacy Study
PD	Pharmacodynamics
PPP	Per Protocol Population
PK	Pharmacokinetics
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SLS	Sjögren-Larsson Syndrome
SMP	Safety Management Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TEWL	Transepidermal Water Loss
TLF	Table, Listing and Figure
VIIS	Visual Index for Ichthyosis Severity
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for Part 1 of protocol ADX-102-SLS-006., Final Version 5.0 28 September, 2018.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Council on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP is a summative and definitive plan. It describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in the SAP, they will be labeled as post-hoc and will be identified in the CSR.

2.1. RESPONSIBILITIES

Syneos Health will perform the statistical analyses described herein and is responsible for the production and quality control (QC) of all tables, figures, and listings associated with these analyses. ECG, Pharmacokinetics (PK) and Pharmacodynamics (PD) analysis will be conducted independently and are outside the scope of this SAP and will be detailed in separate analysis plans.

2.2. DATA SAFETY MONITORING BOARD

An independent, unblinded DSMB has been established. The DSMB will review safety data upon completion of Part 1 clinical trial. The assessment of safety will be determined from dermatological endpoints, vital sign measurements, physical examinations, hematology and chemistry laboratory testing, ECG readings, use of concomitant medications, and review of adverse events. The DSMB will review efficacy data to assess risk/benefit, but will not perform a formal interim analysis of efficacy or futility. Based on the safety data provided, the DSMB will provide recommendations about stopping or continuing the trial. Please defer to the DSMB Charter Version 1.0, dated May 3rd 2018 for further details.

3. STUDY OVERVIEW

ADX-103-SLS-006 is a multicenter, randomized, double-blind, vehicle-controlled, parallel-group Phase 3 clinical trial to evaluate the safety and efficacy of ADX-102 1% topical dermal cream in subjects with Sjögren-Larsson Syndrome (SLS).

This is a two-part clinical trial, with an initial assessment of increasing BSA treatment (Part 1). After the completion of Part 1, a separate set of eligible subjects will be enrolled into Part 2.

Subjects 3 years of age or older with genetically-confirmed diagnosis of SLS and active ichthyosis are eligible for enrollment. For detailed inclusion and exclusion criteria, see Section 4.1 and 4.2 in the protocol, version 5.0.

Part 1 Design:

Part 1 will evaluate the safety, tolerability, and efficacy of treatment to the affected area of ichthyosis initially on approximately 20% BSA and then increasing up to 90% BSA over 24 weeks of exposure and will confirm an appropriate sample size for Part 2.

Subjects will be consented and screened for eligibility. Approximately nine subjects will be randomized in a 2:1 ratio to receive ADX-102 1% or vehicle.

Subjects or caregivers will apply study drug (i.e., ADX-102 1% or vehicle) to a treatment area identified by the Investigator.

The initial treatment area will be defined as approximately 20% BSA with Grade 2 or higher on the Visual Index for Ichthyosis Severity (VIIS) scaling score, as assessed by the Investigator, and will include one of the body sites as defined in the VIIS tool (target efficacy area). From Week 1 through Week 12, subjects will receive treatment once daily in the initial treatment area only.

If the Investigator determines that there are no safety or tolerability issues at the end of Week 12, the treatment area will increase to all of the affected areas of ichthyosis on one-half of the body (approximately 40-45% BSA in a typical SLS patient). From Week 13 through Week 20, subjects will receive treatment once daily on the expanded treatment area.

If there are still no safety or tolerability issues at the end of Week 20, the treatment area will further increase to all affected areas of ichthyosis on the entire body (approximately, 80-90% BSA in a typical SLS patient). Subjects will receive treatment once daily treatment on all affected areas from Week 21 through Week 24.

Subjects completing the 24 weeks of study drug treatment will then be monitored for an additional four weeks for safety.

Part 2 Design:

Part 2 will evaluate the safety, tolerability, and efficacy of treatment to the affected area of ichthyosis on the body (approximately 80-90% BSA in a typical SLS patient) over 24 weeks of exposure.

4. STUDY PROCEDURES AND FLOWCHART

Table 4.1.1-Part 1 Schedule of Events

Evaluation	Screening[1]	Baseline Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	ET Visit 8[2]	Safety Follow-Up Visit 9
	Day -7 to -1	Week 1 Day 1	Week 1 Day 2	Week 4 ± 3 days	Week 8 ± 3 days	Week 12 ± 5 days	Week 16 ± 3 days	Week 20 ± 5 days	Week 24 ± 5 days	Week 28 ± 3 days
	Site Visit	Site Visit	Site Visit	Home Visit	Home Visit	Site Visit	Home Visit	Site Visit	Site Visit	Home Visit
Informed consent / assent	X									
Eligibility review	X	X								
Demographics / medical history	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Urinalysis/ urine pregnancy test[3]	X	X				X		X	X	
12-Lead ECG	X	X				X		X	X	
Vital Signs	X	X	X			X		X	X	
Physical exam[4]	X	X	X			X		X	X	
Dermatologic exam	X	X	X	X	X	X	X	X	X	X
Digital photography[5]		X		X[6]	X[6]	X	X[6]	X	X	X[6]
VIIS (Investigator-assessed)		X	X			X		X	X	
Global impression of severity		X				X		X	X	
Patient/Observer-reported scales[7]		X				X		X	X	
PD sample collection[8]		X				X		X	X	
Clinical laboratory testing[9]	X	X		X		X		X	X	
PK sample collection[10]		X	X			X		X	X	
Randomization		X								
Administer study drug		X[11]	X	X	X	X[11]	X	X[11]	X	
Dispense study drug & diary			X			X		X		

Collect study drug & diary						X		X	X	

ET = early termination; ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic; VIIS = Visual Index for Ichthyosis Severity

1. Samples collected for urinalysis and clinical laboratory tests may be analyzed at a local lab.
2. Subjects who terminate early from the study will not require post-dose assessments at Visit 8 (Week 24).
3. Urine pregnancy test for female subjects of child-bearing potential only. Test can be analyzed at the study site.
4. Complete physical exam, including height and weight collection, performed at Screening Visit only; symptom-directed physical exams at all other timepoints.
5. Subjects should refrain from bathing and applying study drug or as-needed topical symptom control therapy (emollients) to the treatment area within 12 hours of obtaining digital photographs.
6. During at-home visits, photographs will only be taken if there are any safety concerns.
7. Patient/Observer-reported scales to be administered: EQ-5D-5L, global impression of severity, global impression of bother, global impression of treatment, itching, scratching, burden of bathing/showering, and Children's Dermatology Life Quality Index (CDLQI) / Dermatology Life Quality Index (DLQI).
8. PD assessments include skin cell samples and transepidermal water loss (TEWL) procedures.
9. Clinical laboratory includes hematology and chemistry. Refer to Sections 6.15.1 and 6.15.2 in the study protocol, for more detail.
10. PK collection includes blood and urine samples.
11. Study drug will be administered daily. At study visits when PK samples are collected, study drug may be administered at the study clinic after pre-dose PK samples have been obtained. At Visit 1, Investigator should apply study drug to the initial treatment area (~20% BSA) during the visit. At Visit 2, study drug may be applied to the initial treatment area during the visit (after pre-dose PK sample collection) by the Investigator or subject/caregiver. At Visit 5, if the treatment area is expanded to up to 45% BSA, the Investigator should apply study drug to the treatment area. At Visit 7, if the treatment area is expanded to up to 90% BSA, Investigator should apply study drug to the treatment area.

Table 4.1.2-Part 1 Pharmacokinetic and Cardiac Monitoring

Visit	Visit 1					Visit 2	Visits 5, 7 and 8				
Time (hours)	Pre-Dose	1	2	4	8	24	Pre-Dose	1	2	4	8
Window	-	± 15 min	± 15 min	± 15 min	± 15 min	± 60 min	-	± 15 min	± 15 min	± 15 min	± 15 min
Adults (age ≥ 12 years old)											
12-Lead ECG	X	X	X	X	X		X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Blood PK Samples	X	X	X	X	X	X	X	X	X	X	X
Urine PK Samples	X				X		X				X
Children (age < 12 years old)											
12-Lead ECG	X	X		X			X	X		X	
Vital Signs	X	X		X		X	X	X		X	
Blood PK Samples	X	X		X		X	X	X		X	
Urine PK Samples	X			X			X			X	

5. STUDY OBJECTIVES

5.1. PRIMARY OBJECTIVE

To evaluate the efficacy of ADX-102 1% topical dermal cream on ichthyosis associated with SLS.

5.2. SECONDARY OBJECTIVE(S)

To evaluate the safety and secondary efficacy endpoints of ADX-102 1% topical dermal cream in subjects with SLS.

5.3. DETERMINATION OF SAMPLE SIZE

Part 1 of the clinical trial will assess the effect size on the VIIS scaling score with ADX-102 1% topical dermal cream, and will confirm the sample size needed for Part 2. Unblinded Part 1 safety and efficacy results will be available to the Sponsor for administrative consideration and use upon completion of Part 1. Efficacy data will be used to confirm the sample size estimation for Part 2 as well as to perform between groups and within group descriptive and inferential statistical analyses

5.4. SUBJECT NUMBERING

Each subject screened for the clinical trial will be assigned a unique subject number that will be used to identify the subject throughout their participation in the clinical trial. If a subject fails to be randomized, the reason should be documented in the source documents and case report form (CRF). The subject will be considered a screen failure.

5.5. RANDOMIZATION AND BLINDING

Subjects will be randomized 2:1 to receive ADX-102 1% or vehicle through interactive response technology (IRT) at Baseline Visit Day 1.

