CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER ATI-502-AD-201

A PHASE 2A SAFETY STUDY OF ATI-502 TOPICAL SOLUTION IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

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PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Number: ATI-502-AD-201

Version 2.0: 17 August 2018

Protocol Title: A PHASE 2A SAFETY STUDY OF ATI-502 TOPICAL SOLUTION IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Sponsor's Signature:

8/17/18

David Gordon, MB, ChB
Chief Medical Officer
Aclaris Therapeutics, Inc.

Date

8-20-2018

Christopher Powala
Chief Regulatory and Development Officer
Aclaris Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

Protocol Number: ATI-502-AD-201

Protocol Title: A Phase 2a Safety Study of ATI-502 Topical Solution in Subjects with Moderate to Severe Atopic Dermatitis

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice and the Declaration of Helsinki.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such materials will only be provided as necessary to site personnel involved in the conduct of the trial, involved IRBs or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document used will have the approval of the IRB appropriate for my institution.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete the case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of the Sponsor, the IRB, and/or local regulatory authorities. I will ensure that I and my staff are available to meet with Sponsor representatives during regularly scheduled monitoring visits.

I will notify the Sponsor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to the Sponsor as soon as possible.

Investigator Signature:

_____ _____

Investigator signature Date

_____

Investigator printed name

1. AMENDMENT HISTORY

1.1. Amendment Rationale

The original protocol dated 23 April 2018 has been amended to change the heart rate inclusion criteria to allow subjects to enter the study if they have a heart that is below 45 or above 100 that is not deemed clinically significant by the investigator. The rationale for this change is ensure that subjects are not excluded from the subject that are clinically stable based upon the treating physician's judgement. The protocol was also amended to allow subjects to enter the study even though their screening photographs were not approved by the panel of 3 dermatologists. The rationale for this change is that due to flash photography and the close-up images of the photos there may be instances in which the photos do not accurately represent the disease status. If a subject's screening photographs are rejected by the review panel, the treating physician will be contacted to review the individual case and allow his/her clinical judgement of the subject to over-ride the photo review assessment.

1.2. Protocol Changes

Protocol Version	Date	Section	Revisions
Version 1.0		NA	Original Protocol
Version 2.0	17 August 2018		
		Synopsis	Revised exclusion criteria number 14 to read that subjects with a resting heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes if considered to be caused by a clinically significant pathology would be excluded. The investigator may enter a patient with a HR outside of these values if considered to have no clinical significance.
		Section 7.5	Revised text to allow those subjects that may have been rejected by the panel reviewers based on screening photographs to be enrolled if the treating physician does not feel that the photographs represent the true state of the disease. New text added: In cases where the photographs do not properly characterize the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject.
		Section 8.0	Updated table of assessments to include language regarding the review of subject screening photos. Following language added to footnote 8: In cases where the photographs do not properly characterize the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject.

Protocol Version	Date	Section	Revisions
		Section 9.3	Revised exclusion criteria number 14 to read that subjects with a resting heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes if considered to be caused by a clinically significant pathology would be excluded. The investigator may enter a patient with a HR outside of these values if considered to have no clinical significance.
		Section 12.1	Deleted the text : All identified target treatment areas will be assessed using the Physician's Global Assessment at Visits 1, 2, 3, 4, 5 and 6. Any new areas of AD that develop after Visit 2 will not be assessed by the PGA.
		Section 12.6	Updated section to add in the following text: In cases where the photographs do not properly characterize the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject.

2. SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company:
Aclaris Therapeutics, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product:
ATI-502 Topical Solution, 0.46%</td></tr>
<tr><td>Protocol Number: ATI-502-AD-201</td><td>Phase: 2a</td><td>Country: USA</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2a Safety Study of ATI-502 Topical Solution in Subjects with Moderate to Severe Atopic Dermatitis</td></tr>
<tr><td colspan="3">Study center(s): Approximately 6 US investigational sites will participate in the study.</td></tr>
<tr><td colspan="2">Studied period (years):
Estimated date first patient enrolled: June 2018
Estimated date last patient completed: Dec 2018</td><td>Phase of development:
2a</td></tr>
<tr><td colspan="3">Study Outcome Measures:
Primary:
The primary outcome measure for this study is to assess the safety and tolerability of ATI-502 Topical Solution, 0.46% in subjects with moderate to severe atopic dermatitis.
Secondary:
The secondary outcome measures for this study are to assess the following:
Change from baseline in Physician Global Assessment (PGA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%
Change from baseline in body surface area affected by atopic dermatitis following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
Change from baseline in Eczema Area and Severity Index (EASI) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
Change from baseline in the subjects Signs of Atopic Dermatitis (SAD) assessment following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
Change from baseline in Subjects Pruritis Assessment (SPA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.</td></tr>
<tr><td colspan="3">Study Design: This is an open label, multicenter, phase 2a study designed to evaluate the safety and tolerability of ATI-502 Topical Solution, 0.46% in male and female subjects with moderate or severe atopic dermatitis (AD) as defined by the Hanifin and Rajka criteria. Subjects will be required to apply ATI-502 study medication to their identified AD treatment areas twice a day for a total of 4 weeks. Subjects will be allowed to treat new disease areas if they appear after Visit 2. All subjects will be required to complete a safety follow up visit 4 weeks post last study medication application.</td></tr>
<tr><td colspan="3">Number of subjects (planned):
30 subjects with moderate to severe atopic dermatitis</td></tr>
</table>

Inclusion Criteria:

Subjects must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female subjects ≥ 18 years old at the time of informed consent.
3. Subject must have diagnosis of AD according to the Hanifin and Rajka criteria.
4. Subject must have a diagnosis of moderate (PGA =3) or severe (PGA=4) AD for a period of ≥6 months prior to the first dose of study medication (Visit 2).
5. Subject Visit 1 photographs are approved for enrollment by the dermatology review panel.
6. Body surface area involvement must be between 2-20% (excluding scalp, face, palms of hands, soles of feet, groin and genitalia).
7. Subject must have an absolute neutrophil count and a platelet count within normal range.
8. Subject must be willing to refrain from washing area of treatment or swimming for 6 hours after each treatment application with ATI-502.
9. Subject must be willing to refrain from excess of sun exposure.
10. Subject is willing and able to follow all study instructions and be willing to attend all study visits.
11. Subjects must refrain from participating in strenuous exercise that would cause profuse sweating for a period of 6 hours after each treatment application with ATI-502.
12. Subject must refrain from using moisturizers, emollients, and sunscreen on target AD treatment area for the duration of protocol therapy.
13. Be in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of the subject or which might expose the subject to an unacceptable risk by study participation.
14. If a woman of childbearing potential (WOCBP), must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2) and agree to: use a highly effective method of birth control for the duration of the study; not be planning a pregnancy during the study duration and use contraception for 30 days after last application of study medication.
15. Sexually active male subjects must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last application of study medication.

