PROTOCOL ADX-102-SLS-006

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF ADX-102 1% TOPICAL DERMAL CREAM IN SUBJECTS WITH SJÖGREN-LARSSON SYNDROME (SLS)

PROTOCOL VERSION AND DATE: VERSION 1.0 17 OCT 2017

ALDEYRA THERAPEUTICS, INC.
131 HARTWELL AVENUE, SUITE 320
LEXINGTON, MA 02421, U.S.A.

[redacted]

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

INVESTIGATOR STATEMENT

Protocol Number: ADX-102-SLS-006

Protocol Title: A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of ADX-102 1% Topical Dermal Cream in Subjects with Sjögren-Larsson Syndrome (SLS).

I understand that all information concerning ADX-102 in connection with this study and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Study Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC) and I understand that any changes in the protocol must be approved in writing by Aldeyra Therapeutics, Inc., and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

I will use only the informed consent form approved by Aldeyra Therapeutics and by my IRB/REB/IEC and will fulfill all responsibilities for submitting pertinent information to the IRB/REB/IEC responsible for this study.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number ADX-102-SLS-006, and will conduct the trial in accordance with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and applicable regulatory requirements.

_____
Site Name

_____
Site Address

_____
Investigator's Printed Name

_____ _____
Investigator's Signature Date

SYNOPSIS

Name of Sponsor Company: Aldeyra Therapeutics, Inc.		**Drug Under Study:** ADX-102
Title of Protocol: A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of ADX-102 1% Topical Dermal Cream in Subjects with Sjögren-Larsson Syndrome (SLS)		
Protocol Number: ADX-102-SLS-006	**Phase:** 3	**Indication:** Sjögren-Larsson Syndrome; Dermatological Signs and Symptoms
Subject Population: Subjects 3 years of age and older with genetically-confirmed diagnosis of SLS and active ichthyosis.		
Number of Subjects: Part 1: Approximately 9 subjects Part 2: Approximately 30 subjects, to be confirmed in Part 1		
Number of Centers: Approximately 8 centers globally		
Test Products / Doses / Mode of Administration: ADX-102 1% drug product is formulated as a topical dermal cream. [redacted] ADX-102 or vehicle topical dermal cream will be applied once daily to the designated treatment area with each application administered approximately 24 hours apart. A standard amount of study drug for the percent body surface area (BSA) under treatment will be measured for application.		
Primary Objective: To evaluate the efficacy of ADX-102 1% topical dermal cream for treatment of ichthyosis associated with SLS. **Secondary Objectives:** To evaluate the safety and secondary efficacy endpoints of ADX-102 1% topical dermal cream in subjects with SLS.		
Study Endpoints Primary Endpoint: The primary efficacy endpoint is the Visual Index for Ichthyosis Severity (VIIS) scaling severity score as assessed by the Investigator in the target efficacy area. [redacted]		

[redacted]

Study Design:

This is a two-part, randomized, double-blind, vehicle-controlled, parallel-group Phase 3 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 to assess all areas affected by ichthyosis (Part 2).

Part 1 Design:

Part 1 will evaluate the safety, tolerability, and efficacy of treatment to the affected area of ichthyosis [redacted]

Qualified 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) once daily to a treatment area identified by the Investigator from Week 1 through Week 12. If the Investigator determines that there are no safety or tolerability issues at the end of Week 12, treatment will increase to all of the affected areas of ichthyosis on one-half of the body from Week 13 through Week 20. If no safety or tolerability issues are identified at the end of Week 20 the treatment will increase to all affected areas of ichthyosis on the entire body from Week 21 through Week 24.

Subjects completing 24 weeks of study drug treatment will then be monitored for an additional 4 weeks for safety.

In total, subjects will be followed for up to 28 weeks and monitored for safety and efficacy at up to 10 study visits: up to 6 site visits and 4 home visits. Apart from the Day 1 and Day 2 visits, each study visit has a ± 5-day window, and home visits have a ± 3-day window.

Study procedures are outlined in the Schedule of Assessments (Table 1 and Table 1-1).

Subjects who are randomized in Part 1 will not be eligible to participate in Part 2.

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.

Qualified subjects will be randomized in a 2:1 ratio to receive either ADX-102 1% or vehicle. The appropriate sample size for Part 2 will be confirmed in Part 1. Subjects will be followed for up to 28 weeks and monitored for safety and efficacy at up to 10 study visits: up to 7 clinic visits and 3 telephone calls with the site. Apart from the Day 1 and Day 2 visits, each study visit has a ± 5-day window, and telephone calls have a ± 3-day window.

Study procedures are outlined in the Schedule of Assessments (Table 2 and Table 2-1).

Subjects who complete Part 1 or Part 2 of the study will be eligible to continue into a separate open-label extension study.

Criteria for Inclusion:

Subjects meeting all the following criteria will be considered eligible for study entry:

1. Subject is aged 3 years or older.
2. Subject has a genetically-confirmed diagnosis of SLS.
3. Subject has active ichthyosis that is Grade 2 or higher on the VIIS scaling severity score.
4. Subject or subject's caretaker is willing and able to provide written informed consent prior to the initiation of any study procedures. Assent will be solicited from pediatric subjects capable of providing assent.
5. Females of child-bearing potential: Negative pregnancy test at Screening and Baseline Visits.
6. Subjects who are sexually active agree to use medically acceptable method (as defined by the Investigator) of birth control as follows:
   - For females: Compliant with a contraceptive regimen during the study if of child-bearing potential or documented to be surgically sterile or post-menopausal.
   - For males: Compliant with a contraceptive regimen during the study or documented to be surgically sterile.

Criteria for Exclusion:

Subjects meeting any of the following criteria will be excluded from the study:

1. Subject has evidence of a serious active infection.
2. Systemic or topical retinoids or other topical medications, not including emollients, within the past 30 days Baseline Visit 1.
3. Subject has received an investigational systemic or topically administered drug within the past 30 days prior to Baseline Visit 1.
4. Subject is currently taking and was unwilling or unable to discontinue any medication excluded in Section 5.7.1.
5. Subject is currently receiving immunosuppressive therapy, including intermittent or low-dose systemic corticosteroids.
6. Subject has a known allergic reaction to any ingredients of study drug formulation.
7. Subject has a history of any malignancy.
8. Subject is known to be human immunodeficiency virus positive or had other known immunodeficiency.
9. Subject has any clinically significant laboratory test abnormalities or a history of any other condition that, in the opinion of the Investigator, could compromise the subject's ability to comply with the protocol or that could compromise the subject's safety or the interpretation of the study results.
10. Subject is currently participating in any other therapeutic clinical study.
11. Subject is pregnant or lactating.

Statistical Analysis:

Part 1 and Part 2 will be analyzed in a similar fashion with the exception that the Part 1 analysis will include a sample size evaluation. Part 1 analyses in some instances may be confined to the descriptive aspect of the evaluation (i.e., inferential p-values may be omitted) due to the small sample size of 6 treated and 3 control patients.

The primary efficacy endpoint (VIIS scaling severity as assessed by the Investigator in the target efficacy area) as well as all secondary efficacy variables that are captured on a continuous or semi-continuous

scale [redacted] will be expressed as baseline to ending change scores. Two-sided 95% confidence intervals (CIs) will be computed and used descriptively for all variables but also to evaluate change relative to a standard for some variables (i.e., by determining whether the CI includes or excludes the standard).

The two-sided 95% CI for VIIS scaling severity will be used to evaluate the primary endpoint as follows. An efficacy claim from Part 2 will be made if: 1) the lower confidence interval is above zero, 2) the mid-point of the confidence interval is at least 0.5 units is size, and 3) at least 50% of subjects have favorable change scores of one or greater.

Response over time will be converted to one or more Area Under the Curve parameters and evaluated using a generalized linear model. VIIS outcome scores and other continuous or semi-continuous outcome variables will be evaluated using a Mixed Model Repeated Measures (MMRM) analysis. Conversion of VIIS or other scales to indicate response (yes/no) will occur (e.g., 0.5 VIIS improvement, 1 unit VIIS improvement) and be evaluated as secondary endpoints. Logistic or Generalized Estimating Equation (GEE) modeling will be used to evaluate incidence of response overall and/or by time. Time to Event analysis (e.g., Kaplan-Meier with log rank test, proportional hazards [PH] modeling) will be used to evaluate time to response.

To increase statistical power, covariates may be incorporated into the computation of 95% confidence intervals (e.g., through the use of a mean centered covariate in a regression model to predict the mean pre-treatment to post-treatment difference) and/or into logistic, GEE, PH, MMRM and generalized linear models.

All analyses will be specified *a priori* in an Statistical Analysis Plan (SAP) to be completed prior to database lock for Part 1. The SAP will serve as the summative and definitive plan of analysis. Analyses not described in the SAP will be labeled as *post-hoc*. The SAP will outline all analyses that will be performed in Part 1 and in Part 2 of this study.

Sample Size Rationale:

Part 1 will assess the effect size on the VIIS scaling severity score, and will confirm the sample size needed for Part 2. Part 2 is expected to require approximately 30 subjects.

Data Safety Monitoring Board:

An independent data safety monitoring board (DSMB) will be established to review all available safety data after approximately 9 subjects have completed Week 24 in Part 1. 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 AEs. Based on the safety data provided, the DSMB will provide recommendations about stopping or continuing the trial.