Subjects will be randomized in a double-blind fashion. Investigators, qualified study personnel, subjects, and caregivers will be blinded to the study drug treatment administered. The Sponsor will also be blinded to the study drug treatment administered until database lock.

In the event a replacement of a subject is required (see Section 4.3 in the protocol), the next available subject number will be assigned to either ADX-102 or vehicle based on the randomization scheme.

In the event that randomization assignment results in an active to vehicle ratio of less than 2:1 then the clinical trial may be extended until the ratio is achieved per sponsor discretion.

5.6. EMERGENCY UNBLINDING

Emergency unblinding should only be performed when necessary to treat the subject. Most often, knowledge of the possible treatment assignments is sufficient to treat a subject who presents with an emergency condition.

Unblinding will result in the subject being discontinued from the clinical trial, irrespective of whether the Investigator the event is deemed related to study drug.

The treatment code for a subject may only be broken by the Investigator or Sponsor for reasons of subject safety or in an emergency when knowledge of the study drug administered would be important for the treatment of the patient. However, the Investigator should make every effort to contact the Medical Monitor to discuss the emergency and the need to unblind, prior to unblinding any subject. Please refer to the Safety Management Plan (SMP), Version 1.0, dated April 12, 2018.

The blind may be broken in the case of a pregnancy should the subject desire this information.

The date, time and reason for breaking the blind are to be recorded in the subject's CRF and source documents.

In the event of a drug-related, serious, unexpected AE, the Sponsor's Unblinded Pharmacovigilance Department or designee will be provided with the treatment assignment for the subject for regulatory reporting (detailed process outlined in ADX-102-SLS-006 Safety Monitoring Plan).

5.7. ADMINISTRATION OF STUDY MEDICATION

A standard amount of study drug for the percent BSA under treatment will be measured and applied to the treatment area once daily to achieve a dose of approximately 8 mg/cm2, with each application administered approximately 24 hours apart. Study drug should only be administered to the treatment area, as directed by the Investigator, during the clinical trial.

The Target Efficacy Area used for the primary endpoint assessment in Part 1 will be based on one of the body sites as defined in the VIIS tool (upper back, upper arm or lower leg/shin) that has a VIIS scaling score of Grade 2 or higher as assessed by the Investigator. The body site with the worst VIIS scaling score should be selected, if applicable. The target efficacy area will be used for all efficacy analyses; for all other treated areas, data will be summarized.

The Treatment Area will be determined by the Investigator as follows:

In Part 1, the initial treatment area will be defined as approximately 20% BSA with Grade 2 or higher on the VIIS scaling score, on one-half of the body, left or right side, and will include the target efficacy area. From Week 1 through Week 12, study drug will be applied in the initial treatment area.

If the Investigator determines that there are no safety or tolerability issues at the end of Week 12, the treatment area will increase to all of the affected areas of ichthyosis on one-half of the body (approximately 40-45% BSA in a typical SLS patient), left or right side. From Week 13 through Week 20, the study drug will be applied to the extended treatment area affected by ichthyosis.

If there are still no safety or tolerability issues at the end of Week 20, the treatment area will further increase to all affected areas of ichthyosis on the entire body (approximately 80-90% BSA in a typical SLS patient). From Week 21 through Week 24, the study drug will be applied to the entire body affected by ichthyosis.

For example, if the left lower leg is determined by the Investigator to be the target efficacy area, then the entire left leg would likely be defined as the initial treatment area. At the end of Week 12, if there are no safety or tolerability issues, the treatment area would extend to the entire left side of the body. At the end of Week 20, if there are no safety or tolerability issues, the treatment area would include the entire body.

6. ENDPOINTS

All endpoints will be based on an evaluation period spanning Day 1 through Week 24 in Part 1.

6.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the Visual Index for Ichthyosis Severity (VIIS) scaling score as assessed by the Investigator in the target efficacy area.

6.2. SECONDARY EFFICACY ENDPOINTS

Secondary endpoints include:

VIIS score

- VIIS erythema score as assessed by the Investigator in the target efficacy area
- VIIS scaling score as assessed by a central reader in the target efficacy area
- VIIS erythema score as assessed by a central reader in the target efficacy area

Clinical Outcome Assessments

- EQ-5D-5L
- Clinician global impression of severity
- Patient/Observer global impression of severity
- Patient/Observer global impression of bother
- Patient/Observer global impression of treatment
- Patient-reported itching
- Patient/Observer-reported scratching
- Patient/Observer Burden of bathing/showering
- Children's Dermatology Life of Quality Index (CDLQI) / Dermatology Life Quality Index (DLQI)

Biomarker Parameters

- Transepidermal Water Loss (TEWL)

Exploratory Biomarker Parameters

- Lipid biomarkers from skin cells

All analyses involving lipid biomarkers will be considered exploratory and will be conducted post-hoc.

6.3. PHARMACOKINETIC ENDPOINTS

Full pharmacokinetic (PK) profile on Day 1 and at steady state following treatment up to 90% BSA. Planned analysis detailed in separate PK analysis plan.

6.4. CLINICAL OUTCOMES ASSESSMENT ENDPOINTS

Clinical Outcomes Assessments are collected at predefined study visits. Data will be analyzed per a separate Clinical Outcomes Assessments Analysis plan.

6.5. SAFETY ENDPOINTS

The safety endpoints include dermatological endpoints, vital sign measurements, physical examinations, hematology and chemistry laboratory testing, ECG readings, use of concomitant medications, and adverse events.

6.6. PLANNED ANALYSES

The following analyses will be performed for the ADX-102-SLS-006 Phase 3 clinical trial Part 1:

- Analyses for the Data Safety Monitoring Board (DSMB)
- Analysis of unblinded data following completion of Part 1

All safety and efficacy data collected from the approximately 9 subjects will be analyzed upon completion of Part 1.

7. ANALYSIS POPULATIONS

7.1. ENROLLED POPULATION

The enrolled population will include all patients who gave informed consent to participate in the clinical trial.

7.2. SAFETY POPULATION

The Safety Population (SAF) consists of all randomized subjects who use at least one dose of study drug, regardless of whether they undergo any clinical trial assessments. Patients will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. The SAF will be used for the analysis of safety data for this clinical trial.

7.3. MODIFIED INTENT-TO-TREAT (M-ITT) POPULATION

The modified-Intent-to-Treat (m-ITT) Population will include all randomized subjects from the SAF who received at least one dose of study drug and have at least one VIIS assessment post visit 2. Subjects will be analyzed according to randomized treatment. Unless otherwise specified, efficacy analysis will be performed on this population.

7.4. PER PROTOCOL POPULATION

The Per-Protocol Population (PPP) will include the patients from the m-ITT population who had no major protocol deviations that could impact the efficacy analysis. The list of protocol deviations that may exclude a patient from the PPP will be reviewed and approved by the sponsor prior to database lock.

Patients could be excluded from the PPP if:

- Subjects did not receive study drug as assigned
- Subject did not meet all inclusion/exclusion criteria
- The final determination on major protocol deviations and potential impact on efficacy parameters and thereby the composition of the PPP, will be made prior to the unblinding of the database and will be documented separately.

Regardless of randomized treatment group, patients will be included in the analysis group based on the treatment actually received for the analysis of efficacy data using the PPP.

Due to the small sample size in Part 1, efficacy analysis will not be conducted on PPP.

7.5. PHARMACOKINETIC (PK) POPULATION

The PK Population will include all subjects who received at least one dose of study drug and have at least one measured post-dose PK concentration in plasma or urine. The PK Population will be used for the analysis of all PK data.

7.6. PROTOCOL DEVIATIONS

Possible protocol deviations will be identified and displayed in a data listing, sorted by subject and clinical trial site (where applicable). Protocol deviations will be evaluated at the data review meeting (DRM), prior to database lock (DBL), to determine protocol deviations considered to have significant impact on patient safety, efficacy or the validity of the data. Patients with protocol deviations may be excluded from the per protocol population if the deviation has an impact on the efficacy analysis.

8. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1. GENERAL METHODS

All patients entered into the database will be included in patient data listings. Summary tables will be provided for all patients.

Unless otherwise specified, all demographic, baseline and safety data will be presented by treatment arm and overall. Efficacy data will be presented by treatment arm.

Quantitative (continuous) data - absolute values and changes from baseline, where appropriate - will be summarized with number of observations (n), mean, standard deviation (SD), median, minimum, and maximum and 1st and 3rd quartiles for efficacy tables only.

Qualitative (categorical) data will be summarized using number of observations (n), and frequency and percentages of patients. Unless stated otherwise, the calculation of percentages will be based on the total number of patients with non-missing data in the set of interest.

Comparisons will contrast outcomes between time points within both ADX-102 1% and Vehicle treatment groups as well as contrast outcomes between each of these treatment groups.

- All primary and secondary efficacy analyses will be performed on the m-ITT population.
- The safety analysis will be performed on the SAF population.

Summary tables will include outcomes for a given treatment at a given time point, the between group differences in change from baseline at each time point, and the within group difference at each time point.

8.2. CONTINGENCIES DUE TO LIMITATIONS INHERENT IN SLS RESEARCH

There will be no adjustment for multiplicity in the analyses of primary and secondary endpoints. The limitations of achieving statistical power due to the limited availability of subjects as well as the longevity and consistency of SLS symptoms make statistical significance difficult to achieve.

In this Phase 3 clinical trial, efficacy decisions must rely upon a clearly observable trend in change in skin scaling, a socially stigmatic symptom of great discomfort that absent a novel treatment will require an inordinate amount of attentiveness on a daily basis for the life of the patient. Thus, significance levels are provided in this clinical trial as an additional index of change rather than an inferential expectation.

If warranted by observed data characteristics relative to model assumptions, non-parametric methods and small sample statistical methods may be substituted for one or more of the below anticipated model based analyses. The rationale for any such change will be provided.