Exclusion Criteria:

1. Subject has any signs or symptoms associated with AD therapy (e.g., history of anaphylaxis, hypersensitivity reactions, skin atrophy, striae, pigmentary changes) which, in the investigator's opinion, might impair evaluation of the AD or which exposes the subject to unacceptable risk by study participation.
2. Subjects unable to complete the following required washout periods:
   - Phototherapy within 4 weeks prior to Visit 1.
   - Systemic immunosuppressant or immunomodulatory therapy (e.g. etanercept, alefacept, infliximab, methotrexate) within 16 weeks prior to Visit 1.
   - JAK inhibitors (systemic and topical) within 4 weeks prior to Visit 1.

- Systemic corticosteroids (intranasal and inhaled corticosteroids are allowed) within 4 weeks prior to Visit 1.
- Cytostatic agents within 4 weeks prior to Visit 1.
- Crisaborole within 2 weeks prior to Visit 1
- Dupilumab or other monoclonal antibody within 3 months prior to Visit 1.
- Systemic antibiotics with 2 weeks prior to Visit 1.
- Topical treatments for atopic dermatitis (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) within 1 week prior to Visit 1.
- Live attenuated vaccine treatment within 12 weeks prior to Visit.

3. Use of prescription moisturizers within 7 days of Visit 1.
4. Subject has used any emollients/moisturizers on the planned treatment area (s) within 4 hours of Visit 1.
5. Subject has clinically infected AD.
6. Subject is currently using an oral H1 antihistamines (e.g. diphenhydramine, terfenadine) UNLESS the subject is on a stable dose for at least 14 days prior to Visit 1.
7. Clinically significant laboratory abnormalities at Visit 1 that, in the opinion of the Investigator, would make the subject a poor candidate for the study.
8. History of, or current, severe, progressive or uncontrolled renal, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (renal disease) or hematological disease, neurologic or cerebral disorders, infectious disease or coagulation disorders that, as determined by the Investigator, would preclude participation in and completion of study assessments.
9. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with: a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (basal or squamous cell carcinoma) treated successfully at least 1 year prior to study entry with no evidence of disease.
10. Evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment or history of incompletely treated or untreated tuberculosis. Subjects who have completed therapy for latent tuberculosis may participate.
11. History of a serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Visit 2. Subjects on an antibiotic for a non-serious, acute local infection must complete the course prior to enrollment into the study.
12. Positive serological test for HIV (antibody), HCV (antibody), or HepB (HBsAg).
13. Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before study enrollment. Subjects with a history of frequent outbreaks of Herpes Simplex Virus (defined as 4 or more outbreaks a year).
14. Screening ECG findings of:
    a. QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose).

b. Resting heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes if considered to be caused by a clinically significant pathology. The investigator may enter a patient with a HR outside of these values if considered to have no clinical significance.
c. Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm).
d. Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block.
e. Acute or chronic signs of ischemia.
f. Left Bundle Branch Block.
g. Prior myocardial infarction.

15. Subject has participated in an investigational drug trial within 30 days prior to Visit 1.

Investigational product, dosage and mode of administration:

Open label ATI-502 Topical Solution, 0.46% will be applied to the identified target treatment AD areas twice a day for 4 weeks. The ATI-502 study medication will be supplied in amber, glass bottles and subjects will use disposable droppers to apply the topical solution to their treatment areas.

Duration of treatment:

All subjects will apply ATI-502 Topical Solution, 0.46% twice a day for 4 weeks followed by a post treatment follow up visit at week 8.

Statistical methods:

Safety and efficacy results will be summarized and presented by visit, with no inferential statistics presented. Parameters related to safety and tolerability will be treated as primary analysis variables. Efficacy parameters will be treated as secondary endpoints.

All data will be summarized by visit, with presentations based on the nature of the parameter. For binary data such as presence or absence of treatment-emergent adverse events, the incidence will be presented along with the overall number of subjects and percentages. External clinical laboratory and similar externally sourced data will be summarized as binary outcomes based on the determination of values beyond applicable normal ranges, and in some cases the assessment of clinical significance of deviations from normal ranges. For ordinal categorical data including efficacy data from PGA, EASI, SPA and SAD scores, and continuous data such as affected body surface area, summary statistics will be presented including N, mean, median, standard deviation, and standard error, by visit. Where applicable, the mean changes from baseline for ordinal categorical and continuous parameters will be presented by visit, along with N, median, standard deviation and standard error.

Analysis of Efficacy Outcome Measures:

Subject responder analyses will be conducted, by visit, based on the following criteria:

- The proportion of subjects whose active-treated lesions are judged to be clear or near clear on the PGA (PGA = ≤ 1) with a 2 grade or greater improvement from a baseline score of PGA=3 or PGA =4;
- The proportion of subjects whose active-treated lesions are judged to be clear on the PGA (PGA = 0);

- The proportion of subjects who had an improvement from baseline of at least 75% in EASI score (EASI – 75).

Other subject responder criteria will be established as appropriate from data observation and the results will be presented as above.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AV	Atrioventricular
BCC	Basil cell carcinoma
BID	Twice a day
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CRAs	Clinical research associates
CS	Clinically significant
DMSO	Dimethylsulfoxide
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C Vaccine
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IC_{50}	Half maximal inhibitory concentration
IRB	Institutional Review Board
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3

Abbreviation or Specialist Term	Explanation
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
PEG400	Polyethylene glycol 400
PGA	Physician Global Assessment
PI	Principal Investigator
SAD	Signs of Atopic Dermatitis
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SI	Subject Identifier
SN	Subject Number
SOPs	Standard operating procedures
SPA	Subjects Pruritis Assessment
sAG	Surface antigen
TSLP	Thymic stromal lymphopoietin
TyK2	Tyrosine kinase 2
ULN	Upper Limit of Normal
WOCBP	Woman of child bearing potential
WBC	White blood cell

5. INTRODUCTION

Aclaris Therapeutics, Inc. is developing ATI-502 Topical Solution for the treatment of stable patchy alopecia areata, vitiligo, androgenetic alopecia and atopic dermatitis. ATI-502 is a potent highly selective inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3).

5.1. Overview of Atopic Dermatitis

Atopic dermatitis or eczema is an inflammatory skin disorder characterized by dry, cracked, pruritic skin lesions that most often develops in childhood. Sixty percent of the reported cases develop within the first year of life and 85% of the cases develop by the age of 5 (Weston, 2017). The disorder often follows a pattern of spontaneous remission with intermittent flares of the disease and often continues into adulthood. The symptoms can range from mild to severe and can interfere with daily activities. While the disease is not a life-threatening illness, atopic dermatitis can significantly impact a patient's quality of life. In patients with moderate to severe disease the symptoms rarely clear without treatment. There are a number of topical treatment options including corticosteroids, calcineurin inhibitors, antihistamines, and antimicrobial agents that are used to treat atopic dermatitis however it has been over 15 years since a new topical therapy with a new mechanism of action has been approved.