The DSMB will be advisory to the Sponsor's clinical trial leadership group Steering Committee which will be blinded during Part 1 until database lock. The Steering Committee will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

Additional DSMB reviews will occur approximately every 6 months throughout the trial, or as deemed necessary by the DSMB or Sponsor to ensure subject safety and well-being. Study enrollment and dosing will continue while the DSMB evaluates data. A DSMB charter will be prepared. The charter will contain the required information for the formation, activities, and conduct of the DSMB.

Table 1. Part 1 Schedule of Events and Assessments

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 / pregnancy test[3]	X	X				X		X	X	
12-Lead ECG (see Table 1-1)	X	X				X		X	X	
Vital Signs (see Table 1-1)	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	X	
Clinical laboratory testing[9]	X	X				X		X	X	
PK sample collection[10] (see Table 1-1)		X	X			X		X	X	
Randomization		X								
Administer study drug		X[11]	X	X	X	X[11]	X	X[11]		
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 undergo, if possible, all of the assessments and procedures scheduled for 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 6.15.1.1 and 6.15.1.2 for more detail.
10. PK collection include 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 1-1. 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	

Table 2. Part 2 Schedule of Events and Assessments

Evaluation	Screening[1]	Baseline Visit 1[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 ± 5 days	Week 12 ± 3 days	Week 16 ± 5 days	Week 20 ± 3 days	Week 24 ± 5 days	Week 28 ± 5 days
	Site Visit	Site Visit	Site Visit	Telephone	Site Visit	Telephone	Site Visit	Telephone	Site Visit	Site 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 / pregnancy test[3]	X	X			X		X		X	
12-Lead ECG (see Table 1-1)	X	X			X				X	
Holter Monitoring		X			X				X	
Vital Signs (see Table 1-1)	X	X	X		X		X		X	
Physical exam[4]	X	X	X		X		X		X	
Dermatologic exam	X	X	X		X		X		X	X
Digital photography[5]		X			X		X		X	X
VIIS (Investigator-assessed)		X[6]	X		X		X		X	X
Global impression of severity		X			X		X		X	X
Patient/Observer-reported scales[7]		X			X		X		X	X
PD sample collection[8]		X	X		X		X		X	
Clinical laboratory testing[9]	X	X			X		X		X	
PK sample collection[10] (see Table 1-1)		X	X		X		X		X	
Randomization		X								
Administer study drug[11]		X	X	X	X	X	X	X		
Dispense study drug & diary			X		X		X			
Collect study drug & diary					X		X		X	
Exit interview									X[12]	

ECG = electrocardiogram; ET = early termination; 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 undergo, if possible, all of the assessments and procedures scheduled for Visit 8 (Week 24).
3. Urine pregnancy test for female subjects of child-bearing potential only. Tests 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. VIIS must be independently assessed by two different Investigators at Baseline Visit 1 only.
7. Patient-/caregiver-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 6.15.1.1 and 6.15.1.2 for more details.
10. PK sample collection (blood and urine) from approximately 16 subjects.
11. Study drug will be administered daily. At study visits when PK samples are collected, study drug may be administered at the study site after pre-dose PK samples have been obtained.
12. Exit interviews should be conducted within 30 days of Visit 8.

Table 2-1. Part 2 Pharmacokinetic and Cardiac Monitoring

Visit	**Visit 1**						**Visit 2**	**Visits 4 and 8**						**Visit 6**
Time (hours)	**Pre-Dose**	**1**	**2**	**4**	**8**	**12**	**24**	**Pre-Dose**	**1**	**2**	**4**	**8**	**12**	**Pre-Dose**
Window	**-**	**± 15 min**	**± 15 min**	**± 15 min**	**± 15 min**	**± 15 min**	**± 60 min**	**-**	**± 15 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	X	X	
Vital Signs	X	X	X	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	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			X
Blood PK Samples	X	X		X			X	X	X		X			X
Urine PK Samples	X			X				X			X			

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

≥	Greater than or equal to
<	Less than
%	Percent
mg/cm^2	Milligram per square centimeter
µM	Micromolar
w/w	Weight per weight
AE	Adverse event
ALP	Alkaline phosphatase
ALT/SGPT	Alanine aminotransferase
AST/SGOT	Aspartate aminotransferase
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CNS	Central nervous system
CO_2	Carbon dioxide
CFR	Code of Federal Regulations
COA	Clinical outcomes assessments
CPK	Creatinine phosphokinase
CR	Central Reader
CRF	Case report form
CRO	Contract Research Organization
CS	Clinically significant
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early termination
FALDH	Fatty aldehyde dehydrogenase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimated Equation
GLP	Good Laboratory Practice
HEENT	Head, eyes, ears, nose, and throat
HR	Heart rate
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IP	Intraperitoneal

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Ichthyosis Severity Score
IV	Intravenous
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NCS	Not clinically significant
PI	Principal Investigator
PD	Pharmacodynamic
PK	Pharmacokinetic
PH	Proportional hazards
PO	Oral
RBC	Red blood cell
REB	Research Ethics Board
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SLS	Sjögren-Larsson Syndrome
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TD	Topical dermal
TEAE	Treatment-emergent adverse event
TEWL	Transepidermal Water Loss
TO	Topical ocular
VIIS	Visual Index for Ichthyosis Score
WBC	White blood cell

1 INTRODUCTION

1.1 Sjögren-Larsson Syndrome

ADX-102 1% is being developed for the treatment of ichthyosis associated with Sjögren-Larsson Syndrome (SLS). SLS (ICD Q87.1) is a rare, chronically-debilitating, autosomal-recessive disorder characterized by generalized ichthyosis, cognitive deficit in a majority of patients, and spastic diplegia or tetraplegia. SLS is caused by mutations in the *ALDH3A2* gene that encodes fatty aldehyde dehydrogenase (FALDH), an enzyme that catalyzes the oxidation of aliphatic aldehydes to fatty acids (3).

In most patients, ichthyosis (dry, thickened, scaly, erythematous skin that is pruritic and, due to frequent excoriation, friable) is moderate or severe, particularly prominent in flexure areas, and involves much of the body surface except the face and glabrous skin (3). The dermal symptoms are generally recalcitrant to therapy, and are associated with significant daily physical and emotional burden and social stigma for patients and caregivers. The cutaneous symptoms are apparent at birth in almost all patients; they become more established by several months of age and remain throughout life (2). Developmental delay, spasticity, and other neurological symptoms become apparent over the first 2 years of life. The onset of neurologic symptoms usually prompts recognition of a diagnosis of SLS rather than another type of ichthyotic disorder (2).

SLS ichthyosis pathophysiology is well understood; fatty aldehydes disrupt dermal function, particularly the epidermal fatty moisture barrier, resulting in pathologic water loss, cutaneous desiccation, and compensatory keratinocytic hypertrophy (1). In epidermal cells, FALDH deficiency results in impaired oxidation of long-chain fatty aldehydes to fatty acids. The consequent accumulation of aldehydes disrupts the normal function and secretion of lamellar bodies and leads to intercellular lipid deposits in the stratum corneum and a defective water barrier in the skin layer, resulting in the cutaneous symptoms of SLS (2).

Ichthyosis related to SLS is a serious disease and there is no currently approved treatment that targets the underlying disease. Bathing several hours per day and over-the-counter moisturizing creams are the main interventions used to attempt to treat the symptoms, but have only limited and variable results, lasting for no more than a few hours. Keratolytic agents, salicylic acid, and urea are also considered for treatment. Patients with severe ichthyosis who are unresponsive to topical agents typically receive treatment with systemic retinoids, which are associated with a variety of toxicities. Patients are not usually maintained on retinoids due to concerns about toxicity, particularly in pediatric patients. No clinical intervention has been well studied in SLS patients, and therapeutic efficacy is generally variable. There is considerable social stigma in SLS since the skin appearance resembles disseminated cutaneous infectious disease and scales often emit a foul odor due to bacterial overgrowth and putrefaction.

1.2 Therapeutic Rationale for ADX-102 in Sjögren-Larsson Syndrome

[redacted]

[redacted]

1.3 Clinical Trials of ADX-102

1.3.1 Sjögren-Larsson Syndrome

Study NS-003 was a randomized, double-blind, vehicle-controlled, parallel group Phase 2 clinical trial evaluating the activity of ADX-102 1% topical dermal cream at a dose of 8 mg/cm^2 in subjects with ichthyosis associated with SLS.

A total of 12 male and female subjects aged 6 years or older (range 8 to 25 years) with genetically confirmed SLS and active ichthyosis on the lower extremities that was determined to be of moderate severity or higher were enrolled and randomized 1:1 to ADX-102 1% or vehicle. Subjects received study drug (ADX-102 1% or vehicle) once daily for 8 weeks.

The target area for treatment was an area on the lateral aspect of the lower leg, up to approximately 10 inches in height by 4 inches wide. In the cases where the lower leg did not have an ideal target area for treatment, the Investigator chose an area on another portion of the body as the target area. The lower leg was not utilized in only one subject whose right upper back was identified by the Investigator as the target treatment area.

[redacted]

In this Phase 2 clinical trial, the reduction in the severity of the ichthyosis in ADX-102-treated subjects was statistically significant relative to baseline. The most common reduction in the severity of the ichthyosis (assessed by the scaling ISS sub-score) in ADX-102-treated subjects over the duration of drug exposure (eight weeks) was one point from a median baseline severity of 3, representing an average change from moderate to mild disease. In addition, the activity of drug was statistically superior to that of vehicle. ADX-102-treated subjects showed greater mean and percentage decreases from baseline, and a higher proportion of ADX-102-treated subjects exhibited favorable individual responses than that of the vehicle-treated subjects for all the ISS sub-scores, except for excoriations.