Finally, if statistical power is materially increased through the addition of one or more continuous or stratification covariates to a statistical model described in this SAP, the model will include the covariate(s). Analogously, if stratification adds power to a non-parametric or small sample procedure, the analysis will include stratification.

8.3. DATA CONSIDERATIONS

Due to the limited sample size for Part 1 of the clinical trial, descriptive statistics are planned for the primary and secondary endpoints. Inferential statistics will be used for the primary analysis.

8.4. KEY DEFINITIONS AND TERMINOLOGY

Reference start date and study day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Baseline Value

For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of study drug.

Change from Baseline.

Change from baseline for a given endpoint is defined as the difference between a post-treatment study day value and the baseline variable value and will be calculated directionally as post-study minus baseline.

Note that for the VIIS, it is planned that a single investigator will complete this instrument prior to randomization on day 1 of Part 1.

Day 1 (Baseline)

Day 1 is the earliest day that the study drug is first initiated.

Age

Age is calculated as the number of whole years from a subject's date of birth to the date of informed consent.

Study Visit.

Study visit is the nominal visit as recorded on the eCRF.

Total Days on Study

Total days on study is defined as the number of days from Day 1 to the date of completion or early termination.

Last Dose of study drug

Last dose of study drug is defined as the number of days from day 1 to the date of last dose of study drug.

Duration of SLS.

The duration of SLS is defined as the number of whole years from the date of onset of SLS diagnosis to the date of informed consent.

Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Treatment Period

The Treatment Period covers the duration that a patient is in the study from Baseline (Day 1) to Week 24.

Safety Follow-up Period

The Safety Follow-up Period continues for 28 days after the last dose of study treatment at Week 24 through Week 28.

Definition of Study Completion

A patient will be defined as "completed" if she or he completes the Week 24 study visit.

End of Study Definition

End of study is defined as the date when the patient has completed one of the following: completed the follow-up visit after the Week 24 visit, permanently discontinued from the study, or lost to follow-up.

Day of Study Termination

Day of study termination = Termination Date – Date of Baseline (Day 1) + 1.

Percent Change from Baseline

Percent CFB = 100 * (Post-baseline value – Value at baseline) / Value at baseline

8.5. MISSING DATA

All available safety, PK and efficacy data will be included in data listings and tabulations. No imputation of missing data is planned for primary and secondary endpoints. Abnormal values for assessments (outliers) will be confirmed during the DRM and the primary analysis may be performed with and without inclusion of outliers.

IMPUTATION OF INCOMPLETE DATES.

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. In an effort to minimize bias, the project statistician will impute dates in a systematic, reasonable manner. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

Incomplete/missing start and stop dates will be handled as follows:

Table 8.4.1: Imputation of missing dates

Missing	Imputation
Start day	The start day will be imputed as the first day of the month with the following exception: if the partial date is the same month and year as the date of first dose of double-blind medication, then the partial date will be imputed as the date of first dose of double-blind.
End Day	The end day will be imputed as the last day (28/29/30/31) of the month.
End Day and Month	The end date will be imputed as the 31st of December or last day of study follow up.

For all other data, all available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, i.e., missing data will not be replaced; missing data will be handled as 'missing' in the statistical evaluation.

8.6. VISIT WINDOWS

The safety and efficacy data will be analyzed per study visit; the named visit as collected on the CRF will be displayed.

During the course of the study, blood draws and certain laboratory measurements for some subjects were delayed. A subset of subjects also experienced a 'treatment interruption' during which treatment was interrupted due to laboratory findings. Further detail will be provided in the Clinical Study Report. As a result, some study visits to occurred outside the pre-specified visit window. In the case where a scheduled study visit was delayed, the labelled study visit from the raw database will be used.

All unscheduled visit values will be excluded from summary tables but will be included on data listings.

8.7. POOLING OF CENTERS

No investigation of center effects is planned. Data from all centers will be pooled.

9. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

9.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized by treatment group and overall in terms of the number and percentage of subjects who were randomized, completed the clinical trial and discontinued from the clinical trial.

The number and percentage of subjects prematurely discontinued from the clinical trial and the reasons for discontinuation will be summarized by treatment group and overall. Subjects who are not discontinued from the clinical trial will be considered completers.

The reasons for study discontinuation that will be summarized include: (AE, protocol violation, administrative reasons (e.g., inability to continue, lost to follow up), sponsor termination of study, subject choice, and other.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects.

All data will be listed.

9.2. EXPOSURE AND TREATMENT COMPLIANCE

9.2.1. Extent of exposure

The duration of exposure during the treatment period will be expressed as the time in days from the first treatment through to last treatment day (inclusive). This is given by the following formula:

A subset of subjects had a treatment interruption. When study drug was reinstated many of these subjects still received the full course of study medication. To account for these cases, exposure to study drug will be calculated using the following formula:

Duration (days) = (date last double blind dose – date first double blind dose + 1)-Total days ‘treatment interruption’.

Duration of exposure, number of doses received and doses delayed, missed or not per protocol will be summarized for the SAF using summary statistics for continuous variables.

Drug exposure in grams, defined as the number of tubes used at each visit converted into grams as 15*number of tubes and %BSA treated for the whole study part and each dosing period (20%, 40-45% and 80-90%) will also be summarized.

9.2.2. Treatment Compliance

Study Treatment compliance (%) will be calculated as the actual number of doses divided by the prescribed number of doses, multiplied by 100 and summarized by treatment group.

These numbers will be determined by the number tubes/day dispensed and returned unused by the patient.

[redacted]

All data will be listed; subjects with a treatment interruption will be flagged in the listing.

9.3. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All demographic and baseline characteristic data will be summarized by treatment group using descriptive statistics for all patients for each of the following analysis sets: SAF, m-ITT and PPP.

- Gender, Ethnicity and Race will be summarized by the number and percentage of patients in each category
- Age (years), height (cm) and weight (kg) captured at Screening will be summarized as a continuous variable
- Body Surface Area (m^2) at captured at Screening
- Estimated Glomerular Filtration Rate (eGFR, ml/min/BSA)
- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Heart Rate (beats/minute)
- Pulse (beats/min)
- Respiratory Rate (breaths/min)

Unless otherwise stated, percentages will be calculated out of the number of patients in the given Analysis Set

All demographic data will be listed.

9.4. MEDICAL HISTORY AND CONCOMITANT DISEASES

Descriptions of medical history and concomitant disease findings prior to the Screening Visit will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher. Information related to the following disease types or systems: head, eyes, ears, nose and throat (HEENT), respiratory, neurological, cardiovascular, musculoskeletal, metabolic/endocrine/nutritional, hematopoietic, allergies, abdominal and general appearance.

Medical history, as recorded at Screening, will be summarized for the Safety Population (SAF) by the number and percentage of patients within each system organ class (SOC) and preferred term (PT), by treatment.

A disease or illness reported as medical history without a start date will be included in medical history without a date assigned.

Medical history will be sorted by descending overall frequency, by SOC and PT in the summary table. Medical history data listings will be sorted by treatment, patient number, start date, SOC and PT.

9.5. OTHER BASELINE CHARACTERISTICS

The age of diagnosis of SLS, genotype, and all prior treatments for SLS at screening will be summarized by treatment group using summary statistics. The presence or absence of SLS symptoms, including motor disability in the arms and/or legs, foot deformity, speech disorder, seizures, and photophobia, will be summarized.

9.6. MEDICATION

Previous and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO-DD). The number and percentage of patients taking prior medications and concomitant medications will be summarized overall by ATC (Anatomical Therapeutic Chemical) Levels 2 and 4, in separate tables, for all patients in the SAF population.

Prior and concomitant medications will be presented in a data listing for all patients in the SAF population.

9.6.1. Prior Medication

Prior medications will be defined as medications documented on the Prior and Concomitant Medications eCRF as having started within 30 days prior to assent/ consent and stopped prior to baseline visit.

9.6.2. Concomitant Medication

Concomitant medications will be defined as medications documented on the Concomitant Medications eCRF as having started within 30 days prior to assent/ consent and ongoing at the time of or after the first dose of double blind study medication or any new medications started after the first dose of double blind study medication.

10. EFFICACY

Overview

All efficacy variables are initially captured on a continuous or semi-continuous scale. Observed values at the time of collection and change from baseline value at each time point will be summarized descriptively. Mixed Model Repeated Measures (MMRM) analysis will be carried out on change from baseline scores for the primary and secondary efficacy variables for reproxalap-treated subjects (not vehicle-treated subjects). Hereinafter, in this Statistical Analysis Plan, drug-treated shall mean reproxalap-treated. Additional analyses in drug-treated subjects will be performed on certain efficacy variables. Further details of the tests to be performed on each endpoint are given in Table 10.2.1 below. The specific additional analyses are described below.

1) The VIIS outcomes will be converted to a binary response variable (yes/no) defined as a 1-unit and 2-unit improvement from baseline. The probability of response in drug-treated subjects will be analyzed over time using generalized estimating equation (GEE) models.

2) Change from baseline over time will be converted into an Area Under the Curve (AUC) value using the trapezoidal rule. AUC for drug-treated subjects will be inferentially compared to zero (0 = no change from baseline) using a linear model.

3) Time to first response (1-unit improvement and 2-unit improvement) for the VIIS outcomes (scaling and erythema) will be evaluated using a Kaplan Meier survival curve for drug-treated subjects.

Tables will be generated for each endpoint presenting appropriate descriptive and inferential statistics to convey the results of the analyses. Tables will be augmented by figures for selected analyses.