5.2. Rationale for the use of ATI-502 in Atopic Dermatitis

The pathogenesis and etiology of atopic dermatitis (AD) is not completely understood as AD is a multifactorial disease developing from complex interactions between genetic, environmental and immunological factors (Bissonnette, 2016). Basic and translational research studies have identified several pathogenic pathways that promote atopic dermatitis. These studies have established that the pathogenesis of atopic dermatitis is complex. It involves a genetic predisposition to an impaired epidermal barrier, a key Th2-domiated immune response (interferon-γ; IFN-γ), immune changes beyond Th2 associated with IL-22, IL4/IL21, and TSLP (thymic stromal lymphopoietin), as well as Th2 allergens (e.g. pollen, house dust mites), microbial allergens and self-antigens(Eyerich, 2013). One commonality among the immune pathways is pivotal signaling through Janus kinases (JAKs): IFN-γ (JAK1/2); TSLP (JAK1/2); IL-22 (JAK1/TYK2); and IL-4/IL-21 (JAK1/3). Inhibition of the immune components of atopic dermatitis via JAK inhibition has become a leading candidate for a clinical treatment strategy (Alves, 2016). Initial clinical studies have confirmed the potential for both oral and topical treatment of atopic dermatitis with JAK inhibitors.

ATI-502 is a JAK1/3 inhibitor with enzyme IC_{50} activities of 2nM and 36nM against JAK1 and JAK3, respectively. At a cellular/physiologic level, ATI-502 inhibits interferon-γ-induced pSTAT1 activation with an IC_{50} of 38nM. The anticipated IC_{90} concentration is approximately 0.4μM. To expect ATI-502 to inhibit JAK1/3 mediated signaling, a significant excess of the inhibitor must be present in the target tissue. Based upon human skin permeation studies (Franz chamber with human skin) using the 0.46% ATI-502 formulation, ATI-502 concentrations in were extrapolated to be in range of 10-20μM in the dermis and epidermis. A 10μM concentration, combined with anticipated drug gradients, is anticipated to deliver sufficient drug to the epidermis and dermis to achieve tissue levels sufficient to inhibit JAK1/3 signaling and thereby, diminish immune mediated inflammation (Levy, 2015)(Bissonnette, 2016).

6. TRIAL OUTCOME MEAURES AND PURPOSE

6.1. Primary Outcome Measure

The primary outcome measure for this study is to assess the safety and tolerability of ATI-502 Topical Solution, 0.46% in subjects with moderate to severe atopic dermatitis.

6.2. Secondary Outcome Measures

The secondary outcome measures for this study are to assess the following:

- Change from baseline in Physician Global Assessment (PGA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%
- Change from baseline in body surface area affected by atopic dermatitis following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in Eczema Area and Severity Index (EASI) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in the subjects Signs of Atopic Dermatitis (SAD) assessment following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.
- Change from baseline in Subjects Pruritis Assessment (SPA) score following 4 weeks of treatment with ATI-502 Topical Solution, 0.46%.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open label, multicenter, phase 2a study designed to evaluate the safety and tolerability of ATI-502 Topical Solution, 0.46% in male and female subjects with a diagnosis of AD as defined by the Hanifin and Rajka criteria. Based on the 5-point Physician's Global Assessment (PGA) scale, subjects must have a score of 3 (moderate) or 4 (severe). Subjects will be required to apply ATI-502 study medication to their identified AD treatment areas twice a day (BID) for a total of 4 weeks. Subjects will be allowed to treat new disease areas with ATI-502 Topical Solution, 0.46% if they appear after Visit 2. All subjects will be required to complete a safety follow up visit 4 weeks post last study medication application.

A total of 30 evaluable subjects who are ≥ 18 years of age with a clinical diagnosis of moderate or severe AD will be enrolled to the study.

Subjects will be required to complete the following treatment visits:

Visit 1: Screening and Photographs for Study Entry Approval

Visit 2: Study Enrollment and First Treatment with Study Medication

Visit 3: Follow up Visit

Visit 4: Follow up Visit

Visit 5: Follow up Visit

Visit 6: End of Study Visit

7.2. Number of Subjects

A total of 30 evaluable subjects will be enrolled to the study at approximately 6 US investigational sites.

7.3. Duration of Treatment

The anticipated time for study enrollment is 6 months. The duration of the screening period could be up to 14 days. Once a subject is enrolled, the maximum duration of study treatment is 63 days (56 days plus a 7-day window).

7.4. Treatment Assignment

This is an open label study. All subjects will be treated twice daily for 4 weeks with ATI-502 Topical Solution, 0.46%.

7.5. Enrollment Procedures

Prior to a subject being allowed to enroll to the study, investigational sites will be required to submit the subject's baseline photographs to Canfield Scientific's database. Once the photos are received into the database a panel of three board certified dermatologists will review the baseline photographs. The panel will review and approve within 24 hours of receipt of the photographs into the Canfield imaging database. In cases where the photographs do not properly characterize

the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject. .

7.6. Subject Identifiers

The Investigator will assign a unique five-digit subject identifier (SI) to each subject at Screening (Visit 1).
The SI format will be NN-NNN, using leading zeroes as appropriate, where:

- The first 2 digits are the investigational site number assigned by Aclaris
- The final 3 digits are the subject number (SN), assigned in ascending numerical order by the Investigator or designee, without omitting or repeating any number, starting with 001.

For example, the SI for the twenty-third subject that signs an informed consent form at site number 01 would be 01-023. The subject will be identified using the SI in all study documentation for the duration of the study.

7.7. Replacement of Subjects

Enrolled subjects that do not complete all visits will be replaced to ensure that 30 evaluable subjects complete the study.

7.8. Criteria for Study Termination

This study may be terminated prematurely in whole or in part due to a change in the benefit/risk profile for ATI-502 Topical Solution such that continuation of the study would not be justified on medical or ethical grounds. This determination may be made by the Study Investigators in conjunction with the Sponsor, or by the Institutional Review Board (IRB) or the U.S. Food and Drug Administration (FDA). The Sponsor may also elect to terminate the study if enrollment is sufficiently slow to prevent the completion of the study in an acceptable timeframe, or if ATI-502 development is discontinued.

If the study is terminated prematurely, the Sponsor will notify the Study Investigators and the FDA. The Investigator must promptly notify all enrolled subjects and the IRB of study termination.

8. STUDY PROCEDURES

Table 2 provides a summary of all study specific assessments that are required for this protocol.