ADX-102 1% w/w topical dermal formulation was generally well-tolerated and there were no significant or serious adverse events (SAE), or treatment-emergent adverse events (TEAEs) that led to treatment discontinuation. [redacted] No pattern of changes was observed with ADX-102 for chemistry analytes, hematology parameters, or vital signs.

Overall, the results of Study NS-003 demonstrated that the ADX-102 1% w/w topical dermal formulation was safe and well-tolerated, and improved SLS ichthyosis in a clinically and statistically significant manner superior to that of vehicle.

1.3.2 Ocular Indications

As a topical ocular formulation, ADX-102 was safe and well-tolerated in a Phase 1 clinical trial and demonstrated efficacy and safety in Phase 2 clinical trials in allergic conjunctivitis and noninfectious anterior uveitis.

Please refer to the Investigator's Brochure for additional information.

1.4 Minimization of Risk

In the Phase 2 clinical trial in SLS patients (NS-003), 8 weeks of daily application of ADX-102 1% w/w topical dermal formulation over ~3% body surface area (BSA) has been shown to be safe and well-tolerated.

ADX-102 has been well-tolerated in multiple nonclinical, single dose and repeat dose pharmacology and toxicology studies in mice, rats, rabbits, dogs, and non-human primates, via topical dermal (TD), topical ocular (TO), oral (PO), intraperitoneal (IP), subcutaneous (SC), and intravenous (IV) routes of administration. Of particular relevance to TD application, Good Laboratory Practice (GLP) studies testing up to ADX-102 5% topical dermal cream have shown that TD administration of ADX-102 to Göttingen minipigs for 21 days and nine weeks was well-tolerated, with no local or systemic adverse effects observed. In a standard battery of genotoxicity tests, ADX-102 was non-mutagenic and non-clastogenic. Furthermore, in vivo central nervous system (CNS), respiratory, and cardiovascular safety pharmacology studies showed no adverse effects with ADX-102. Please refer to the Investigator's Brochure for additional information.

The Phase 3 study design includes an assessment of increasing BSA treatment (Part 1) lasting 24 weeks in approximately 9 eligible subjects receiving ADX-102 1% or vehicle topical dermal cream initially over approximately 20% BSA then increasing to up to 90% BSA. The assessment in Part 1 will allow for real-time evaluation of the safety and effectiveness of ADX-102 1% relative to vehicle treatment dosed over longer durations and greater BSA than in the Phase 2 study. After completion of Part 1 of the Phase 3 study, a separate set of eligible subjects will be enrolled into Part 2 that allows for the assessment of the safety of vehicle relative to ADX-102 1% treatment on all areas of ichthyosis.

In addition, an independent Data Safety Monitoring Board (DSMB) will be established to review all available safety data after approximately 9 subjects have completed study Week 24 in Part 1. Additional DSMB reviews will occur approximately every 6 months throughout the trial, or as deemed necessary by the DSMB or Sponsor to ensure subject safety and well-being. The assessment of safety will be determined from dermatological endpoints, vital sign measurements, physical examinations, hematology and chemistry laboratory testing, cardiac monitoring, use of concomitant medications, and review of adverse events (AEs). Refer to Section 3.4.1.

1.5 Potential Benefit

As described above, SLS ichthyosis is generally recalcitrant to therapy. Phase 2 clinical trial results in SLS patients treated over ~3% BSA with ADX-102 1% for 8 weeks demonstrated that ADX-102 was effective in treating the ichthyosis associated with SLS.

The Phase 3 study will assess he activity of ADX-102 1% after 24-weeks of dosing over all skin area affected by ichthyosis (approximately 80 – 90% BSA in a typical SLS patient).

1.6 Rationale for Dose Selection

It has been shown that free aldehydes are cytotoxic. In one study, free all-trans-retinal resulted dose-dependent cell death of ARPE19 cells, with complete or nearly complete cell death observed at 10 µM (5). A similar phenomenon was observed in HEK293 cells. Since tissue necrosis is not evident in the skin of SLS patients, the theoretical maximum aldehyde concentration likely less than 10 µM. Because ADX-102 binds aldehydes with a 1:1 stoichiometry, maximal drug target levels in skin are 10 µM. GLP nonclinical studies in Göttingen minipigs have shown that once-daily application of 1% w/w ADX-102 topical dermal cream results in ADX-102 skin concentrations that meet or exceed this target. The Phase 2 clinical trial results confirmed the activity of once-daily ADX-102 1% administration.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objective

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

2.2 Study Endpoints

2.2.1 Primary Endpoint

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

[redacted]

[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a two-part, randomized, double-blind, vehicle-controlled, parallel-group Phase 3 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.

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 9 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 VIIS scaling severity score, as assessed by the Investigator, and will include one of the body sites as defined in the VIIS tool (target efficacy area).[1] 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 4 weeks for safety.

Subjects who are randomized in Part 1 will not be eligible to participate in Part 2.

[1] Dorsal foot cannot be selected as the target efficacy area.

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.

Subjects will be consented and screened for eligibility. Qualified subjects will be randomized in a 2:1 ratio to either ADX-102 1% or vehicle. The appropriate sample size for Part 2 will be confirmed in Part 1. Subjects or caregivers will apply study drug (i.e., ADX-102 1% or vehicle) once daily to all affected areas of ichthyosis on the body (approximately 80 – 90% of BSA in a typical SLS patient).

The target efficacy area for all efficacy analyses at Week 24 will be one of the body sites as defined in the VIIS tool with Grade 2 or higher on the VIIS scaling severity as assessed by the Investigator.[1]

3.2 Assigning Subjects to Treatment Groups

3.2.1 Subject Numbering

Each subject screened for the study will be assigned a unique subject number that will be used to identify the subject throughout their participation in the study. 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.

3.2.2 Randomization

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

3.3 Blinding and Unblinding

3.3.1 Blinding

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 (Part 1 and Part 2).

3.3.2 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 study subject who presents with an emergency condition.

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

[1]Dorsal foot cannot be selected as the target efficacy area.

There is no known antidote to ADX-102, so symptomatic and supportive management of any suspected and treatment-related adverse event, if necessary, is clinically indicated.

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 subject's emergency and the need to unblind, prior to unblinding any subject.

In situations in which the Investigator has tried but is unable to reach the Medical Monitor, the Investigator should use his/her best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor. Once a subject's treatment assignment has been unblinded, the Medical Monitor should be notified within 24 hours of unblinding of the treatment, without revealing the study treatment.

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 Pharmacovigilance Department or designee will be provided with the treatment assignment for the subject for regulatory reporting.

3.4 Safety Oversight

During the study, subject safety will be monitored on a continuous basis by the Medical Monitor until the last subject completes his or her last scheduled study assessment.

3.4.1 Data Safety Monitoring Board

An independent DSMB will be established to review all available safety data after approximately 9 subjects have completed Week 24 in Part 1. 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. Based on the safety data provided, the DSMB will provide recommendations about stopping or continuing the trial.

The DSMB will be advisory to the Sponsor's clinical trial leadership group Steering Committee which will be blinded during Part 1 until database lock. The Steering Committee will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

Additional DSMB reviews will occur approximately every 6 months throughout the trial, or as deemed necessary by the DSMB or Sponsor to ensure subject safety and well-being. Study enrollment and dosing will continue while the DSMB evaluates data. A DSMB charter will be prepared. The charter will contain the required information for the formation, activities, and conduct of the DSMB.

3.5 Study Duration for Individual Subjects

Following the Screening Visit, eligible subjects will enter the study for up to 28 weeks in each Part 1 and Part 2. This comprises of a 24-week study treatment phase followed by a 4-week follow-up period.

4 STUDY POPULATION SELECTION

4.1 Inclusion Criteria

Subjects meeting all the following criteria will be considered eligible for study entry:

1. Subject is aged 3 years or older.
2. Subject has a genetically-confirmed diagnosis of SLS.
3. Subject has active ichthyosis that is Grade 2 or higher on the VIIS scaling severity score.
4. Subject or subject's caretaker is willing and able to provide written informed consent prior to the initiation of any study procedures. Assent will be solicited from pediatric subjects capable of providing assent.
5. Females of child-bearing potential: Negative pregnancy test at Screening and Baseline Visits.
6. Subjects who are sexually active agree to use medically acceptable method (as defined by the Investigator) of birth control as follows:
   - For females: Compliant with a contraceptive regimen if of child-bearing potential during the study, or documented to be surgically sterile or post-menopausal.
   - For males: Compliant with a contraceptive regimen during the study or documented to be surgically sterile.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Subject has evidence of a serious active infection.
2. Systemic or topical retinoids or other topical medications, not including emollients, within the past 30 days Baseline Visit 1.
3. Subject has received an investigational systemic or topically administered drug within the past 30 days prior to Baseline Visit 1.
4. Subject is currently taking and was unwilling or unable to discontinue any medication excluded in Section 5.7.1.
5. Subject is currently receiving immunosuppressive therapy, including intermittent or low-dose systemic corticosteroids.
6. Subject has a known allergic reaction to any ingredients of study drug formulation.
7. Subject has a history of any malignancy.
8. Subject is known to be human immunodeficiency virus positive or had other known immunodeficiency.
9. Subject has clinically significant laboratory test abnormalities or a history of any other condition that, in the opinion of the Investigator, could compromise the subject's ability to

comply with the protocol or that could compromise the subject's safety or the interpretation of the study results.