10.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary endpoint for the clinical trial is change from baseline in the VIIS scaling score in drug-treated subjects, as assessed by the investigator, in the target efficacy area. The VIIS provides five-point Likert scales (range 0-4) for erythema and scaling that increases in severity with increasing score values.

The target efficacy area for all efficacy analyses will be one of the body sites as defined in the VIIS tool (with the exception of Dorsal foot) with Grade 2 or higher on baseline VIIS scaling score as assessed by the Investigator.

The within-group change from baseline will be the primary focus of interest in the primary analysis.

Primary Analysis

A Mixed Model Repeated Measures (MMRM) model will be used to perform the primary analysis of the VIIS scaling score in drug-treated subjects (not vehicle-treated subjects). Change from baseline VIIS scaling score will serve as the dependent variable. The model will include the baseline value (Visit 1) as a covariate (if useful) and visit (treated as a factor; the visit term will cover Visit 1, 5, 7, and 8). An unstructured covariance structure will be assumed and a Type III model will be evaluated. If the unstructured covariance structure matrix results in a lack of convergence, then Toeplitz (TOEP), first-order autoregressive (AR1), compound symmetric (CS) covariance structure will be used in that order. If the MMRM model cannot hit convergence with any correlation structure, then a within-subject t-test (baseline-adjusted, if useful) will be used to compare baseline to Visit 8. It should be noted that improvement will be signified by the existence of a negative change score.

The primary efficacy endpoint will be summarized descriptively by visit and across all visits. The table will contain descriptive statistics on observed values and change from baseline at each time point.

The primary analysis using the MMRM model will be summarized in a consolidated table containing the following:

- Descriptive statistics for change scores at baseline and each post-treatment time point.
- The LS mean change scores with accompanying standard errors and 95% confidence intervals for each visit.
- Within-group contrasts for each given visit.
- Significance levels for the visit effects.

Along with the table detailing the results of the MMRM model, a consolidated table presenting the essential information for the primary analysis will be constructed. The primary endpoint will be deemed to have been met if the Visit 8 (week 24) term is significant, and the term coefficient is negative.

Secondary and Sensitivity Analyses Related to the Primary Outcome Variable

The following analyses will be performed to provide additional insight into VIIS scaling.

Responder Analysis

For drug-treated subjects, responder status will be assigned to a subject if at a given post treatment time point an improved change from baseline of at least 1 VIIS scaling

unit occurs. A Generalized Estimating Equation (GEE) model will be used to evaluate the predicted log odds, odds and probability of response. The model will include the effect of visit (treated as a factor). An unstructured covariance structure will be assumed and a Type III model will be evaluated. If the unstructured covariance structure matrix results in a lack of convergence, then first-order autoregressive (AR1) and compound symmetric (CS) covariance structure will be used in that order.

Results will be captured in a consolidated table that contains the following information:

- Number and percent of observed responders and non-responders at all post-treatment time points;
- Significance levels for the visit effects;
- The model predicted log odds, odds and probability of response with standard errors and 95% confidence intervals for each visit;
- Within-group contrasts expressed as an odds ratio, accompanied by a 95% confidence interval.

AUC Analysis

For drug-treated subjects, AUC for change from baseline over all post-treatment time points will be calculated for each subject using the trapezoidal rule. A linear model comparing AUC to zero (no change from baseline) will be performed.

Survival Analysis

For drug-treated subjects, time to first response (i.e., a one-unit VIIS scaling improvement) will be captured in a Kaplan Meier plot. A hazard rate estimate will be generated.

Analysis for Patients Experiencing one or more Treatment interruptions

The impact of Treatment interruptions on the primary outcome will be evaluated through sensitivity analysis. Patients with a treatment interruption of more than 1 week will be flagged. The same MMRM model of the primary analysis will be conducted on the ITT population with the treatment interruption as a categorical variable and the treatment interruption by treatment interaction as an additional independent variable. The analysis outcome will be summarized in the similar way as the primary analysis. Estimates of the treatment interruption effect variable will also be tabulated.

10.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

Change from baseline will be calculated for all secondary efficacy variables, namely:

VIIS Scores:

- VIIS erythema score
- Central reader assessed VIIS scaling and erythema scores

  Clinical Outcomes Assessments

- The EQ 5D 5L patient/caregiver overall assessment score
- The clinical global impression of severity scale, the patient/observer global impression scales
- The patient-/observer-reported scratching scales,
- The patient-/observer-reported burden of bathing/showering, the patient reported itching scale,
- The CDLQI/DLQI scales,
- Lipid biomarker measurements and TEWL (exploratory biomarkers).

It will be noted that in addition to an overall Visual Analog Scale (0 to 100) assessment that measures self-reported health, the EQ-5D-5L also evaluates, by category (no problem, slight problems, moderate problems, severe problems and extreme problems), the status of a subject in five domains (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression). Guidance documentation for the use of the EQ-5D-5L specifically warns against the conceptualization of these categories as a mathematically meaningful 5-point scale, thus only the VAS scale (not individual domain categorical results) will be statistically evaluated.

The secondary efficacy variables are given in section 6, with further detail of each score given in Table 10.2.1 below. The schedule of assessments is given in Section 4 and each individual score is shown in Appendix 1-Outcome Scales.

Table 10.2.1: Description of secondary efficacy variables

	[redacted]
EQ-5D-5L	[redacted]
Clinical Global Impression of Severity	[redacted]
Patient/Observer Global Impression of	[redacted]

Bother	
Patient/Observer Global Impression of Treatment	[redacted]
Patient/Observer Global Impression of Severity	[redacted]
Patient/Observer Reported Scratching	[redacted]
Patient-Reported Itching	[redacted]
Patient/Observer Burden of Bathing/Showering	[redacted]
Children's Dermatology Life of Quality Index (CDLQI) or Dermatology Life Quality Index (DLQI)	[redacted]
Lipid Biomarkers	Lipid biomarkers will be analyzed from skin cells samples taken from the target efficacy area
TEWL	Evaporation rate value in $g/h/m^2$

Secondary Analysis

The secondary efficacy variables will be analyzed using one or more of the following analyses applied to the primary endpoint:

1. A MMRM generalized linear model applied to secondary efficacy variable change scores derived from observed values;

2. A GEE model applied to secondary efficacy variable scales after dichotomization to reflect response (yes/no);

3. A linear model applied to secondary efficacy variable observed values after transformation to an AUC measurement;

4. A log rank analysis and a proportional hazards model applied to time to first response.

These analyses will be carried out in an analogous fashion as for the primary efficacy variable (*see above for a description of each analysis applied to the primary efficacy variable*).

As with the primary efficacy variable (VIIS scaling), the within-group change from baseline will be the primary focus of interest in the MMRM analysis. Because SLS patient symptoms do not spontaneously improve over time, the within-group comparison provides a clinically meaningful evaluation. The planned analyses for selected secondary efficacy endpoint are outlined in Table 10.2.2.

Table 10.2.2: Analyses of the Secondary Efficacy Variables

Secondary Efficacy Variable	Analyses			
	MMRM	RESPONDER ANALYSIS (Estimating Equation)	AUC (Linear Model)	Survival
VIIS Erythema (Investigator Assessment)	✓		✓	✓
VIIS Scaling (Photographic Assessment by Central Reader)	✓	✓	✓	✓
VIIS Erythema (Photographic Assessment by Central Reader)	✓		✓	✓

[1]The 100 mm VAS will be analyzed using MMRM. Categorical outcomes will be displayed in a contingency table (Treatment x Category) containing frequency and percent occurrence of categorical outcomes.

[2]The total score (i.e., sum of 0 – 3 rating on 10 individual questions) will be analyzed using MMRM for change scores and a linear model for AUC. Responses to individual questions will be provided in a listing.

10.3. SUBGROUPS ANALYSIS

Subgroup analysis on age group

To account for treatment differences between age ranges of subjects, analyses of efficacy and laboratory summary tables will be displayed by adult only (≥ 18 years), pediatric only (<18 years) and combined adult and pediatric.

- Pending the final number of pediatric patients enrolled and distribution of age; additional analysis may be performed for patients ≤ 10 years of age and >10 to < 18 years of age

10.4. EXPLORATORY ANALYSES

Efficacy Endpoint

Additional exploratory analysis maybe conducted on primary efficacy endpoint by sponsor. Exploratory analysis will be conducted for both targeted efficacy area and for combined regions as appropriate, such as but not limit to:

1) Repeat primary analysis MMRM model on drug-treatment patients to evaluate change from baseline for combined visits (Visit 5, Visit 7 and Visit 8)

2) Repeat primary analysis MMRM model on all treated patients (including both drug-treatment and vehicle-treated patients) to evaluate change from baseline for combined visits (Visit 5, Visit 7 and Visit 8) and each individual visit

3) all patients (including both drug-treatment and vehicle treated patients)

4) Responder analysis for patient with at least 2 units VIIS scaling improvement from baseline at any post treatment time point

5) Survival analysis for the time to first response defined as 2 units VIIS scaling improvement from baseline

6) AUC analysis for change from baseline of all VIIS regions combined

7) Analyze change from baseline of VIIS total score at week 24 analysis using MMRM model

8) Contralateral analysis of between group contrast comparing VIIS scaling score change from baseline between treated area vs. untreated area

9) To further evaluate the impact of 'treatment interruption' on treatment effect, the same analysis approach used for primary analysis on primary endpoint may be repeated on following subgroups:

    a. patient with 'treatment interruption' for at least 1 week

b. patient without 'treatment interruption' or with 'treatment interruption' for less than 1 week

Biomarker Endpoint

Selected skin lipid bio markers, captured as the post-treatment value at Week 24 or at an early termination visit as the post-treatment minus baseline value (change score), may be correlated with various outcome symptom scales or functions of outcome symptom scales. Such skin lipid biomarkers are listed in Table 10.3.1.