Table 2: Schedule of Assessments

	Screening	Baseline	Treatment			Post Treatment Safety Follow up Visit[13]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Week		0	1	2	4	8
Treatment Day	-14 to 0	1	8	15	29	56
Treatment Window(days)	N/A	N/A	± 3	± 3	± 3	+7
Informed consent[1]	▲					
Inclusion/exclusion criteria	▲	▲				
Physical exam[2]	▲					▲
Demographics & Medical History	▲					
Vital Signs[3]	▲	▲	▲	▲	▲	▲
Fitzpatrick Skin Type	▲					
Atopic Dermatitis History [4]	▲					
Clinical Chemistry and CBC[5]	▲	▲	▲	▲	▲	▲
QuantiFERON Gold[6]	▲					
Virology [HepB (HBsAg), HCV (antibody), HIV (antibody)]	▲[7]					
Serum Pregnancy	▲					
Urine Pregnancy		▲				▲
ECG	▲		▲	▲	▲	▲
Physician's Global Assessment (PGA)	▲	▲	▲	▲	▲	▲
Body Surface Areas Assessment	▲	▲	▲	▲	▲	▲
Identification of AD Treatment Area	▲	▲				
Eczema Area and Severity Index (EASI)	▲	▲	▲	▲	▲	▲
Subjects Pruritis Assessment (SPA)		▲	▲	▲	▲	▲
Signs of Atopic Dermatitis (SAD)		▲	▲	▲	▲	▲
Standardized Photography[8]	▲	▲	▲	▲	▲	▲
Dispensing of study medication[9]		▲	▲	▲		
Treatment with ATI-502		▲[10]	▲	▲	▲	
Subject Instructions[11]	▲	▲	▲	▲	▲	
Concomitant medications/therapies	▲	▲	▲	▲	▲	▲
Adverse Events[12]	▲	▲	▲	▲	▲	▲
[1]A written, signed ICF must be obtained from each subject prior to performing any study related procedure						

[2] A physical exam includes: general appearance, examination of head, eyes, ears, nose and throat, extremities, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment.
[3] Vital signs include: oral or ear temperature, blood pressure, heart rate, respiration rate (height and weight at baseline only).
[4] Prior therapies or treatments a subject received to treat AD must be documented for each subject.
[5] Serum chemistry panel to include: albumin, alkaline phosphatase, ALT, AST, BUN, bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, uric acid, total cholesterol, LDL, HDL triglycerides, and complete blood count including differential.
[6] All subjects must have a blood sample drawn to test for the tuberculosis virus (QuantiFERON Gold). The blood sample will be sent to a central laboratory for analysis and results must be received prior to enrolling the subject.
[7] All subjects will be required to have virology testing for HepB (HBsAG), HCV(antibody), and HIV (antibody). If a subject demonstrates to have serological evidence HepB (HBsAG), HCV (antibody) or HIV (antibody), the subject will not be allowed to enroll to the study.
[8]Canfield staff will review all photographs within 2 days of the photographs being submitted. If a re-take is required, Canfield will notify the site and the re-take photographs will need to be performed within 7 days of the visit. Prior to enrollment to the study, each subject's Visit 1 photos will be reviewed by a panel of board certified dermatologists to ensure that the subject's target areas for treatment meet the study entry criteria. In cases where the photographs do not properly characterize the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject.
[9]At visit 2, following confirmation that the subject is approved for enrollment to the study, the site will weigh and dispense supplies of ATI-502 study medication and disposable droppers to the subject for at home application of the study medication.
[10] All subjects will have their first application of study medication applied in the clinic during Visit 2. Subjects will continue to apply ATI-502 Topical Solution, 0.46% to all target areas twice a day for 4 weeks (Day 28) unless the subject meets the criteria for treatment interruption. If new areas of AD develop, subjects will be allowed to treat these areas with the ATI-502 study medication.
[11]Sites will be required to review with each subject the proper application of the study medication and remind that they must refrain from exercise that may cause excessive sweating, bathing or swimming for a period of 6 hours after the application of study medication. Subjects are also to be reminded that they may not apply moisturizers, emollients, or sunscreen to target AD areas during protocol treatment.
[12] All non-serious AEs will be collected from the time of first study medication application until the final study visit. Serious AEs will be collected from the time of consent through the final study visit.
[13]A final safety follow up visit will be conducted at week 8 (Visit 6). For those subjects that discontinue the study early, they must return to the clinic 4 weeks following the last study medication application for a final safety visit.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Subject Inclusion Criteria

Subjects must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Male or non-pregnant, non-nursing female subjects ≥ 18 years old at the time of informed consent.
3. Subject must have diagnosis of AD according to the Hanifin and Rajka criteria.
4. Subject must have a diagnosis of moderate (PGA =3) or severe (PGA=4) AD for a period of ≥6 months prior to the first dose of study medication (Visit 2).
5. Subject Visit 1 photographs are approved for enrollment by the dermatology review panel.
6. Body surface area involvement must be between 2-20% (excluding scalp, face, palms of hands, soles of feet, groin and genitalia).
7. Subject must have an absolute neutrophil count (ANC) and a platelet count within normal limits
8. Subject must be willing to refrain from washing area of treatment or swimming for 6 hours after each treatment application with ATI-502.
9. Subjects must be willing to refrain from excess of sun exposure.
10. Subject is willing and able to follow all study instructions and be willing to attend all study visits.
11. Subject must refrain from participating in strenuous exercise that would cause profuse sweating for a period of 6 hours after each treatment application with ATI-502.
12. Subject must refrain from using moisturizers, emollients, and sunscreen on target AD treatment area for the duration of protocol therapy.
13. Be in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair evaluation of the subject or which might expose the subject to an unacceptable risk by study participation.
14. If a woman of childbearing potential (WOCBP), must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2) and agree to: use a highly effective method of birth control for the duration of the study; not be planning a pregnancy during the study duration and use contraception for 30 days after last application of study medication.
15. Sexually active male subjects must agree to use a barrier method of contraception from the first application of study medication to at least 30 days after the last application of study medication.

9.2. Subject Exclusion Criteria

1. Subject has any signs or symptoms associated with AD therapy (e.g., history of anaphylaxis, hypersensitivity reactions, skin atrophy, striae, pigmentary changes) which, in the investigator's opinion, might impair evaluation of the AD or which exposes the subject to unacceptable risk by study participation.
2. Subjects unable to complete the following required washout periods:
   - Phototherapy within 4 weeks prior to Visit 1.
   - Systemic immunosuppressant or immunomodulatory therapy (e.g. etanercept, alefacept, infliximab, methotrexate) within 16 weeks prior to Visit 1.
   - JAK inhibitors (systemic and topical) within 4 weeks prior to Visit 1.
   - Systemic corticosteroids (intranasal and inhaled corticosteroids are allowed) within 4 weeks prior to Visit 1.
   - Cytostatic agents within 4 weeks prior to Visit 1.
   - Crisaborole within 2 weeks prior to Visit 1.
   - Dupilumab or other monoclonal antibody within 3 months prior to Visit 1.
   - Systemic antibiotics with 2 weeks prior to Visit 1.
   - Topical treatments for atopic dermatitis (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents) within 1 week prior to Visit 1.
   - Live attenuated vaccine treatment within 12 weeks prior to Visit1.
3. Use of prescription moisturizers within 7 days of Visit 1.
4. Subject has used any emollients/moisturizers on the planned treatment area (s) within 4 hours of Visit 1.
5. Subject has clinically infected AD.
6. Subject is currently using an oral H1 antihistamines (e.g. diphenhydramine, terfenadine) UNLESS the subject is on a stable dose for at least 14 days prior to Visit 1.
7. Clinically significant laboratory abnormalities at Visit 1 that, in the opinion of the Investigator, would make the subject a poor candidate for the study
8. History of, or current, severe, progressive or uncontrolled renal, hepatic, gastrointestinal, pulmonary, cardiovascular, genitourinary (renal disease) or hematological disease, neurologic or cerebral disorders, infectious disease or coagulation disorders that, as determined by the Investigator, would preclude participation in and completion of study assessments.
9. History of, current or suspected systemic or cutaneous malignancy and /or lymphoproliferative disease, other than subjects with: a history of adequately treated and well healed and completely cleared non-melanoma skin cancers (basal or squamous cell carcinoma) treated successfully at least 1 year prior to study entry with no evidence of disease.