10. Subject is currently participating in any other therapeutic clinical study.
11. Subject is pregnant or lactating.

4.3 Subject Withdrawal and Replacement

Subjects and caregivers will be informed that they have the right to withdraw the subject from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment,
- Development of an unacceptable AE or SAE,
- Subject or Sponsor request,
- Subject non-adherence to study drug dosing or protocol requirements, or
- Pregnancy.

The reason for study withdrawal is to be documented in the subject's source documents and CRF. Withdrawn subjects may be replaced at the discretion of the Sponsor.

Subjects who prematurely discontinue from the study should be seen as soon as possible for Week 24 assessments (Part 1:Table ; Part 2:Table 2).

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show due diligence by documenting in the source documents all steps taken to contact the subject (e.g., dates of telephone calls, registered letters, etc.).

5 STUDY TREATMENT

5.1 Description of Study Treatment

[redacted]

5.2 Packaging and Labeling

[redacted]

Labels will be in the local language and comply with the legal requirements of each country. Clinical supplies are to be dispensed only in accordance with the protocol. Study drug labels will not bear any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

5.3 Study Drug Storage

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location. [redacted]

5.4 Study Drug Accountability

The Investigator or designee will maintain accurate records of receipt and condition of study drug, including dates of receipt. In addition, accurate records will be kept of the date dispensed, quantity dispensed, and the subject to whom study drug was dispensed. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

The Investigator or designee is responsible for monitoring the inventory of study drug and for the accountability of all used and unused study drug. Drug accountability will be verified by the study monitor during site visits and at the completion of the trial.

Refer to the Pharmacy Manual for additional details.

5.5 Study Drug Retention

Study drug must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used study drug should be destroyed at the site or returned to the distributor, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused study drug may be disposed until fully accounted for by the study monitor.

5.6 Treatment Administration

The target efficacy and treatment areas will be identified by the Investigator as noted below. The Investigator will apply the initial dose of study drug and at designated timepoints when study drug will be applied to expanded treatment areas. These applications will be observed by the subject and caregiver at the study center. Thereafter, subjects or caregivers will apply subsequent doses throughout the duration of the study.

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/cm^2, 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 study.

Subjects or caregivers are required to wear protective gloves during application and thoroughly wash their hands after application to prevent study drug exposure.

At scheduled study visits at the site, subjects may not bathe or apply study drug or as-needed topical symptom control therapy (emollients) to the treatment area within 12 hours of examination or photographic assessment. Subjects should refrain from applying as-needed topical symptom control therapy and bathing within 4 hours of applying study drug to the treatment area. The treated area should be covered by loose clothing to minimize light exposure.

Target Efficacy Area used for the primary endpoint assessment in Part 1 and Part 2 will be based on one of the body sites as defined in the VIIS tool (upper back, upper arm or lower leg/shin)[1] that has a VIIS scaling severity score of Grade 2 or higher as assessed by the Investigator. The body

[1] Dorsal foot cannot be selected as the target efficacy area.

site with the worse VIIS scaling severity score should be selected, if applicable. The target efficacy area will be used for all efficacy analyses.

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 severity 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.

In Part 2, the treatment area will be defined as all affected areas of ichthyosis on the body (approximately 80 – 90% of BSA in a typical SLS patient). Subjects will be treated for 24 weeks followed by a safety follow-up visit 4 weeks after the end of dosing.

Refer to the Pharmacy Manual for detailed information regarding treatment administration.

5.7 Concomitant Therapy and Procedures

5.7.1 Prohibited Concurrent Therapies and Procedures

The following therapies are prohibited during study participation:

- Systemic or topical retinoids or other topical medications, not including emollients
- Immunosuppressive therapy, including intermittent or low-dose systemic corticosteroids

5.7.2 Allowed Concurrent Therapies and Treatment

5.7.2.1 Standard of Care

During the study, emollients used as standard of care may be applied to other areas of the body affected by ichthyosis not being treated with study drug.

Subjects may apply as-needed topical symptom control therapy (emollients) to areas of the body being treated with study drug. As-needed therapy should not be applied within 4 hours of applying study drug. At scheduled study visits at the site, subjects may not apply as-needed topical symptom control therapy to the treatment area within 12 hours of examination or photographic assessment.

5.8 Restrictions

5.8.1 Bathing

Subjects should refrain from bathing 4 hours after applying study drug to the treatment area.

On scheduled study visits at the site, subjects should refrain from bathing for at least 12 hours prior to obtaining digital photographs.

5.9 Treatment Compliance

To evaluate the safety, tolerability, PK, pharmacodynamic (PD), and exploratory activity of the study drug, it is critical that subjects and caregivers apply the study drug as directed. Subjects and caregivers will be trained on proper study drug application by watching the Investigator apply the initial dose of study drug. Subjects and caregivers will also be given detailed instructions on how to measure the amount of study drug to apply to the treatment area.

A dosing diary will be used to record the amount, date and time of each study drug application and any missed doses of the study drug. The reason for the missed doses must be documented. The dosing diary and all used and unused study drug will be brought to the designated study visits to assess compliance with the protocol. Qualified study personnel will review the information with the subject and caregiver.

6 STUDY PROCEDURES

Study assessments and evaluations should be performed by the Investigator and/or qualified study personnel according to Study Activities (Section 7). Unless specified otherwise, procedures listed will be performed in both Part 1 and Part 2. Refer to the Study Activities Schedule for Part 1 (Table 1) and Part 2 (Table 2).

6.1 Informed Consent / Assent

Informed consent and assent forms must be approved for use by the reviewing Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC). Informed consent, and assent when applicable, must be obtained for all subjects participating in the study prior to performing any study procedures. The informed consent process must be adequately documented in the source records.

6.2 Eligibility Review

The Investigator or qualified study personnel will confirm that all inclusion and exclusion criteria have been met.

6.3 Demographics and Medical History

Demographic information to be captured include subject initials (where locally permitted), date of birth (alternatively year of birth, if full date of birth is not allowed to be collected for legal reasons), age, sex, race and ethnicity will be obtained from the subject and recorded in the CRF.

Medical history will be recorded in the CRF and will include information relating to any prior to existing medical conditions involving the following disease types or systems: infectious diseases, allergic, metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, head,

eyes, ears, nose and throat (HEENT), breasts, respiratory, cardiovascular, gastrointestinal/hepatic, genitourinary/renal, neurological, and psychiatric/psychosocial.

This will also include date and/or age of diagnosis of SLS, genotype, and all prior treatments for SLS. The presence or absence of SLS symptoms, including motor disability in the arms and/or legs, foot deformity, speech disorder, seizures, and photophobia, are to be documented. The location and nature of ichthyosis and presence and intensity of associated symptoms, including scaling, pruritus, and erythema, are to be documented.

6.4 Concomitant Medications

Concomitant medications used 30 days prior to consent/assent to treat any medical conditions will be recorded in the CRF. Any changes in dosage or new medications added must be recorded in the subject's CRF. The Sponsor and Investigator or qualified study personnel will review and evaluate concomitant medication usage on an ongoing basis.

6.5 Adverse Events

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last dose of study drug. AEs must be recorded in the subject's CRF. The Sponsor and Investigator or qualified study personnel will review and evaluate adverse events on an ongoing basis. See Section 9 for further detail on AE reporting.

6.6 Electrocardiography / Holter Monitoring

A standard 12-lead ECG (single recording) will be collected at the designated timepoints at specific scheduled visits. Refer to Table 1-1 and 2-1 for details of these timepoints. The date and time of each ECG and its results will be documented in the source documents and CRF.

A Holter monitor will record ECG activity for 12 hours at specific scheduled visits in Part 2 only. The date and time and results of the monitoring will be documented in the source documents and CRF.

Both ECGs and Holter data will be sent to a central reader for assessment.

6.7 Vital Signs

Vital sign assessments will be taken with the subject in the sitting or supine position after 5 minutes at rest and will include body temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR).

6.8 Physical Examination

A complete physical examination including height, weight and BSA, will be conducted for all subjects during the Screening Visit in Part 1 and Part 2 only. The complete physical examination should include the following systems: HEENT, respiratory, cardiovascular, gastrointestinal, hepatic, musculoskeletal, neurological, metabolic/endocrine/nutritional, hematopoietic, psychiatric/psychosocial, genitourinary/renal, allergies, breasts, infectious disease, and general appearance. Dermatological examinations should be conducted as per Section 6.12.

Symptom-directed physical examinations will be conducted for all other designated study visits.

6.9 Visual Index for Ichthyosis Severity

The Investigator will utilize the VIIS tool to evaluate the scaling and erythema components of ichthyosis in each body site/region (upper back, upper arm, lower leg/shin, and dorsal foot) as define in the VIIS scale.

At baseline, two Investigators should administer the VIIS in Part 2.

6.10 Clinician Global Impression of Severity

The Investigator will rate the severity of a subject's ichthyosis on a 5-point scale.

6.11 Patient-/Caregiver-Reported Scales

At designated site visits, subjects 12 years of age and older with proper cognitive and expressive capacity will rate their experience on the scales listed. In addition, for all subjects, the caretaker will rate on a similar scale their observation of the subject's experience.

- EQ-5D-5L (Patient/Proxy)
- Patient-Reported Itching
- Patient/Observer-Reported Scratching
- Patient/Observer Global Impression of Severity
- Patient/Observer Global Impression of Bother
- Patient/Observer Global Impression of Treatment
- Patient/Observer-Reported Burden of Bathing/Showering
- Children's Dermatology Life Quality Index / Dermatology Life Quality Index

6.12 Dermatologic Exam

A complete dermatological exam will be performed during the designated study visits.