Exploratory analyses will be performed on lipid biomarkers from skin cell analysis and TEWL using the following methodologies:

Analysis between biomarkers and outcome scales (investigator and central reader VIIS scaling and erythema) for time matched assessments will be performed using appropriate correlation procedures.

Table 10.3.1: Lipid Values Selected for correlational analysis (captured as post treatment values or change score values)

Table 10a. Lipid Values Selected for Correlational Analysis (Captured as Post Treatment Values or Change Score Values)

Abbreviation	Variable
Total CER	Total Ceramides
CE	Cholesterol Ester
CHOL	Cholesterol
CE/CE + CHOL	Ratio Cholesterol Ester/ Cholesterol Ester plus Cholesterol
CHOL:CER	Ratio Cholesterol/Ceramide
CER1 EOS	Omegahydroxysphingosine (aka. Ceramide 1)
CER2 NS	NS: Nonhydroxysphingosine (aka. Ceramide 2)
CER5 AS	Alphahydroxysphingosine (aka. Ceramide 5)
EOS: tCER	Ratio Omegahydroxysphingosine/Total Ceramides
tEO	Total omega-esterified ceramides
EOS 68:3;2	Omegahydroxysphingosine subspecies with a 68-carbon total chain length, containing 3 double bonds and 2 hydroxyls
EOS 70:3;2	Omegahydroxysphingosine subspecies with a 70-carbon total chain length, containing 3 double bonds and 2 hydroxyls

11. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF population.

The safety outcomes include dermatological endpoints, vital sign measurements, physical examinations, hematology and chemistry laboratory testing, ECG readings, use of concomitant medications, and incidence, severity and duration of adverse events and TEAEs.

Safety tables will be presented by treatment and overall.

Tables variously organized by preferred terms, system organ class, treatment emergence, treatment relationship, severity and study termination will be presented for AEs, TEAEs, unexpected AEs and SAEs.

Descriptive statistics will be presented by treatment and time for safety laboratory values or in change tables for categorized lab variables (e.g., normal vs. abnormal, present vs. absent). Other safety information (e.g., normality of dermatological endpoints, normality of vital signs, normality of physical examinations, normality of ECG outcomes, concomitant medication usage) will be summarized in tables and medically evaluated.

No inferential statistical testing is planned on the safety data, all data will be summarized and listed only. If any post-hoc inferential testing of any variable seems appropriate, the comparison will be made using an appropriate statistical test.

11.1. SAFETY NARRATIVES

Treatment and vehicle group safety narratives will be written. If required a safety narrative will be written for selected subjects.

11.2. ADVERSE EVENTS / ADVERSE DRUG REACTIONS

Adverse events (AEs) will be coded using a Medical Dictionary for regulatory Activities (MedDRA) version 20.0 or later preferred term (PT) and system organ classification (SOC).

Patients with multiple events within the same System Organ Class and/or same Preferred Term are only counted once within the respective frequencies.

All reported AEs (whether treatment emergent or not) will be included in by-patient AE listings. Sorting will be by patient, date of event, SOC, PT and then verbatim description.

An AE will be considered treatment emergent (TEAE) if it begins or worsens in severity after the first dose of the double-blind Study Treatment through 28 days after the last dose of Study Treatment, or the date of initiation of another investigational agent or surgical intervention or rollover to the extension study, whichever occurs first. Partial AE start dates will be imputed as detailed in Section 8.5.

ALL AEs and TEAEs.

Incidence of AE and TEAEs will be presented by SOC and PT. The AE and TEAEs listings will include treatment group, the duration of the event, it severity and whether it was considered to be related to treatment. The listings will also include the number of days between first dose and event.

SOC and PT will be presented, where the severity per patient will be counted at each level of summarization. In addition, a summary of all TEAEs by relationship to Study Treatment (related, not related), SOC and PT will be presented, where the strongest relationship to Study Treatment per patient will be counted at each level of summarization.

SEVERITY.

Severity is classified as mild, moderate, severe or life-threatening.

Missing severity for TEAEs will be counted as ‘Severe’.

RELATIONSHIP TO STUY MEDICATION.

Relationship, as indicated by the investigator, will be defined as definitely, possibly, unlikely or not related.

Adverse events with a missing relationship to study medication will be noted as “related” to study medication. If a patient reports the same AE more than once within the same SOC/PT, the AE with the strongest relationship to study medication will be used in the relationship summaries.

TEAEs LEADING TO STUDY DRUG DISCONTINUATION.

TEAEs leading to permanent discontinuation of study medication are those events that are marked as ‘discontinued from study’ under action taken with study medication in the adverse events page of the CRF.

For TEAEs leading to permanent discontinuation, a summary table with incidence rates (frequencies and percentages) by SOC and PT will be prepared.

SERIOUS ADVERSE EVENTS.

Serious adverse events (SAEs) are those events recorded as a "serious Adverse Event (Y)" on the adverse events page of the CRF. A summary of serious TEAEs and Serious treatment related TEAEs by SOC and PT will be prepared.

ADVERSE EVENTS LEADING TO DEATH.

Adverse events leading to death are those events with 'Death' recorded under Outcome in the adverse events page of the CRF. A summary of TEAEs and SAEs leading to death by SOC and PT will be prepared. A listing of AEs leading to death will be included with the TEAEs flagged.

SUMMARY TABLES AND LISTINGS.

Summary tables will be based on treatment emergent adverse events (TEAEs). The incidence of TEAEs will be presented using counts and percentages of patients with TEAEs and tabulated by SOC and PT. SOC will be sorted in descending frequency and PT within SOC will be sorted by descending frequency based on the incidence across patients overall. If a patient has multiple occurrences (start and stop) of an event associated with a specific SOC or PT within a SOC, a patient will only be counted once in the incidence count for the SOC or PT within SOC respectively.

An overall summary table of AEs by treatment group will be presented detailing the number and percentage of patients, and number of events for the following categories:

- At least one AE
- At least one TEAE;
- Serious TEAEs;
- Treatment Related TEAEs;
- Treatment Related Serious TEAEs;
- TEAEs leading to Discontinuation from Study Treatment;
- TEAEs resulting in death;

The incidence of all TEAEs by SOC and PT will be presented for the following:

- All TEAEs;
- Serious TEAEs;
- Treatment Related TEAEs;
- Treatment Related Serious TEAEs;
- TEAEs leading to Discontinuation from Study Treatment;
- TEAEs resulting in death;

Treatment listings will include the treatment group, start and stop dates/times of the AE, and days on study relative to the day of first dose of Study Treatment.

The following additional listings will be provided:

- Listing of deaths
- Listing of Serious TEAEs
- Listing of non-treatment-emergent SAEs
- Listing of TEAEs leading to withdrawal or temporary withdrawal of Study Treatment
- Listing of all AEs with a flag for TEAEs and onset (Prior = prior to first dose of double-blind medication, or Treatment = on or after first dose of double-blind medication.)

11.3. CLINICAL LABORATORY EVALUATIONS

Laboratory tests will be performed at Screening and periodically throughout the clinical trial as described in the schedule of events, Section 4. Only data collected by the central laboratory will be included in the analyses with the exception of the screening safety data. Standard international units will be used for all summaries. Laboratory tests within each category and scheduled visit are given in Table 9.4.1. Data for all visits, scheduled or unscheduled, will be listed.

At least one laboratory measurement obtained subsequent to at least one dose of Study Treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline or screening measurement is also required.

Table 11.3.2: Laboratory Tests and Scheduled Study Visits

Laboratory Category	Laboratory Tests Included
Hematology	hemoglobin, hematocrit, red blood cell (RBC) count, RBC morphology, white blood cell (WBC) count with differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and absolute platelet count.
Chemistry	albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO2), chloride, creatinine, creatinine phosphokinase (CPK), glucose, phosphate, potassium, sodium, total protein, and uric acid.
Urinalysis	bilirubin, glucose, ketones, blood, nitrite, pH, protein, specific gravity, and microscopy (if indicated by macroscopic findings).
Other	Urine Pregnancy Test for Female Subjects
Estimated Glomerular Filtration Rate (eGFR)	Adult population (≥ 18 years of age): eGFR will be calculated by the MDRD equation at baseline:

	eGFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American) (Levey 2009) Pediatric population (3 – < 18 years of age): eGFR will be calculated by the Schwartz equation at baseline: eGFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / Creatinine in mg/dL (Schwartz 2009)

- Actual (observed) values and changes from baseline in hematology and clinical chemistry laboratory parameters will be summarized by treatment group at each scheduled visit

- The number and percentage of subjects with laboratory measurements outside of the normal range will also be summarized by treatment group and visit.

- Shift from Baseline at each post-Baseline visit will be provided by treatment group in a 3-by-3 contingency table. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

- Box and Whiskers Plots by visit will be produced for all quantitative hematology and clinical chemistry parameters.

- Actual (observed) values in urinalysis and other laboratory parameters will be summarized by treatment group.

- The number and percentage of subjects with laboratory measurements outside of the normal range will also be summarized by treatment group and visit.

- Incidence of patients that have Potentially Clinically Significant (PCS) values at any post-baseline visit.

All data will be listed.

11.4. VITAL SIGNS

The following vital sign data will be collected at all study visits:

- Sitting Systolic Blood Pressure (SBP) (mmHg)
- Sitting Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (beats/min)
- Respiratory Rate (breaths/min)
- Body Temperature (degree Celsius or Fahrenheit)
- Body Weight (kg)
- Height (cm)

At least one vital sign measurement obtained subsequent to at least one dose of Study Treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a Baseline or screening measurement is also required.

For all parameters, actual (observed) values will be presented and summarized for all scheduled study visits by treatment and overall.