10. Evidence of active or latent bacterial (including tuberculosis) or viral infections at the time of enrollment or history of incompletely treated or untreated tuberculosis. Subjects who have completed therapy for latent tuberculosis may participate.
11. History of a serious local infection (*e.g.*, cellulitis, abscess) or systemic infection including but not limited to a history of treated infection (*e.g.*, pneumonia, septicemia) within 3 months prior to Visit 2. Subjects on an antibiotic for a non-serious, acute local infection must complete the course prior to enrollment into the study.
12. Positive serological test for HIV(antibody), HCV (antibody), or HepB (HBsAg).
13. Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months before study enrollment. Subjects with a history of frequent outbreaks of Herpes Simplex Virus (defined as 4 or more outbreaks a year).
14. Screening ECG findings of:
    a. QTcF >450msec for males or >470msec for females (use of the ECG algorithm is acceptable for this purpose)
    b. Resting heart rate ≤ 45 or Heart Rate ≥ 100 beats/minutes if considered to be caused by a clinically significant pathology. The investigator may enter a patient with a HR outside of these values if considered to have no clinical significance.
    c. Rhythm disturbance other than sinus arrhythmia or ectopic supraventricular rhythm (ectopic atrial rhythm)
    d. Conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    e. Acute or chronic signs of ischemia
    f. Left Bundle Branch Block
    g. Prior myocardial infarction
15. Subject has participated in an investigational drug trial within 30 days prior to Visit 1.

9.3. Subject Withdrawal Criteria

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue the study. Examples of other reasons subjects may be discontinued from the study are: a change in compliance with an inclusion or exclusion criteria, occurrence of AEs, occurrence of pregnancy, use of a prohibited therapy or subject is unwilling or refuses to continue with the protocol defined procedures, treatments and/or study visits and/or subject withdraws consent.

The date the subject is withdrawn from the study and the reason for discontinuation must be recorded in the subject's electronic case report forms (eCRFs). All withdrawn subjects will be required to complete one last safety follow up visit approximately 30 days after last study medication application. If the subject withdrawals their consent to have this visit completed this needs to be appropriately documented in the subject's source notes and on the subject's eCRF.

Subjects will be permanently discontinued from the study in the event of any of the following:

- Severe infection requiring parental antimicrobial therapy or hospitalization
- Symptomatic herpes zoster

- Malignancy – except for non-melanoma skin cancer (SCC or BCC) not in or near the treatment area
- Anaphylactic or severe allergic reaction
- WBC Count: $< 1 \times 10^9$/L or second occurrence of $< 2 \times 10^9$/L
- ANC: $< 0.5 \times 10^9$/L or second occurrence of $< 1 \times 10^9$/L
- Lymphocyte count: $< 0.3 \times 10^9$/L or second occurrence of $< 0.5 \times 10^9$/L
- Platelet count: $< 50 \times 10^9$/L or second event of $< 75 \times 10^9$/L - in each case, value should be confirmed by retesting before treatment discontinuation
- Hemoglobin: < 6.5 g/dL or second occurrence of < 8 g/dL - in each case, value should be confirmed by retesting before treatment discontinuation
- AST or ALT:
    - > 5 x ULN persisting for 2-weeks of study medication interruption or second event of > 5 x ULN
    - 3 x ULN with total bilirubin >2 x ULN or symptoms of hepatocellular injury [fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/ or eosinophilia (>5%)].
- Any subject who develops any of the following ECG findings during the active treatment phase will be instructed to stop study medication and will be withdrawn from the study:
    - Clinically significant rhythm disturbance other than sinus rhythm or ectopic supraventricular rhythm (ectopic atrial rhythm)
    - Clinically significant conduction disturbance including PR >240msec, pre-excitation (delta wave and PR <120msec), second degree or higher AV block
    - New finding of QRS>120ms (if not present at screen. For example, subjects with Right Bundle Branch Block at screening would not need to be withdrawn from the study if their subsequent ECGs remained unchanged).
    - Evidence of QT-interval prolongation, defined as an increase in the QT_cF interval>60ms from Visit 1
    - Acute signs of ischemia or infarction
    - Any ECG abnormality which may, in the opinion of the investigator, represent a new medical issue of concern

A subject that experiences any of the above events must be discontinued from study medication treatment, the site staff must inform the Aclaris medical monitor of the event, and the site staff must perform protocol-required procedures for trial discontinuation and follow-up.

10. STUDY MEDICATION AND MANAGEMENT

10.1. Description of Study Drug

The study medication for this study is ATI-502 Topical Solution, 0.46%. It is a clear, colorless to light pink solution. The inactive ingredients include: purified water, transcutol P, propylene glycol, PEG400, dimethyl sulfoxide (DMSO), kolliphor CS 20, benzyl alcohol, poloxamer 188, and povidone K30.

Table 3: Investigational Product

STUDY MEDICATION INFORMATION	
Study medication name	**ATI-502**
Dosage Strength	0.46%
Manufacturer	PMRS, Inc., Horsham, PA
Pharmaceutical Form	Topical Solution
Container	Amber Glass Bottle, 120 mL with screw cap
Storage Conditions	59°F to 77°F (15°C to 25°C)
Dose regimen	
Route	Topical
Frequency	Twice-daily
Duration of administration	4 weeks
Other supplies	Disposable, single-use droppers will be provided.

10.2. Subject Randomization

This is an open label study therefore, no randomization schema will be generated for this study. All subjects will receive open label ATI-502 Topical Solution, 0.46%.

10.3. Study Drug Packaging, Labeling and Storage

The study medication must be used by the study subjects only. Investigational site staff will explain the application of the study medication to subjects.

Study medication will be provided by Aclaris Therapeutics, Inc. and labeled according to regulatory requirements. Study medications must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions. Study medication should be stored at controlled room temperature 59°F - 77°F (15°C – 25°C). Subjects will be instructed to store the study medication in the original glass bottle (in the carton provided) at room temperature, away from heat, moisture, direct light, and to keep it from freezing and out of the reach of children.

The study medication will be supplied in amber glass 120 mL bottles. Disposable droppers with 1 mL calibration mark will be provided to the investigational sites for dispensing to enrolled subjects.

Study drug for this study is ATI-502 Topical Solution 0.46%. The study medication will be supplied to subjects enrolled to the study at Visit 2.

10.4. Study Drug Accountability and Disposal

The Principal Investigator or designee is responsible for ensuring accountability for the investigational agent, including reconciliation of medications and maintenance of medication records. Upon receipt of study medication, the clinical site will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided. One copy of this document will be returned to Aclaris Therapeutics, Inc. (or designee) and one copy will be maintained in the study file at the site. In addition, an accurate study medication disposition record will be kept, specifying the amount dispensed for each subject and the date of dispensing. This inventory record will be available for inspection at any time. At the completion of the study, the original inventory record will be available for review by Aclaris Therapeutics, Inc. upon request. Final medication accountability will be performed by the study monitor at the completion of the study and all used and unused study medication bottles will be returned to Aclaris Therapeutics, Inc. or designee for disposal.