The VIIS scaling severity scale will be utilized to document ichthyosis.

6.13 Digital Photography

Photography equipment and services will be provided by the photography vendor, Canfield Scientific (Parsippany, NJ) to document cutaneous disease using a series of half-body images (anterior and posterior, from neck down and from feet up) to document the extent of involvement as well as close-up views of select target area(s) at required visits. Additional images may be taken if there are any safety concerns. For standardization across investigative sites and visits, all study photographs will be captured using the equipment, supplies, and guidelines provided by Canfield. Images will be uploaded to a secure website hosted by Canfield and monitored for technical quality. Detailed instructions for all aspects of the photography procedures will be supplied separately in the Investigator user manuals to be provided by Canfield.

Prior to obtaining digital photographs at the study site, 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 photographic assessment.

6.14 Pharmacodynamic Assessments

6.14.1 Skin Cell Samples

Skin cell samples for exploratory biomarker analyses will be collected from the target treatment area of using a non-invasive tape-stripping method.

The sampling site must not be cleaned with water, detergents, or solvents prior to collection of skin samples. Full details of equipment and procedures for skin cell sample collection will be listed in the Laboratory Manual.

6.14.2 Transepidermal Water Loss

TEWL will be measured during the study. Full details of equipment and procedures for TEWL measurement will be listed in the Laboratory Manual.

6.15 Clinical Laboratory Tests

Full details of equipment and procedures for laboratory testing will be listed in the Laboratory Manual.

The amount of blood drawn assessments from adult subjects for clinical laboratory testing and PK will not exceed 450 mL over any eight-week period. The amount of blood drawn in pediatric subjects will not exceed 8 mL/kg over any eight-week period.

6.15.1 Laboratory Parameters

Samples of blood and urine will be collected for clinical laboratory tests which includes general safety parameters (hematology, serum chemistry, and urinalysis) and pregnancy tests.

Blood samples for laboratory assessments will be collected at the site by the Investigator, or qualified study personnel.

Samples collected at the Screening Visit may be analyzed at a local lab. All other samples will be shipped to a central laboratory. Full details of equipment and procedures for laboratory testing will be listed in the Laboratory Manual.

The Investigator must categorize all abnormal urine, hematology and chemistry laboratory values as either clinically significant (CS) or not clinically significant (NCS). Clinical significance is defined as any variation in laboratory parameters, which has medical consequences that result in an alteration in the subject's medical care. In case of CS laboratory results, the Investigator will continue to monitor the subject with additional laboratory assessments until values have reached normal range and/or baseline levels. CS laboratory results should be reported as an adverse event in accordance with Section 9.

Biological material will be stored and secured in a manner that ensures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or accidentally or illegally destroyed.

6.15.1.1 Hematology

Hematology profile includes 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.

6.15.1.2 Chemistry

Serum chemistry profile includes albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bilirubin (total and direct), blood urea nitrogen (BUN), calcium, carbon dioxide (CO_2), chloride, creatinine, creatinine phosphokinase (CPK), glucose, phosphate, potassium, sodium, total protein, and uric acid.

6.15.1.3 Urinalysis

Urinalysis includes bilirubin, glucose, ketones, blood, nitrite, pH, protein, specific gravity, and microscopy (if indicated by macroscopic findings).

6.15.1.4 Pregnancy Test

For female subjects of child-bearing potential, a urine pregnancy test will be collected. Results must be available and confirmed to be negative before the subject may be enrolled in the study. Study drug must be discontinued for any subject with a positive pregnancy test result.

6.16 Pharmacokinetic Assessments

Blood and urine samples will be collected to evaluate the levels of ADX-102 and its metabolites.

In Part 1, samples will be obtained from all subjects. In Part 2, samples will be obtained from approximately 16 subjects.

Refer to Table 1-1 and Table 2-1 for details of PK collection timepoints. Full details of equipment and procedures for laboratory testing will be listed in the Laboratory Manual.

6.17 Randomization

After eligibility is confirmed, subjects will be randomized as described in Section 3.2.2..

6.18 Study Drug Treatment

Refer to Section 5.6 for details on study drug treatment.

6.18.1 Study Drug Dispensation and Collection

Study drug will be dispensed to subjects or caregivers at designated study visits by the Investigator, study personnel, or appropriate designees. In certain cases, subjects will require study drug to be shipped. All used and unused study drug dispensed to subjects or caregivers will be collected at designated study visits to assess compliance with the protocol. The requirements for maintaining study drug accountability are provided in Section 5.4.

Refer to the Pharmacy Manual for additional details.

6.18.2 Study Drug Diary

A dosing diary will be dispensed at the designated study visits to record the date and time of each study drug application and any missed doses of the study drug. The reason for the missed doses must be documented. Subjects and caregivers will be instructed to bring the completed diary to the designated study visits. Study personnel will review the information with the subject and caregiver.

6.19 Home Visits

Subjects will be visited by a home nurse on designated study visits. The home nurse will conduct the following procedures/assessments: collection of concomitant medication(s), AE(s), and vital signs and conduct dermatological exams. Digital photographs will only be taken to document any safety-related concerns. Refer to Section 6.13 for details on digital photography.

6.20 Site Telephone Check-In

The Investigator or qualified study personnel are to contact subjects at the designated study visit. The following will be conducted over the phone: collection of concomitant medication(s) and AE(s).

6.21 Exit Interview

Subject exit interviews will be conducted with study participants and/or their caregivers. The actual interviews will be semi-structured in nature, conducted one-on-one, either face-to-face or over the telephone, and facilitated by an interviewer trained in qualitative research methods. Each interview will be audio-recorded and transcribed for analysis. The primary aim of these interviews is to enrich understanding of the patient's disease experience, treatment journey, and treatment outcomes; support the development and interpretation of the trials clinical outcome assessments (COAs); and inform future trial design.

7 STUDY ACTIVITIES FOR PART 1

Study activities for Part 1 are summarized in the Study Activities Schedule (Table 1).

7.1 Screening Visit (Day -7 to -1) – Site Visit

- Obtain written informed consent/assent (Section 6.1)
- Review eligibility criteria (Section 6.2)
- Collect demographic information and document medical history (Sections 6.3)
- Record concomitant medications and AEs (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis[1] and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)

[1] Samples collected for urinalysis and clinical laboratory tests at the Screening Visit may be analyzed at a local lab.

- 12-lead ECG (Section 6.6)
- Collect vital signs (Section 6.7)
- Complete physical examination, including height and weight collection (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Collect blood samples for hematology and chemistry[4] (Sections 6.15.1.1 and 6.15.1.2)

7.2 Baseline Visit 1 (Week 1/Day 1) – Site Visit

- Review eligibility criteria (Section 6.2)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete Global Impression of Severity (Section 6.10)
- Collect Patient/Observer-reported scales (Section 6.11)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)
- Randomization to treatment (Section 6.17)
- Apply study drug to target treatment area[1] (Section 5.6)

7.3 Visit 2 (Week 1/Day 2) – Site Visit

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Complete VIIS (Section 6.9)

[1] Investigator should apply study drug to the initial treatment area (~20% BSA) during the visit.

- PD sample collection (Section 6.13)
- PK sample collection (blood only) (Section 6.16)
- Apply study drug to target treatment area[1] (Section 5.6)
- Dispense study drug supply and diary (Sections 6.18.1 and 6.18.2)

7.4 Visits 3 and 4 (Weeks 4 and 8 ± 3 days) – Home Visit (Section 6.19)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)

7.5 Visit 5 (Week 12 ± 5 days) – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Collect study drug supply and diary (Sections 6.18.1 and 6.18.2)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete Global Impression of Severity (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)
- Apply study drug to target treatment area[2] (Section 5.6)
- Dispense study drug supply and diary (Sections 6.18.1 and 6.18.2)

[1] Study drug may be applied to the initial treatment area (~20% BSA) by the Investigator during the visit (but after the collection of pre-dose PK samples) or may be applied by the subject/caregiver after the study visit.
[2] If treatment area will be expanded up to 45% BSA, Investigator should apply study drug to this expanded treatment area during the visit but after the collection of pre-dose PK samples.

7.6 Visit 6 (Week 16 ± 3 days) – Home Visit (Section 6.19)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)

7.7 Visit 7 (Week 20 ± 5 days) – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Collect study drug supply and diary (Sections 6.18.1 and 6.18.2)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete Global Impression of Severity (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)
- Apply study drug to target treatment area[1] (Section 5.6)
- Dispense study drug supply and diary (Sections 6.18.1 and 6.18.2)

7.8 Visit 8 (Week 24 ± 5 days) – Early Termination – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Collect study drug supply and diary (Sections 6.18.1 and 6.18.2)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG (Section 6.6)

[1] If treatment area will be expanded up to 90% BSA, Investigator should apply study drug to this expanded treatment area during the visit but after the collection of pre-dose PK samples.

- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete Global Impression of Severity (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)

7.9 Visits 9 (Week 28 ± 3 days) – Safety Follow-up - Home Visit (Section 6.19)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)

8 STUDY ACTIVITIES FOR PART 2

Study activities for Part 2 are summarized in the Study Activities Schedule (Table 2).

8.1 Screening Visit (Day -7 to -1) – Site Visit

- Obtain written informed consent/assent (Section 6.1)
- Review eligibility criteria (Section 6.2)
- Collect demographic information and document medical history (Sections 6.3)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis[1] and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG (Section 6.6)
- Collect vital signs (Section 6.7)
- Complete physical examination, including height and weight collection (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Collect blood samples for hematology and chemistry[9] (Sections 6.15.1.1 and 6.15.1.2)

[1] Samples collected for urinalysis and clinical laboratory tests at the Screening Visit may be analyzed at a local lab.