Vital signs data will be fully described using descriptive statistics. Actual values and change from baseline will be summarized.

Vital signs data will be summarized by parameter, visit and time point, treatment group and overall for all subjects in the SAF.

All vital signs data shall be listed chronologically by treatment group for subjects in the SAF.

11.5. ECG

Electrocardiograms (ECGs) will be read centrally and the following ECG parameters will be reported:

- Overall assessment of ECG (by central reader) will be tabulated:
    - Normal
    - Abnormal, Not Clinically Significant
    - Abnormal, Clinically Significant.
    - The results will be included in a per patient listing.

ECG data, along with the date and time of assessment, will be listed for all subjects in the SAF population. Any clinically significant ECG/ Holter results may be recorded as an AE.

ECG data will be classified as “Normal”, “Abnormal, Not Clinically Significant” or “Abnormal, Clinically Significant”.

ECG data will be summarized by visit, and by treatment group and overall for all subjects in the SAF population. Summary tables will show the number and percentage of subjects with normal, abnormal non-clinically significant (NCS) or abnormal clinically significant (CS) findings at each visit.

Shift tables for ECG result to each study visit on treatment will be provided. Subjects with both a non-missing baseline and at least one non-missing post-baseline finding will be included in the shift table.

ECG data will also be listed chronologically for all subjects in the SAF.

11.6. PHYSICAL EXAMINATION

A physical examination will be performed according to the Schedule of Assessments described in Section 4. Body systems findings will be classified as “Normal” or “Abnormal” and abnormalities are described. Any physical examination findings are reported as medical history or adverse events.

Physical examination findings will be fully summarized using the frequency and percentage of subjects under each classification for each body system with an indication as to whether the finding is clinically significant. Summary tables will be sorted by parameter, visit/time point and treatment group, and overall, for all subjects in the SS.

Results from physical examinations will be listed chronologically for all subjects in the SAF population.

11.7. DERMATOLOGY EXAMINATION

A full dermatological examination will be performed according to the Schedule of Assessments described in Section 3.8 and will comprise of the dermatological examination of the following body systems: Scalp and Hair, Face, Neck, Chest and Abdomen, Back, Arms, Hands and Fingernails, Legs, Feet and Toenails and Other. Any clinically significant dermatological examination results may be recorded as an AE.

Body systems will be classified as “Normal” or “Abnormal” and abnormalities are described.

Dermatological examination findings will be fully summarized using the frequency and percentage of subjects under each classification for each body system. Summary tables will be sorted by parameter, visit/time point and treatment group, and overall, for all subjects in the SS.

12. INTERIM ANALYSES

No interim analyses are planned for this clinical trial. The analysis at the end of Part 1 is a per-protocol planned analysis and will be fully unblinded.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Analysis visit windows will not be applied given that the analysis visits are not going to be within the 3-5 days as stated in the protocol, instead the visits will be displayed as collected on the CRF.

14. PROGRAMMING CONSIDERATIONS

14.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format and pdf format.
- Numbering of TFLs will follow ICH E3 guidance (or other logical order for *studies performed according to GPP)*

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size eight which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TLFs will have a minimum 1-inch margin on all four sides.
- Headers and footers for figures will be in Courier New font, size eight which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
  Aldeyra Protocol ADX-102-SLS-006 (Syneos Health study number 1009367)
  Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

14.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation, etc.), then only those categories for which there is at least one subject represented in one or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for one or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to one more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX

Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to three decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than one term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values that cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just one category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the clinical trial.
- Units will be included where available

14.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. INDEX OF TABLES

See Excel spreadsheet

17. INDEX OF FIGURES

See Excel spreadsheet

18. INDEX OF LISTINGS

See Excel spreadsheet

19. MOCK-UPS

19.1. TABLE MOCK-UPS

Table templates should be included for all unique tables. Include footnotes and any programming notes, if appropriate.

19.2. FIGURE MOCK-UPS

Figure templates should be included here, if required. A detailed description of the figure may be used in lieu of a figure template. For example:

Figures 14.4.1.4: Mean Plasma Concentration Over Time by Treatment Group (PK Analysis Set)

PROGRAMMING NOTES:

- This figure is a line plot and corresponds to Data Listing XXXXX Drug Concentration Data.
- Axes: Vertical axis: Mean plasma drug concentration (units), with range dependent on the observed values. Include vertical axes on both the left and right sides of the figure. Horizontal axis: Nominal time Post-Dose (hours), with range from 0 hour (pre-dose) to X hours post-dose.
- Solid lines should connect the data points for the means. One line per treatment group will be plotted.
- Solid circles will be used for mean values in treatment group X; triangles will be used for mean values in treatment group Y. Include a legend that indicates the treatment group a circle represents and the treatment group a triangle represents.
- Error bars should be used at each visit that represents inter-quartile ranges
- Include the number of subjects with data at each time point below the horizontal axis.
- Include footnote “Values below limit of quantification were imputed to xxxxx.”
- The Syneos Health stamp (program name, date, etc.) should appear at the bottom of the figure.

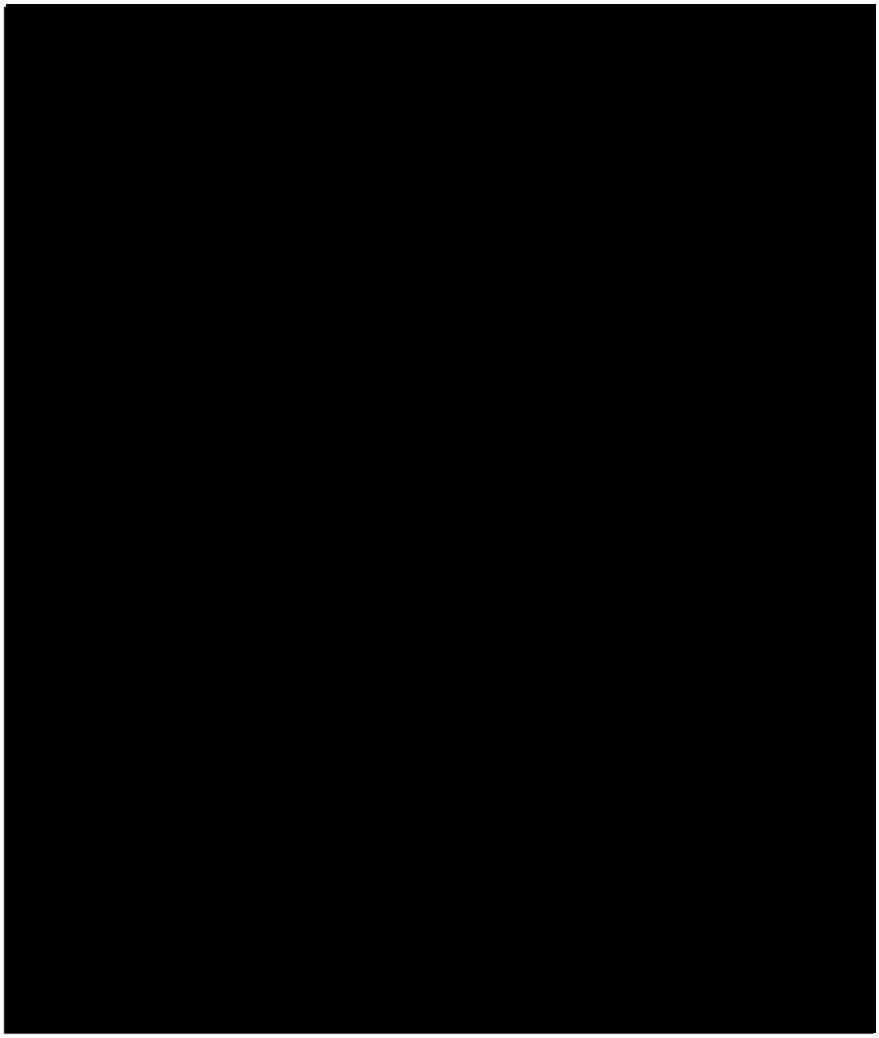
19.3. LISTING MOCK-UPS

Include the analysis set in the title, if appropriate. All listings should be sorted by centre, and either randomized treatment (usually baseline/efficacy) or actual treatment (usually safety/PK/PD). Add in programming notes for additional direction

on sort order as well as any other programming issues, as applicable.