10.5. Additional Clinical Supplies

In addition to the study medication supplies, each site will be supplied with the following clinical supplies to conduct the study:

- Disposable study medication dispensing droppers
- Insulated bags for subjects to transport study medication supplies
- Canfield photography equipment
- Central laboratory testing kits

11. TREATMENT OF SUBJECTS

11.1. Identification of Target Treatment Area

At Visit 1 and Visit 2, the investigator will identify a target treatment area(s) that meets all inclusion criteria (e.g. a diagnosis of AD based on the criteria of Hanifin and Rajka, BSA between 2-20%, and a PGA score of 3 or 4). The target treatment area can not include the scalp, face, palms of hands, soles of feet, groin or genitalia. The investigator will record the identified target treatment area on the body map in the subject's source documents and eCRF. These target treatment areas will be photographed at each specified protocol time point (Refer to Table 2). Sites will use colored stickers to mark the treatment areas prior to the photographs being taken. (Refer to Section 12.6 for photography instructions)

If new areas of atopic dermatitis develop while the subject is on study, these areas may be treated with the ATI-502 study medication (excluding the face, scalp, soles of feet and palms of hands). The treating investigator must identify these new treatment areas at a treatment visit (Visit 2, 3 or 4) to ensure that the area meets the protocol defined treatment criteria. These new treatment areas will be documented in the subject's source documents and in the eCRF.

11.2. Application of Investigational Product

Subjects will be instructed to apply a thin film of ATI-502 Topical Solution 0.46%, twice-daily - once in the morning and approximately 8-12 hours later - to the identified target AD areas. The ATI-502 study medication should be applied to clean dry skin. The subject must wash her/his hands thoroughly before and after each study drug application. If new areas of AD develop while the subject is on study, ATI-502 study medication may be applied to these sites.

Investigational site staff will dispense 2 bottles of study medication along with disposable droppers to the subject Visit 2. Subsequent study drug dispensing will be determined by the site based on the amount used between visits. Study medication bottles will be weighed by the site staff at the time of dispensing and when the bottles are returned. Subjects are to return used and unused study medication at each study visit so that the bottles can be weighed. Sites can re-dispense partially used bottles of study medication at a visit. The disposable droppers should be disposed of at the subject's home.

11.3. Study Medication Interruption

Treatment with ATI-502 Topical Solution, 0.46% should be temporarily interrupted in the event of severe adverse events considered related to ATI-502 Topical Solution, 0.46%, or in the event of one or more of the abnormal laboratory values in Table 4.

Table 4: Study Medication Interruption Criteria

Laboratory Test	Hold Study Medication if:	Resume Study Medication if:
WBC count	$< 2 \times 10^9$/L	$\geq 2.5 \times 10^9$/L
ANC	$< 1 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Lymphocyte count	$< 0.5 \times 10^9$/L	$\geq 0.75 \times 10^9$/L
Platelet count	$< 75 \times 10^9$/L	$\geq 100 \times 10^9$/L

Hemoglobin	< 8 g/dL or a decrease > 2g/dL	≥ 10 g/dL
AST or ALT	> 3 x ULN	< 2 x ULN or within 20% of Baseline values
Serum creatinine	>2 x ULN	<1.5 x ULN or within 10% of Baseline value

If a subject has one or more of the abnormal laboratory values noted in Table 4, the investigator or designee upon receipt and review of the central laboratory report should instruct the subject to hold study medication applications. The investigator or designee should ask the subject about symptoms, concomitant illnesses and medications and repeat the test(s) as soon as possible. The Medical Monitor must be notified of dose interruptions due to SAEs considered related to study medication or laboratory abnormalities noted in Table 4.

If the retest confirms the abnormal laboratory value, then the study medication should continue to be held followed by repeat testing once a week or sooner at the discretion of the investigator. The subject should be followed until the laboratory abnormality(s) returns to normal or to baseline values.

11.4. Skin Care while on Study

Prior to the application of the ATI-502 study medication, the identified AD treatment area should be washed and cleaned using the subject's routine cleansing products. The area should be dried completely prior to the application of the study medication. Subjects must not wash the treatment area, go swimming or perform physical exercise that may cause perfuse sweating for a period of 6 hours after applying the ATI-502 study medication. While on study, subjects should continue to use their routine cleansing and cosmetic products on study.

Subjects may not use a non-therapeutic, bland emollient/moisturizer or sunscreens on the AD target treatment area for the duration of the study. Moisturizers, emollients, and sunscreens may be used on NON-AD target treatment areas. Subjects must take special precautions to try and limit sun exposure to all identified treatment areas by wearing protective clothing and applying sunscreen to NON -AD target treatment areas only.

11.5. Concomitant Medications

Concomitant therapies are any new or existing therapy received from Visit 1 until discharge from the study.

Concomitant therapies include drug (*e.g.*, prescription, over-the-counter [OTC]) and non-drug (*e.g.*, chiropractic, physical therapy, energy-based treatments) therapies. Subjects will refrain from receipt of any therapy in compliance with the inclusion/exclusion criteria. Subjects should refrain from changing the use of any concomitant therapies during the study.

All new or modified concomitant therapies used during the study must be recorded.

Any new or modified concomitant therapy must be considered to determine if it is related to an AE. An AE must be reported unless the therapy is modified for non- medical reasons (*e.g.*, health insurance purposes) or it is for prophylaxis (*e.g.*, vaccinations).

11.6. Prohibited Medications

While subjects are participating in this study they are prohibited from using the following medication/therapies:

- Phototherapy -Subjects must refrain from excessive sunlight (natural or artificial) and must apply sunscreen to all treatment areas if excessive exposure cannot be avoided.
- Systemic immunosuppressant or immunomodulatory therapy (e.g. etanercept, alefacept, infliximab, methotrexate)
- JAK inhibitors (systemic or topical)
- Systemic corticosteroids (intranasal and inhaled corticosteroids are allowed)
- Cytostatic agents
- Crisaborole
- Dupilumab or other monoclonal antibody for the treatment of AD
- Systemic antibiotics
- Topical treatments for atopic dermatitis (corticosteroids, calcineurin inhibitors, topical H1 and H2 antihistamines, topical antimicrobials, and other medicated topical agents)
- Prescription moisturizers
- Topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products.
- Vaccine treatments

11.7. Treatment Compliance

The investigator or designee will be responsible for monitoring subject compliance through questioning the subject, documenting missed doses, if any, weighing the bottle before dispensing and after return and visual inspection of the quantity in the study medication bottles (used and unused). Study staff will counsel the subjects, as required to make sure subjects are compliant with study medication applications.

12. STUDY ASSESSMENTS

12.1. Physician's Global Assessment (PGA)

The PGA is the investigator's assessment of the average overall severity of subject's AD at a particular point in time. At every study visit, the investigator will assess the PGA using the scale below and report the one integer that best describes the average overall severity of each target evaluation area of AD per subject. One assessment will be conducted for each target treatment area.