8.2 Baseline Visit 1 (Week 1/Day 1) – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Review eligibility criteria (Section 6.2)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG and Holter monitoring (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete clinician-reported global impression of severity scale (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)
- Randomize subject (Section 6.18)
- Apply study drug to all areas of ichthyosis (Section 5.6)

8.3 Visit 2 (Week 1/Day 2) – Site Visit

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Complete VIIS (Section 6.9)
- PD sample collection (Section 6.14)
- PK sample collection[1] (blood only) (Section 6.16)
- Apply study drug to all areas of ichthyosis (Section 5.6)
- Dispense study drug supply and diary (Sections 6.18.1 and 6.18.2)

8.4 Visit 3 (Week 4 ± 3 days) – Telephone Check-In (Section 6.20)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)

[1] Study drug may be administered at the study site after pre-dose PK samples have been collected.

8.5 Visit 4 (Week 8 ± 5 days) – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG and Holter monitoring (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete clinician-reported global impression of severity scale (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection[1] (blood and urine) (Section 6.16)
- Apply study drug to all areas of ichthyosis (Section 5.6)
- Dispense and collect study drug supply and diary (Sections 6.18.1 and 6.18.2)

8.6 Visit 5 (Week 12 ± 3 days) – Telephone Check-In (Section 6.20)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)

8.7 Visit 6 (Week 16 ± 5 days) – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete clinician-reported global impression of severity scale (Section 6.10)

[1] Study drug may be administered at the study site after pre-dose PK samples have been collected.

- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection[11] (blood only) (Section 6.16)
- Apply study drug to all areas of ichthyosis (Section 5.6)
- Dispense and collect study drug supply and diary (Sections 6.18.1 and 6.18.2)

8.8 Visit 7 (Week 20 ± 3 days) – Telephone Check-In (Section 6.20)

- Record concomitant medications and adverse events (Sections 6.4 and 6.5)

8.9 Visit 8 (Week 24 ± 5 days) – Early Termination – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Collect urine sample for urinalysis and pregnancy test, if applicable (Sections 6.15.1.3 and 6.15.1.4)
- 12-lead ECG and Holter monitoring (Section 6.6)
- Collect vital signs (Section 6.7)
- Symptom-directed physical exam (Section 6.8)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)
- Complete VIIS (Section 6.9)
- Complete clinician-reported global impression of severity scale (Section 6.10)
- PD sample collection (Section 6.14)
- Collect blood samples for hematology and chemistry (Sections 6.15.1.1 and 6.15.1.2)
- PK sample collection (blood and urine) (Section 6.16)
- Collect study drug supply and diary (Sections 6.18.1 and 6.18.2)
- Conduct Subject Exit Interview[1] (Section 6.21)

8.10 Visit 9 (Week 28 ± 5 days) – Safety Follow-up – Site Visit

- Collect Patient/Observer-reported scales (Section 6.11)
- Record concomitant medications and adverse events (Sections 6.4 and 6.5)
- Complete dermatologic examination (Section 6.12)
- Take digital photography (Section 6.13)

[1] Subject Exit Interview should be conducted within 30 days of the scheduled visit.

- Complete VIIS (Section 6.9)
- Complete Global Impression of Severity (Section 6.10)

9 ADVERSE EVENT REPORTING

AEs will be collected from the time the subject signs the informed consent form through 30 days after the last study drug administration.

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered related to the study drug.

Abnormal laboratory and other abnormal investigational findings (i.e., physical exam) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are otherwise considered clinically relevant by the Investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

9.1.1.1 Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the Screening Visit that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

Pregnancies are not considered AEs but must be reported, see Section 9.1.8.

9.1.1.2 Recording Adverse Events

All AEs must be recorded in the site's study records and the AE CRF. Investigators should use correct medical terminology when recording events and avoid abbreviations.

The Investigator should attempt to establish a diagnosis of the AE based on signs, symptoms and/or other clinical information. The diagnosis, and not the individual signs/symptoms or laboratory abnormalities, should be documented in the subject's source documents and the CRF unless the etiology of the event is unknown. If signs/symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE. If a diagnosis is subsequently established, it should be reported as follow-up information.

An assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to study drug, the interventions required to treat it, and the outcome.

9.1.1.3 Assessment of Causality and Severity

For each AE recorded, the Investigator will make an assessment of causality and severity as follows:

1. Relationship to Study Drug: The Investigator must assess whether they consider an AE to be drug-related. In assessing this relationship, the Investigator must use information about the drug as outlined in the Investigator's Brochure, the subject's pre-existent medical conditions/concurrent medication, and chronology of the event relative to drug administration. The following definitions will be used:
   - **Definitely or possibly related** applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered by the Investigator (or other qualified physician) to have at least a possible relationship to study drug.
   - **Unlikely or not related** applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered by the Investigator (or other qualified physician) to have no relationship, or an unlikely possibility of a relationship, to study drug.
2. Event Severity: The Investigator will be asked to use their medical judgment to assess the severity of the AE.

   The following are guidelines to be used by the Investigator to judge the event severity of an AE:

   - Mild - awareness of sign or symptom, but easily tolerated
   - Moderate - discomfort enough to cause interference with usual activity
   - Severe - incapacitating with inability to work or perform usual activity
   - Life-Threatening
3. Duration: Start and end dates and times, or if continuing.
4. Frequency: whether the event is a single episode, recurrent or continuous.
5. Action taken.
6. Whether it constitutes a SAE, per definition below.
7. Outcome: resolved, resolved with sequelae, continuing, death, or unknown (only for subjects that are lost to follow-up).

9.1.2 Treatment-Emergent Adverse Events

A TEAE will be an AE that occurred during the study after the first dose of study drug or that was present prior to dosing and exacerbates after the first dose of study drug.

9.1.3 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death: This includes death unrelated to the study drug (e.g., car accident). If some subject dies during the study and an autopsy is performed, autopsy results will become part of the subject's study chart and a copy should be sent to the Sponsor.
- Life-threatening experience: Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Required or prolonged inpatient hospitalization: Exceptions will be hospitalizations for a) elective or preplanned treatment for a pre-existing condition that is unrelated to the

indication under study and has not worsened since the start of study drug or b) treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.

- Persistent or significant disability/incapacity.
- Congenital anomaly.
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered a SAE when, based upon medical judgment, they may jeopardize the patient and may require intervention to prevent one of the outcomes listed above.

9.1.4 Unexpected Adverse Event

An unexpected adverse event is defined as an AE, the nature or severity of which is not consistent with the information in the Investigator's Brochure.

9.1.5 Reporting Serious Adverse Events

The Investigator is responsible for reporting all SAEs, regardless of causality, to the Sponsor designee within 24 hours of learning of the occurrence. SAEs should be sent to:

[redacted]

(Local toll-free numbers will be provided on the SAE report form cover sheet.)

The reporting timeframe starts when the subject signs the informed consent or assent form through 30 days after the last study drug administration. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. These preliminary reports will be followed by detailed descriptions that will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

A follow-up SAE Report must be submitted within 24 hours of the Investigator receiving the follow-up information (such as information regarding complications, progression or resolution).

An SAE that is considered completely unrelated to a previously reported event should be reported separately as a new SAE.

The procedures for reporting SAEs are as follows:

- Complete the "Serious Adverse Event Report Form." The Investigator may contact Pharmacovigilance via the telephone hotline for assistance with SAE reporting.
- Fax or email the SAE Form to the attention of Pharmacovigilance within 24 hours of the Investigator's knowledge of the event.

The original copy of the SAE Report Form and the fax confirmation sheet (or email) must be kept with the source documentation at the study site.

Follow-up information should be communicated the same way, using a new SAE Report Form stating that it is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

The Investigator and study personnel should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include clinical laboratory

tests not specified in the protocol, histopathologic examinations, or consultations with specialists. The Sponsor or their designee may also request the Investigator to conduct supplemental assessments.

If the SAE was not previously documented in the Investigator's Brochure and is thought to be related to study drug, the Sponsor or their designee may urgently require further information from the Investigator for regulatory authority reporting. The Sponsor may need to issue an Investigator Notification to inform all Investigators involved in any study with the same drug that this SAE has been reported.

The Investigator should notify Pharmacovigilance of any death or SAE occurring after a subject has withdrawn from the study when such a death occurs within 30 days of the last dose of study drug and may reasonably be related to the study drug.

9.1.6 Follow-up of Adverse Events

All AEs will be followed until stabilization/resolution or until clinical database lock.

All SAEs will undergo active follow-up until resolved or the event becomes chronic or stable. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the safety database.

9.1.7 Reporting Serious Adverse Events to Regulatory Health Authorities/ Institutional Review Boards/Research Ethics Boards/Independent Ethics Committees

The Investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to their local IRB/REB/IEC.

The Investigator must promptly report to his or her local IRB/REB/IEC all unanticipated problems involving risks to subjects. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of study drug.

The Sponsor or their designee is responsible for appropriate reporting of relevant AEs, suspected unexpected serious adverse reactions (SUSARs) involving study drug, to all regulatory authorities.

In addition, the Sponsor or designee will be responsible for the submission of safety letters (e.g., SUSARs) to the central IRB/REB/IEC and to participating Investigators of all SUSARs involving study drug according to applicable regulations.