20. APPENDIX 1-OUTCOME SCALES

20.1. VIIS DESCRIPTION



ADX-102-SLS-006_Visual Index for Ichthyosis Severity_V1.0_20Feb2018
Confidential

20.2. VIIS COLLECTION FORM

Subject ID: _____
Site: _____
Visit / Week: _____/ _____

Visual Index for Ichthyosis Severity

Note: The body site that has been selected as the Treatment Efficacy Area should be the first site assessed

Body Site	Erythema Score (0-4)
Left Upper Back	
Right Upper Back	
Left Upper Arm	
Right Upper Arm	
Left Lower Leg	
Right Lower Leg	
Left Dorsal Foot	
Right Dorsal Foot	

Body Site	Scale Standard Used (Indicate "L" for lamellar or "K" for keratoderma)	Scale Score (0-4)
Left Upper Back		
Right Upper Back		
Left Upper Arm		
Right Upper Arm		
Left Lower Leg		
Right Lower Leg		
Left Dorsal Foot		
Right Dorsal Foot		

ADX-102-SLS-006_Visual Index for Ichthyosis Severity_Collection Form_V1.0
Confidential

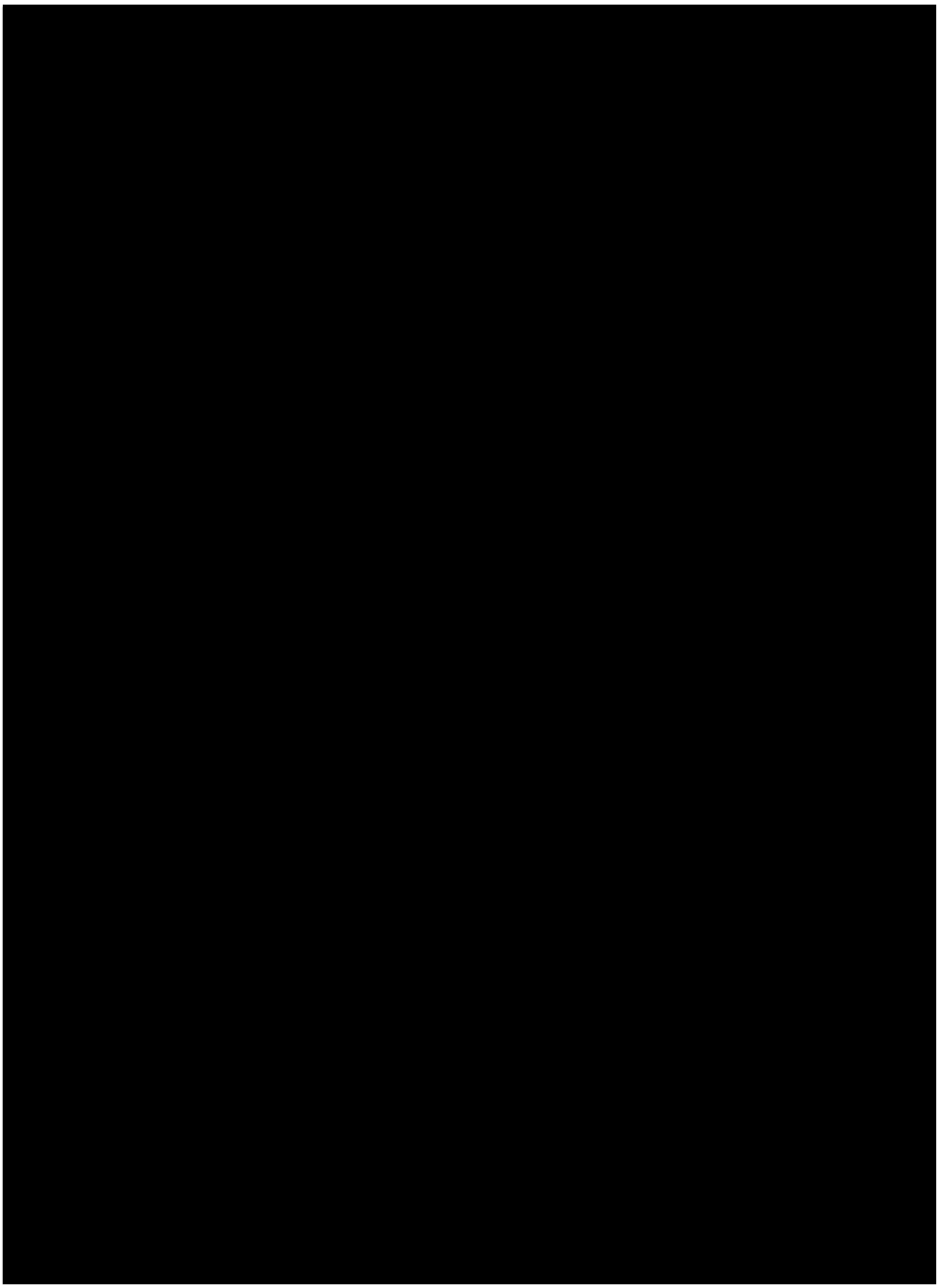
Investigator initials: _____

20.3. EQ-5D-5L

20.3.1. EQ-5d-5l descriptive system scoring

ODAY.