Table 5: Physician's Global Assessment

PHYSICIAN'S GLOBAL ASSESSMENT	
Grade	**Descriptor**
0	Clear: No erythema or induration; no oozing/crusting; barely perceptible residual post-inflammatory hypo- or hyperpigmentation may be present
1	Almost Clear: Minimal light red erythema and/or induration; no oozing/crusting
2	Mild: Light red erythema with mild induration; no oozing/crusting
3	Moderate: Red erythema with moderate induration; oozing/crusting may be present
4	Severe: Bright or deep red erythema with severe induration; oozing/crusting present

12.2. Body Surface Area (BSA)

For this study, 1% Body Surface Area (BSA) is defined as the area of the subject's hand with the fingers and thumb together. The subjects are required to have 2-20% total BSA of active AD to be enrolled in the study. Body surface area of each target treatment area will be assessed at each treatment visit. If new areas of AD develop while the subject is on study, these new areas will not be assessed.

12.3. Eczema Area and Severity Index (EASI)

Investigators will use the EASI to assess each subject's extent and severity of atopic dermatitis at Visit 1 and then at every protocol defined treatment visit.

The EASI divides the subject's body down into four body regions:

- Head and Neck
  - Face occupies 33% (17% each side), neck 33% (17% front and back) and scalp 33% of the head and neck region
- Trunk (including genital areas)
  - Front occupies 55% and back 45% of the trunk
- Upper limbs

  - Each arm occupies 50% of the upper limbs region (front or back of one arm is 25%)

- Lower limbs (including buttocks)
  - Each leg occupies 45% (front or back of one leg is 22.5%) and buttocks 10% of the lower limbs region

An area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by AD for each body region.

Table 6: Area Score

Area Score	Percentage of skin affected by AD in each region
0	No active AD in this region
1	1-9%
2	10-29%
3	30-49%
4	50-69%
5	70-89%
6	90-100%; the entire region is affected by AD

The severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs. The four signs are:

- Redness (erythema, inflammation)
- Thickness (induration, papulation, swelling-acute AD)
- Scratching (excoriation)
- Lichenification (lined skin, furrowing, prurigo nodules-chronic AD)

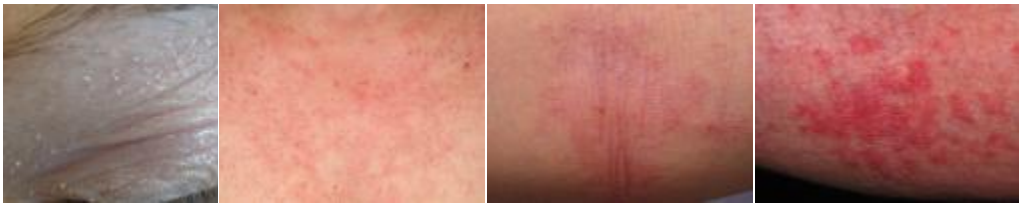
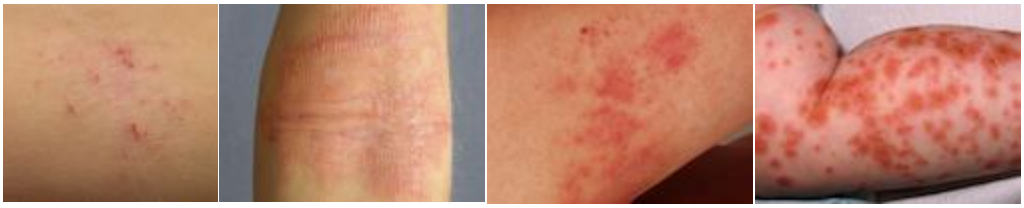
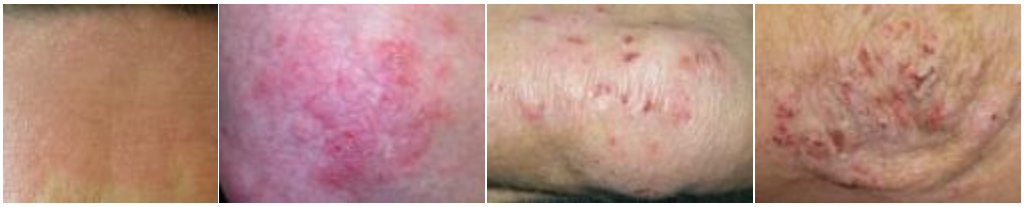
The *AVERAGE* intensity of each sign in each body area is assessed according to the following table:

Table 7: Severity Score

Score	Intensity of redness, thickness/swelling, scratching, lichenification
0	None, absent
1	Mild (just perceptible)
2	Moderate (obvious)
3	Severe

Half scores are allowed. In darker skin type subject's, it may be difficult to assess redness and in this case increase the average redness score by 1 level.

Table 8: Four signs of AD used to calculate EASI severity score

Intensity	None	Mild	Moderate	Severe
Redness	 Score 0	Score 1	Score 2	Score 3
Thickness/induration papulation/oedema	 Score 0	Score 1	Score 2	Score 3
Scratching	 Score 0	Score 1	Score 2	Score 3
Lichenification/prurigo	 Score 0	Score 1	Score 2	Score 3

(Hanifin, 2001)

12.4. Signs of Atopic Dermatitis (SAD)

The Signs of Atopic Dermatitis (SAD) assessment is the investigator's assessment of the average overall severity of signs of AD in each target AD evaluation area at a particular time-point. The investigator should NOT refer to any other assessments to assist with these assessments.

At Visits 2 through 6, the investigator will assess the signs of AD using the scales below and report the one integer that best describes the average overall severity of each of the signs in each target treatment area. Any new areas of AD that develop outside the baseline identified target treatment areas will not be assessed by the SAD.

This assessment must be done at Visit 2 prior to the first study medication application. This assessment must be done at Visits 3-6 either prior to the first study medication application or approximately 4 hours after the most recent study medication application.

ERYTHEMA (REDNESS)	
Grade	**Descriptor**
0	None: No redness
1	Mild: Barely perceptible, light redness
2	Moderate: Definite redness, easily detectable
3	Severe: Marked, deep/dark red

INDURATION (ELEVATION)	
Grade	**Descriptor**
0	None: No elevation
1	Mild: Barely perceptible elevation, may be more palpable than visually perceptible; scattered
2	Moderate: Definite visually perceptible elevation; not extensive/moderate coverage
3	Severe: Marked and obvious elevation; extensive presence/significant coverage

LICHENIFICATION (EPIDERMAL THICKENING)	
Grade	**Descriptor**
0	None: No epidermal thickening
1	Mild: Minimally perceptible epidermal thickening, skin lines may be slightly accentuated
2	Moderate: Definite epidermal thickening, skin lines accentuated/pronounced
3	Severe: Marked epidermal thickening, skin lines and very pronounced

EXCORIATION (SIGNS OF SCRATCHING)	
Grade	**Descriptor**
0	None: No skin damage
1	Mild: Minimal damage to the top layer of skin, there may be a suggestion of linear pattern to the damage
2	Moderate: Definite damage/loss of the top layer of the skin with perceptible linear pattern
3	Severe: Marked damage/loss of the top layer of the skin, pronounced linear pattern of damage

OOZING/CRUSTING (EXUDATION)	
Grade	**Descriptor**
0	None: No oozing or crusting

1	Mild: Barely perceptible oozing, lesions may or may not be moist, no crusting
2	Moderate: Definite oozing, lesions damp to the touch, crusting may be present
3	Severe: Marked oozing, lesions are wet, crusting present

12.5. Subjects Pruritis Assessment (SPA)

The SPA is the subject's assessment of the worst severity of pruritus, a symptom of AD, in each of the target evaluation areas of AD during the 24 hours prior to each follow up visit. The subject should NOT refer to any other assessments or any other active areas of AD outside the bilateral target evaluation areas to assist with these assessments.