After termination of the clinical study (determined as last subject, last visit), any unexpected safety issue that changes the risk-benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

9.1.8 Reporting Pregnancies

Pregnancies will be reported from the time the subject signs the informed consent form through final study visit or 30 days after the last study drug administration, whichever is later.

To ensure subject safety, each pregnancy in a subject on study drug must be reported to Pharmacovigilance within 24 hours of learning of its occurrence. Subjects who become pregnant will be withdrawn from the study. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a subject's source documents and a Pregnancy Notification and Outcome Form and reported by the Investigator to Pharmacovigilance using the same procedure for reporting SAEs detailed in Section 9.1.5. A pregnancy, by itself, is not an SAE. Pregnancy follow-up should also be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any pregnancy-related SAE (e.g., spontaneous abortion, birth defect) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form and reported per SAE reporting procedures in Section 9.1.5.

10 STATISTICS

Part 1 and Part 2. Safety data will be systematically reviewed throughout Part 1 and Part 2 of the study by the independent, unblinded DSMB. Statistical analyses for Part 1 and Part 2 will be described *a priori* in a Statistical Analysis Plan (SAP) generated prior to Part 1 database lock. Any *post-hoc* analyses in either of the Part 1 or Part 2 final reports will be clearly labeled as such. Because both Part 1 and Part 2 will evaluate active treatment and vehicle subjects randomly assigned under a 2:1 active to vehicle schedule, it is anticipated that the Part 1 and Part 2 final reports will present a common set of analyses except for an additional sample size calculation in Part 1. Efficacy and Safety parameters will be statistically evaluated under separate final reports for Part 1 and for Part 2 of the study.

Part 1. Statistical analyses for Part 1 will address both efficacy and safety. Both safety and efficacy data obtained throughout the Part 1 period will be evaluated at the end of Part 1 by the sponsor and/or a contracted statistical organization, both of whom will have remained blinded until Part 1 data lock. The limited sample size of Part 1 may confine certain analyses to the descriptive aspect of the evaluation due to a limited sample size (i.e., inferential p-values may be omitted). *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 generate a sample size estimation for Part 2 as well as to perform between groups and within group descriptive and inferential statistical analyses. Baseline to ending Part 1 change scores for the primary efficacy endpoint (VIIS scaling severity) will be used to calculate a Part 2 samples size under the assumption of a mean change score of .5 units, a standard deviation obtained during Part 1, an alpha of 0.05 and a power of 90%. The sample size will be based on the initial target efficacy area that will have been selected at the beginning of Part 1 and independently evaluated over the 24-week course of the Part 1 study period. Assuming the absence of a safety impairment, the existence of a mean active treatment change score near or greater than 0.5 units, and recruitment feasibility of the estimated sample size, the Sponsor will instigate Part 2 of the trial.

Part 2. Statistical analysis of all Part 2 data will be carried out at the end of Part 2 by the Sponsor and/or a contracted statistical organization, both of whom will have remained blinded until Part 2 data lock. Part 2 analyses will be independent of Part 1 analyses with respect to efficacy parameters and will be used exclusively to support the sponsor's claim. However, at the end of Part 2, all available safety data will be stratified by Part 1 and Part 2 and presented in the Part 2 final report by stratum and overall.

10.1 Sample Size

Part 1 of the study will assess the effect size on the VIIS scaling severity score with ADX-102 1% topical dermal cream, and will confirm the sample size needed for Part 2. Part 2 is expected to require approximately 30 subjects.

The approximate number of 30 subjects for Part 2 was based on the NS-003 Phase 2 study which used the ISS endpoint. The mean ISS Scaling sub-score change from baseline was -0.7 with a standard deviation of 0.52. Conservatively, the change was set to -0.5 and the standard deviation to 0.6. A sample size of 20 achieves 94% power to detect a difference of 0.5 between the null hypothesis mean of 0.0 and the alternative hypothesis mean of -0.5 with an estimated standard deviation of 0.6 and with a significance level (alpha) of 0.05 using a two-sided one-sample t-test. If the above assumptions remain, except that the standard deviation is increased to 0.7, then a sample size of 20 achieves a power of 85%. The sample size of 30 is therefore based on these estimates requiring 20 subjects to be treated with ADX-102 1%. As subjects will be randomized in a 2:1 ratio, 10 subjects will be treated with vehicle.

10.2 Analysis Populations

The statistical analysis will be based on the analysis populations as defined below

Safety Population	All randomized subjects who use at least one dose of study drug, regardless of whether they undergo any study assessments.
Intent-to-Treat (ITT) Population	All randomized subjects who use at least one dose of study drug and have any post-dose assessments. Subjects are evaluated according to the study drug to which they are randomized.
Per-Protocol (PP) Population	All ITT subjects will be considered PP if they dose with study drug and do not deviate from the protocol.

The following is a list of protocol violations which would exclude subjects from the PP population:

- Subject did not receive study drug as assigned.
- Subject did not meet all inclusion/exclusion criteria.

10.3 Accountability and Background Characteristics

10.3.1 Enrollment and Disposition

The number of subjects enrolled, by study population and Investigative site, will be presented by treatment group. The primary reasons for discontinuation will be summarized by treatment and based on the safety population. The number and percentage of subjects with protocol deviations or subjects requiring rescue therapy leading to exclusion from the PP population will be presented by reason for exclusion, stratified by treatment. All deviations and rescued subjects will be listed.

10.3.2 Subject Characteristics

Subject characteristics will be obtained at the Screening prior to randomization and will be summarized by treatment group and overall. Summaries will include descriptive statistics for

continuous measures (sample size, mean, standard deviation [SD], median, minimum, maximum) and for categorical measures (sample size, frequency and percentages).

Subject characteristics will be summarized on all study populations.

10.3.3 Treatment Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the subjects and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group by means of descriptive statistics (sample size, mean, SD, median, minimum and maximum).

10.4 Efficacy Analyses

A conclusion concerning efficacy will be based on evaluation of data in Part 2. A primary efficacy analysis will be conducted as well as a number of secondary efficacy analyses.

The primary efficacy endpoint (VIIS scaling severity as assessed by the Investigator in the target efficacy area) as well as all secondary efficacy variables that are captured on a continuous or semi-continuous scale (e.g., VIIS erythema score, central reader assessed VIIS scales, EQ-5D-5L, clinical global impression of severity, Patient/Observer impression scales, Patient-Reported Itching, CDLQI/DLQI, lipid biomarkers and TEWL) will be expressed as baseline to ending change scores. Two-sided 95% confidence intervals (CIs) will be computed and used descriptively for all variables but also to evaluate change relative to a standard for some variables (i.e., by determining whether the CI includes or excludes the standard).

The two-sided 95% CI for VIIS scaling severity will serve as the primary analysis and will be used to evaluate this primary endpoint as follows. An efficacy claim will be made if: 1) the lower confidence interval is above zero, 2) the mid-point of the confidence interval is at least 0.5 units is size, and 3) at least 50% of subjects have favorable change scores of one or greater.

The primary and secondary scores measured on a continuous or semi-continuous scale also will be evaluated using Mixed Model Repeated Measures to assess the effects of treatment (active vs. vehicle), time (per collection schedule), and treatment x time. In addition to descriptive statistics for the raw data used in each model, the LS means and standard errors will be reported for each main effect and interaction, as well as for treatment contrasts (i.e., active LS mean minus vehicle LS mean) at each data collection time point. If informative, covariates may be added to one or more models. Statistical significance unadjusted for multiplicity for main effects, interactions and contrasts will be reported. However, neither the main effect of treatment nor the treatment contrasts at time points are expected to be statistically significant ($p \leq 0.05$) due to power restrictions at the between group level imposed by recruiting realities.

Response over time will be converted to one or more Area Under the Curve parameters and evaluated using a generalized linear model. VIIS outcome scores and other continuous or semi-continuous outcome variables will be evaluated using a Mixed Model Repeated Measures (MMRM) analysis. Conversion of VIIS or other scales to indicate response (yes/no) will occur (e.g., 0.5 VIIS improvement, 1 unit VIIS improvement) and will be evaluated as secondary endpoints. Logistic or Generalized Estimating Equation (GEE) modeling will be used to evaluate incidence of response overall and/or by time. Time to Event analysis (e.g., Kaplan-Meier with log rank test, proportional hazards [PH] modeling) will be used to evaluate time to response.

To increase statistical power, covariates may be incorporated into the computation of 95% confidence intervals (e.g., through the use of a mean centered covariate in a regression model to

predict the mean pre-treatment to post-treatment difference) and/or incorporated into logistic, GEE, PH, MMRM and generalized linear models.

Categorical variables other than responder status will be descriptively summarized in contingency tables. Selective inferential analysis at each time point or across time points will be conducted using non-parametric or exact statistics with or without further stratification as described in the SAP.

10.5 Safety Analyses

10.5.1 Adverse Events

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 SAP will contain mock tables for all safety relevant information which will be produced for each study part and over the entire study.

Safety tables will contain by treatment and combined treatments information concerning AEs, TEAEs, SAEs, unexpected AEs and clinical safety laboratory values. Treatment and vehicle group safety narratives will be written. If required a safety narrative will be written for selected subjects. AEs, TEAEs, unexpected AEs and SAEs will be coded according to the Medical dictionary for Regulatory Activities (MedDRA) preferred terms. 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.