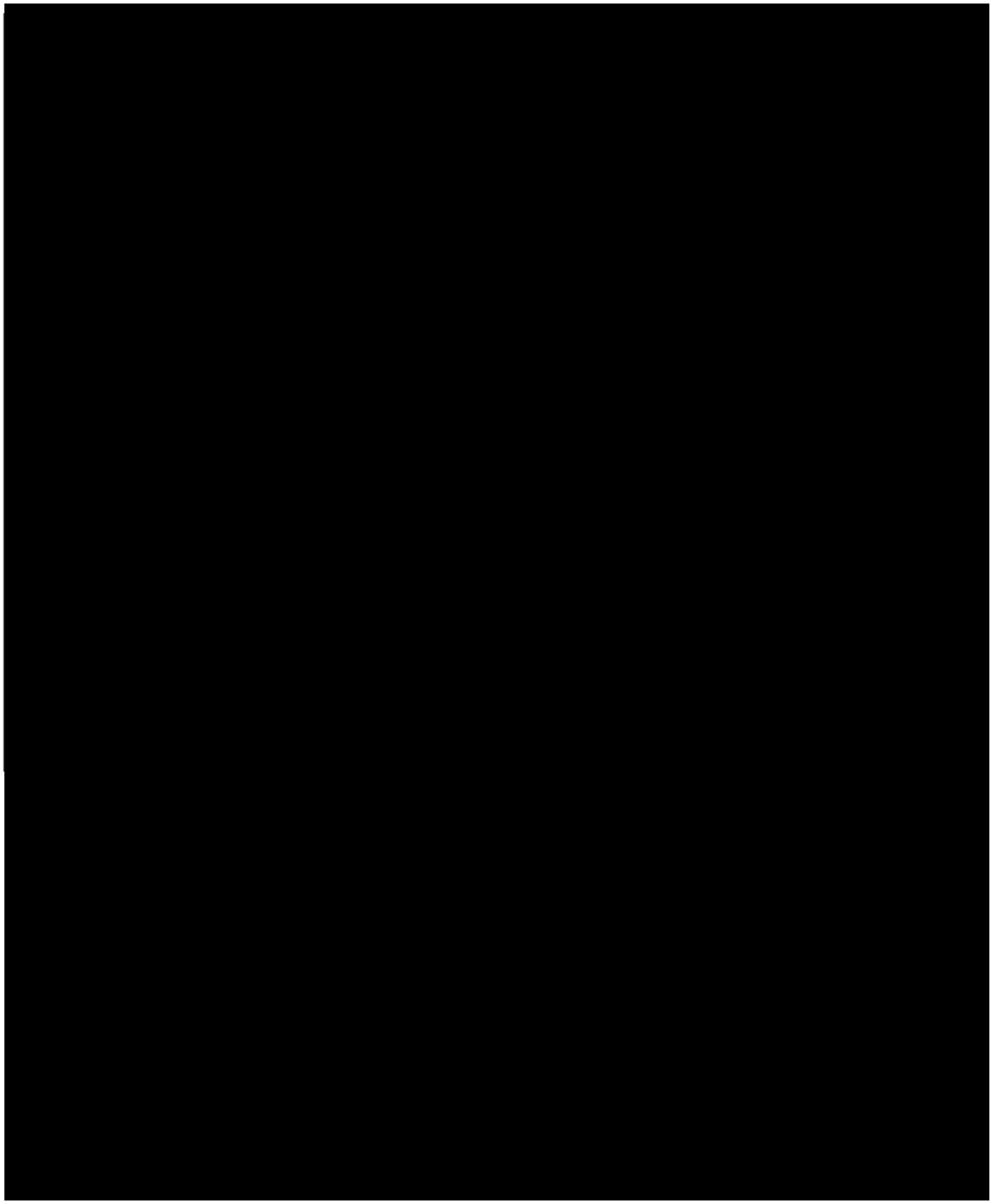
20.3.2. EQ-5D-5L VAS scoring



20.4. CLINICIAN GLOBAL IMPRESSION OF SEVERITY (CGIS)

20.5. PATIENT REPORTED OUTCOME SCALES

20.5.1. Patient Global Impression of Severity (PGIS)

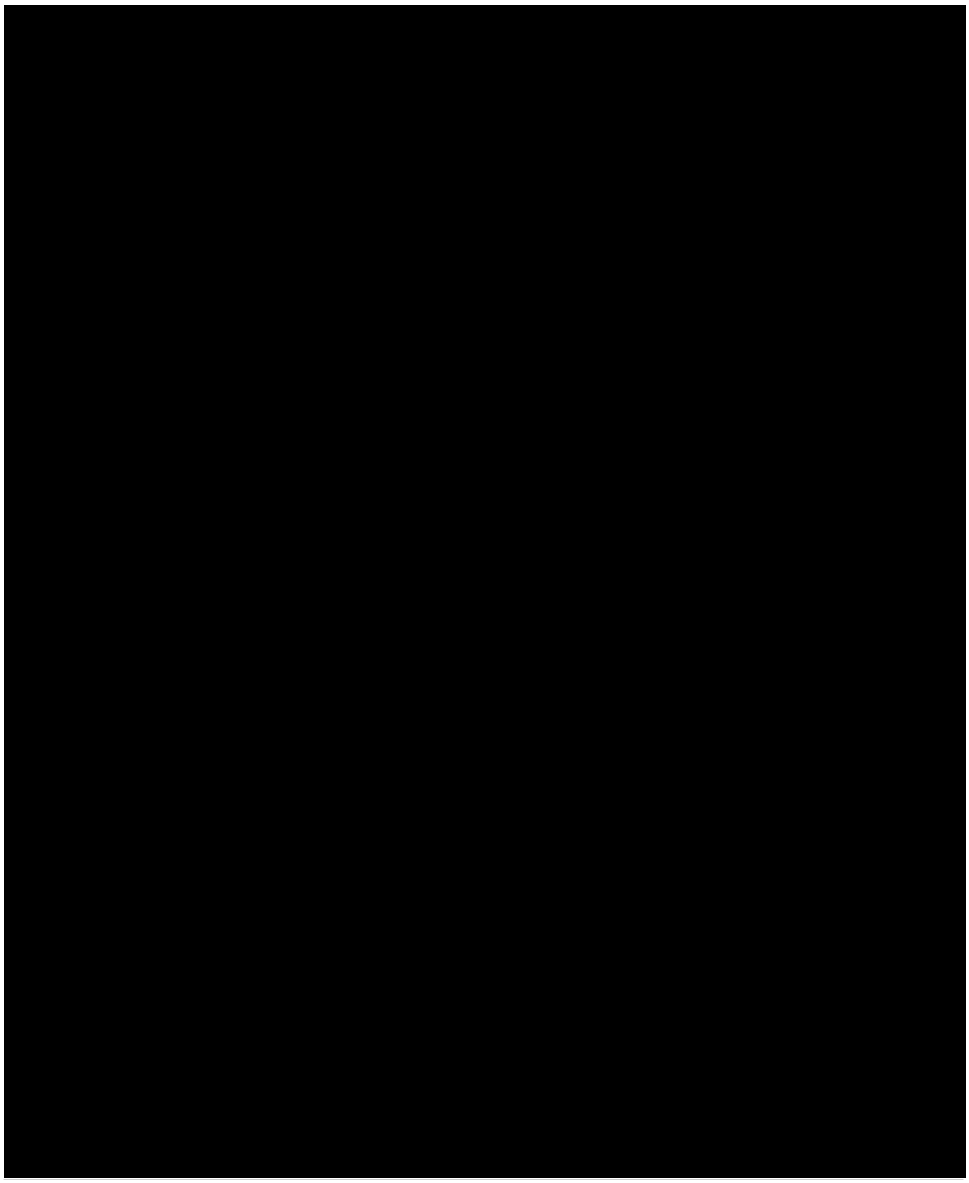


20.5.2. Patient Global Impression of Bother (PGIB)

20.5.3. Patient Global Impression of Treatment (PGIT)

20.5.4. Patient-Reported Itching/ Scratching Questionnaire (PRIQ/PRSQ)

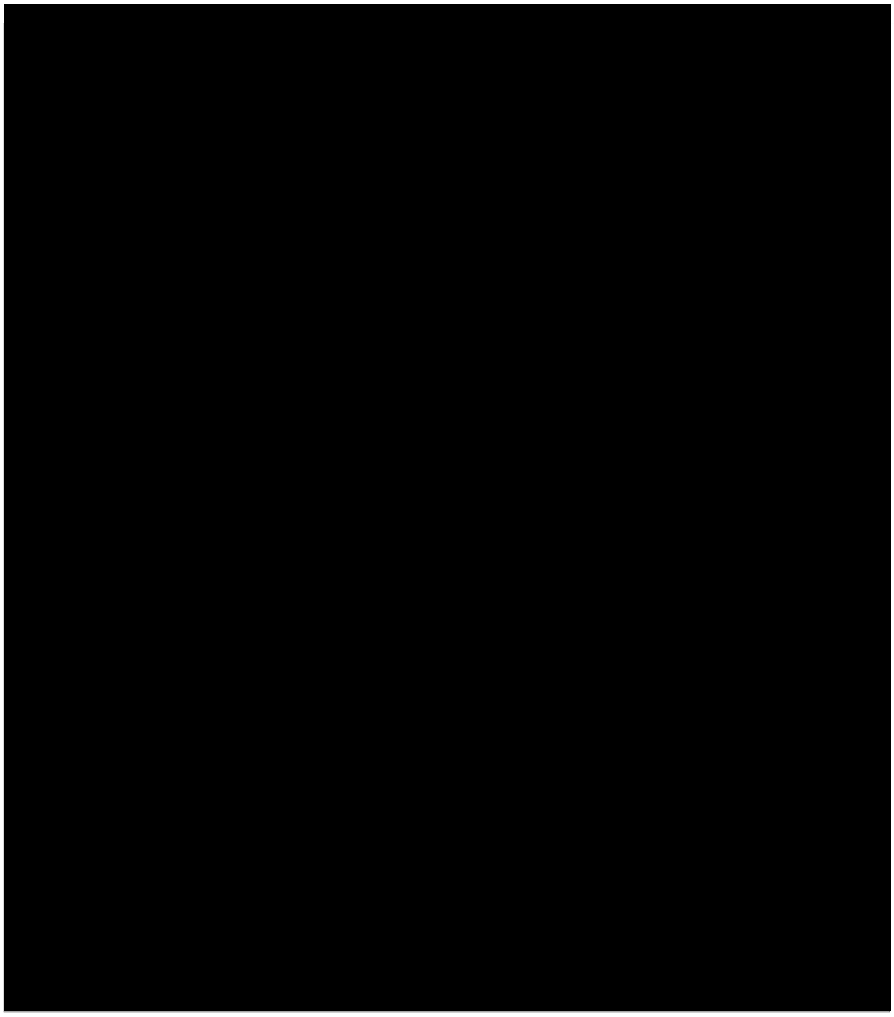
20.5.5. Patient Reported Burden of Bathing / Showering Questionnaire (PRBBQ)



20.6. OBSERVER REPORTED OUTCOME SCALES

20.6.1. Observer Reported Scratching Questionnaire (ORSQ)

20.6.2. Observer-Reported Burden of Bathing/Showering Questionnaire (ORBBQ)

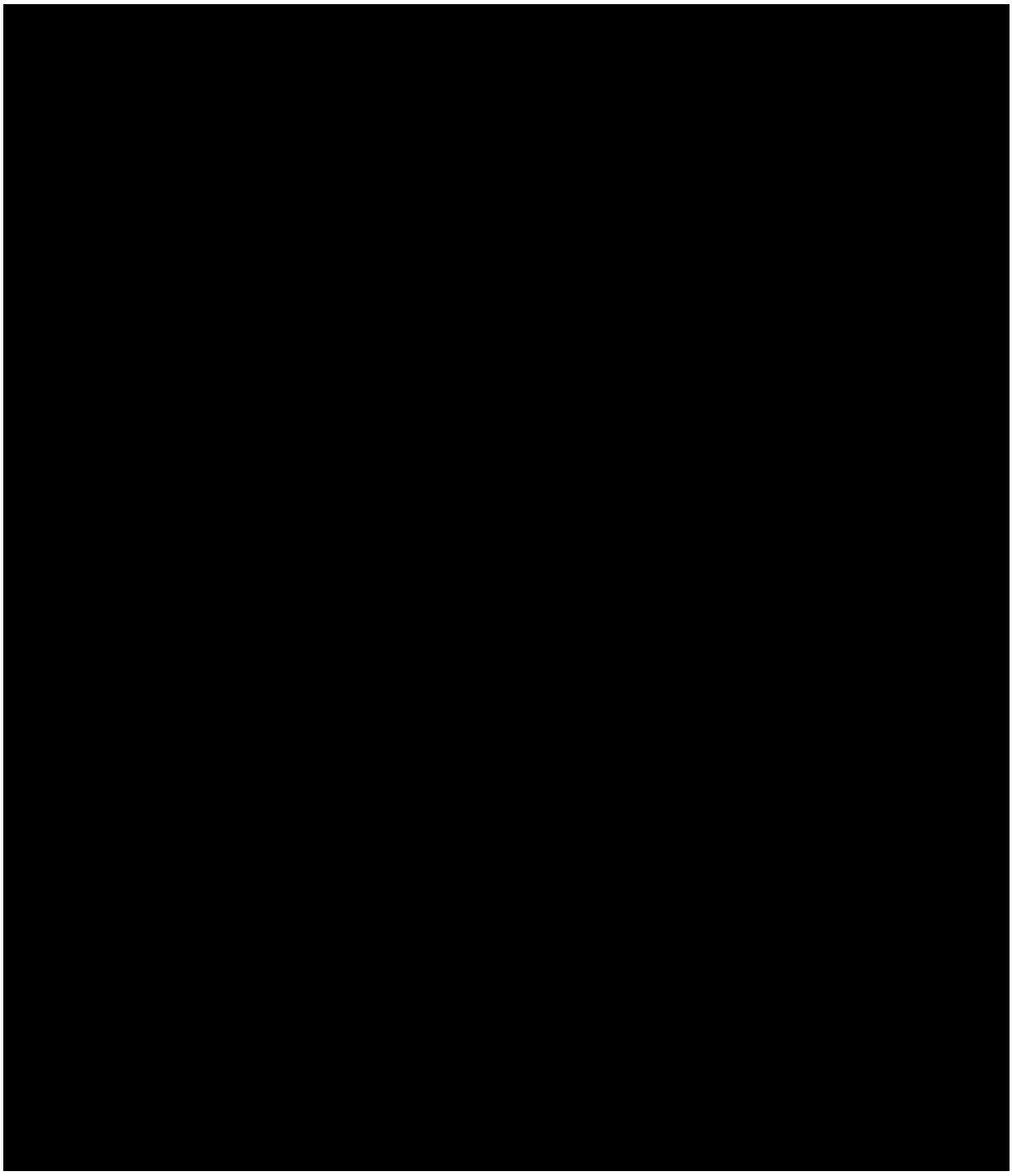


20.6.3. Observer-Reported Scales: Observer Global Impression of Severity (OGIS)

20.6.4. Observer-Reported Scales: Observer Global Impression of Bother (OGIB)

20.6.5. Observer-Reported Scales: Observer Global Impression of Treatment (OGIT)

20.7. DERMATOLOGY LIFE QUALITY INDEX (DLQI)



20.8. CHILDRENS DERMATOLOGY LIFE QUALITY INDEX (CDLQI)