If inferential analysis for any safety variable seems appropriate, the comparison will be made using an appropriate statistical test and designated as *post-hoc*.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and the Contract Research Organization (CRO) conducting trial management will implement a system of quality assurance that includes all elements described in this protocol. Within this system, standard operating procedures (SOPs) from the Sponsor and CRO will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and Good Clinical Practices (GCP). Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

12 STUDY ADMINISTRATION

12.1 Institutional Review Board / Research Ethics Board / Independent Ethics Committee

The protocol and all protocol amendments must be signed and dated by the Investigator and approved in writing by the applicable IRB/REB/IEC in accordance with GCP prior to

implementation. In addition, the IRB/REB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects prior to implementation.

The Investigator must provide an annual report to the IRB/REB/IEC on the progress of the study including number of subjects enrolled, discontinued, and SAEs, unless otherwise specified by the IRB/REB/IEC. It is required that a yearly review of the protocol by the IRB/REB/IEC be documented in a letter from the IRB/REB/IEC. The Investigator must provide notification to the IRB/REB/IEC of the completion, termination or discontinuation of the study.

The Investigator must supply the Sponsor with copies of all written correspondence with the IRB/REB/IEC.

The Investigator will make all attempts to ensure that the IRB is constituted and operates in accordance with regulatory requirements, ICH GCP and any local requirements.

12.2 Ethical Conduct of the Study

The clinical study will be carried out in keeping with national and local legal requirements, including in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) Code of Federal Regulations (CFR) Title 21 [Part 50, Part 54, Part 56, Part 312 and Part 11] as well as the ICH GCP E6 Guidelines. This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations [including European Directive 2001/20/EC, US CFR Title 21], and with the ethical principles laid down in the Declaration of Helsinki.

12.3 Subject Informed Consent / Assent

The Sponsor will provide sample Informed Consent and Assent Forms for use in this trial. Any changes to the proposed consent and assent forms suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB/REB/EC. The Investigator or designee will provide the Sponsor with a copy of the IRB/REB/IEC-approved informed consent and assent forms prior to the start of the study.

Before each subject is enrolled in the clinical study, written informed consent will be obtained according to the regulatory and legal requirements of the participating site. Subjects who are under the age of 18 (or lower if age of consent is less than 18 in a specific country) and whose legal guardian or caretaker has provided written informed consent will provide their assent to participate.

The subjects should sign the current final IRB/REC/EC approved consent form. The process of obtaining informed consent and assent should be documented in the subject source documents. Each Investigator must retain the original signed and dated informed consent and assent forms. A copy of the signed and dated informed consent and assent forms will be given to the subject. No subject can enter the study, or have study specific assessments performed before his/her informed consent has been obtained.

The Informed Consent and Assent Forms should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the patient to participate. Revisions to the consent forms required during the study must be approved by the Sponsor, and a copy of the revised consent forms provided to the Sponsor. For any updated or revised forms, the subjects must be re-consented for continued participation in the study.

12.4 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and qualified study personnel must not disclose such information without prior written approval from the Sponsor. The Investigator agrees not to use or disclose protected health information other than as permitted or required by the subject authorization or as required by law.

Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified on the CRFs and other documents submitted to the Sponsor by their initials (if locally permissible) and/or assigned subject number; not by name. Documents that identify the subject (e.g., the signed informed consent form) must be maintained in confidence by the Investigator. All study documents are provided by the Sponsor in confidence to the Investigator and his/her qualified study personnel. None of this material may be disclosed to any party not directly involved in the study without Sponsor's written permission. The Investigator must assure that subjects' anonymity will be maintained. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

12.5 Protection of Subject Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational study drug(s) used in this study and to support the development and interpretation of the trials clinical outcomes assessments.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the collection and processing of personal data and for the Investigator to allow direct access to his or her original medical records for study-related monitoring, audit(s), IRB/REB/EC review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

12.6 Study Monitoring

Prior to initiation of the study at a study site, the Study Monitor, who is an authorized individual designated by the Sponsor, will visit the study site to verify the qualifications of the Investigator and study team, inspect the adequacy of the facilities and inform the study team of their responsibilities and the procedures to ensure proper conduct of the study. During the conduct of the study the Study Monitor will visit the sites to verify adherence to the protocol, assess drug accountability, data integrity and subject safety. The monitors will conduct 100% source document verification of subject data by comparing the CRFs with the source documents to ensure accuracy and consistency.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will have access to all records necessary to ensure integrity of the data and safety of the subject, and will periodically review the progress of the study with the Investigator.

Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately.

12.7 Case Report Forms and Source Documents

An electronic data capture (EDC) system will serve as the data management system for this study.

The Investigator will be responsible for the accuracy of the data entered in the EDC system and ensure that the data collected are accurate and complete. Data will be monitored within the EDC system by the study monitor who has only reading rights. Any changes required following monitoring will be made by the Investigator or qualified study personnel and will be documented with a full audit trail within the EDC system. The responsible study monitor will check data at the monitoring visits to the clinical study site.

The Investigator or qualified study personnel will prepare and maintain adequate and accurate study documents (e.g., medical records, ECGs, AE and concomitant medication reporting, source data collection forms, etc.) designed to record all observations and other pertinent data for each subject. It is recommended that the author of an entry in the source documents be identifiable.

Source data may be directly captured from devices, transferred from third parties (e.g., laboratory data), or entered manually into the EDC system in use at the clinical center. In such case, many of the source data will only be available electronically. The remainder of the data, captured initially on paper, may be entered retrospectively into the EDC system.

For each subject, CRF and corresponding source records will be maintained at each clinical site. CRFs should be completed in a timely manner, and every effort should be made to have forms completed and current in anticipation of a visit by the Sponsor or designee. Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 13.

The Investigator will allow the Sponsor or designee(s), contract designees, authorized regulatory authority inspectors, and the IRB/REB/IEC to have direct access to all documents pertaining to the study.

12.8 Access to Source Documents and Audits

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The Investigator should immediately notify the Sponsor of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative or designee. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB/REB/IEC. Such audits/inspections may take place at the Sponsor's site(s), the CRO, or at the clinical sites, including laboratories, pharmacies and any other facilities used for the study. The Investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the EDC system.

12.9 Protocol Deviations and Violations

Exceptions to the eligibility criteria will not be granted. It is expected that subjects will meet all eligibility criteria. Departures from the protocol should be avoided, unless required for the safety of the subject. Should other unexpected circumstances arise that will require deviation from protocol-specific procedures, the Investigator should contact the Sponsor to discuss the appropriate course of action.

The Investigator should document all protocol deviations/violations in the subject's CRF and source documents or the Investigator Site File, if appropriate. Protocol deviations will be documented by the study monitor and will be included in the final clinical study report. Protocol deviations should be submitted to IRB/REB/IEC, in accordance with the site's IRB/REB/IEC requirements.

12.10 Amendments to the Protocol

To alter the protocol, amendments must be written by the Sponsor and approvals must be received from all parties that approved the original protocol (IRB/REB/IEC, and if applicable, the local regulatory authorities) before implementation. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.

The Sponsor may make administrative changes (i.e., changes that do not significantly affect subject safety, the study's scope or scientific quality) without a formal protocol amendment.

12.11 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

12.12 Investigator Responsibilities

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IEC/REB/IRB, and/or the regulatory authority(ies).

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and local requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

12.13 Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the Investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

12.14 Registration of Clinical Studies and Disclosure of Results

The Sponsor or designee will register and/or disclose the existence of and the results of clinical studies as required by law.

12.15 Publication and Disclosure Policy

As is customary for multicenter trials, publication by individual study sites or Investigator/Institution will not be allowed without the explicit written permission of the Sponsor. The Sponsor will determine authorship of the principal study manuscript(s) in conjunction with the Investigators, in abiding with current guidelines and requirements of medical journals. For such manuscript(s), masthead roles for Investigators will be determined based on subject enrollment and scientific contributions to the study.

13 RETENTION OF RECORDS

The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents, as listed below, must be retained by the Investigator for as long as required by national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required.

Essential documents include but are not limited to:

- IRB/REB/IEC approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies
- Subjects' informed consent / assent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study document

All source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, study drug dispensing/disposition records) that support data in the CRFs of each study subject must be retained in the files of the responsible Investigator.

According to ICH guidelines for GCP, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by relevant regulatory or legal authorities.

If the responsible Investigator retires, relocates or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

No records should be disposed of without written approval of the Sponsor.

14 REFERENCES

1. Rizzo WB, S'Aulis D, Jennings MA, Crumrine DA, Williams ML, Elias PM. Ichthyosis in Sjögren-Larsson syndrome reflects defective barrier function due to abnormal lamellar body structure and secretion. Arch Dermatol Res. 2010 Aug;302(6):443-51.
2. Rizzo WB. The role of fatty aldehyde dehydrogenase in epidermal structure and function. Dermatoendocrinol. 2011 Apr-Jun; 3(2): 91–99.
3. Rizzo WB. Fatty aldehyde and fatty alcohol metabolism: review and importance for epidermal structure and function. Biochim. Biophys. Acta., 2014. 1841(3): 377 - 89.

4. Rizzo WB, Bailey Z, S'Aulis D., Ergasheva N. Aldehyde Trapping Agent NS2 Blocks Formation of Fatty Aldehyde Adducts with Phosphatidylethanolamine and Suggests Potential Therapeutic Approach for Sjogren-Larsson Syndrome. [Abstract] Mol Genet and Metab, 2015 Mar; 114 (3): Page 362A.
5. Maeda A, Maeda T, Golczak M, Chou S, Desai, A, Hoppel CL, Matsuyama S, Palczewski K. Involvement of all-*trans*-retinal in acute light-induced retinopathy of mice. J Biol. Chem. 2009 May; 284 (22): 15173-15183.