At Visits 2 through 6, the subject will perform the SPA using the 11-point numeric rating scale below and report the one integer that best describes the worst severity of pruritus on each target evaluation area (identified at baseline) over the previous 24 hours.

PRURITUS (ITCHING)	
Grade	**Descriptor**
0	No itch
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	Worst possible itch

To complete the SPA, the study coordinator should show the SPA scale to the subject, explain the scale and ask the subject to indicate which integer best describes the worst pruritus the subject experienced on each target evaluation area of AD over the previous 24 hours.

This assessment must be done at Visit 2 prior to the first study medication application. This assessment must be done at Visits 3-6 either prior to the first study medication application or approximately 4 hours after the most recent study medication application.

12.6. AD Treatment Area Photography

Canfield Scientific will supply all investigational sites with study specific camera equipment to photograph each subject's identified target AD treatment areas. Sites will be supplied with color stickers to identify each target area. Details regarding the use of the equipment and how to upload the photographs to the Canfield database will be supplied to the sites in a study specific Canfield study manual.

At Visit 1, investigational sites must identify and photograph the proposed target AD treatment areas that will be treated and followed throughout the duration of the study. These standardized photographs will be submitted to Canfield and reviewed by a panel of 3 dermatologists prior to allowing the subject to be enrolled to the study. The photographs will be assessed by the panel of dermatologists to confirm that the subject meets the protocol defined inclusion in the study. In cases where the photographs do not properly characterize the disease (due to flashback and whitening on the photographs) the subjects will be allowed to enroll to the study based upon the Principal Investigator's clinical assessment of the subject.

Sites will be required to photograph each target AD treatment area at all protocol defined treatment visits.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety will be assessed throughout the study by the investigator or a designated and appropriately trained staff member.

13.1.1. Demographic/Medical History

During the screening visit (Visit 1), the investigator or designee will interview each subject to obtain demographic information including date of birth, sex at birth, Fitzpatrick skin type, race and, if appropriate, ethnicity. The investigator or designee will interview each subject to obtain medical history information related to all medical conditions, surgeries and disease states that, at screening: are ongoing, require concomitant therapy or are, in the opinion of the investigator, relevant to the subject's study participation. In addition, the medical history of women who are not of childbearing potential should reflect the reason e.g. post-menopausal for 1 year or greater, total hysterectomy. Information regarding the subject's prior treatments or therapies related to AD must be documented.

13.1.2. Vital Signs

Vital signs will be measured at each visit during the study. The following items will be measured:

- Body temperature
- Heart rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 2 only)
- Weight (at Visit 2 only)

Any measure that is, in the opinion of the investigator, abnormal AND clinically significant (CS) must be recorded as history if found prior to the first study medication application, or as an AE if found after the first study medication application begins.

13.1.3. Physical Examination

The investigator or designee will perform a physical examination for all body systems (general appearance, examination of head, eyes, ears, nose and throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, lymphatic and skin assessment) at Screening (Visit 1) and end of study (Visit 6).

13.1.4. Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed by a qualified staff member at Screening (Visit 1), Day 8 (Visit 3), Day 15 (Visit 4), Day 29 (Visit 5) and Day 56 (Visit 6/End of Study). The ECGs must be obtained using a standard 12-lead ECG with a 10mm/mV amplitude, at 25mm/sec and a 5 to 10 second duration. To ensure a steady heart rate the subject must rest quietly in the supine position for at least 5 minutes prior to performing the ECG.

A central cardiology laboratory will provide ECG equipment, supplies and site training. In addition, the central cardiology laboratory will process ECGs received by the sites and report results via a secure study portal. The ECG results will be interpreted by a qualified health professional (evaluator) and the interpretation reported either directly on the tracing or in a separate report. The evaluator will interpret the results of every ECG and define the ECG as "normal" or "abnormal". Variations such as minor ST changes (i.e., <0.5mm depression) and early re-polarization are considered normal.

The investigator must review the evaluator's interpretation of each subject's screening ECG prior to Visit 2. The investigator will review the evaluator's interpretation of all ECG reports in a timely manner and comment on the clinical relevance of any result that is defined by the evaluator as abnormal.

Any abnormalities that are, in the opinion of the investigator, clinically significant, must be reported as history if found prior to the start of the first dose of study medication or as an AE if found after the start of the first dose of study medication

13.1.5. Pregnancy Testing

Subjects who are WOCBP must have a negative serum pregnancy test result at Screening (Visit 1) to continue in the study, and a negative UPT at Baseline (Visit 2) prior to study entry. If the result of any post-treatment urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed. In addition, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at Visit 6 (Post Treatment Safety Follow Up Visit).

13.1.6. Laboratory Assessments

All subjects are required to have a blood chemistry panel performed at Visit 1 (Screening) and at each protocol defined visit. A qualified staff member will collect non-fasting blood samples and ship the samples to a central laboratory for analysis. The following tests will be performed:

Chemistry Panel	**Complete Blood Count**
Albumin	Hematocrit
Alkaline phosphatase	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Aspartate aminotransferase (AST)	Red blood cell morphology
Blood urea nitrogen (BUN)	Red blood cell count
Bicarbonate	White blood cell count
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils
Glucose	Eosinophils
Lactate dehydrogenase (LDH)	Lymphocytes
Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total bilirubin	
Total protein	

Uric Acid
Total cholesterol, LDL, HDL
Triglycerides

13.1.7. Virus Serology

All subjects will be required to have a QuantiFERON TB Gold, HIV, Hepatitis B and HCV serological blood test performed at screening. If the subject demonstrates to have serological evidence of any of these viruses, they will not be allowed to enroll to the study.

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

The investigator should, when certain, report a diagnosis rather than the signs, symptoms or clinically significant abnormal laboratory values associated with the AE. Otherwise, signs, symptoms or abnormal laboratory values may be used to describe the AE.

Any CS abnormality discovered prior to the first study medication treatment should be reported as medical history, not as an AE.

All AEs that occur from the time of first study medication application (Visit 2) until 30 days after last study medication application must be documented in the subject's source documents and in Aclaris' EDC system.

13.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The term "life threatening" refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not be immediately life threatening, result in death or hospitalization, but are clearly of major clinical significance and may jeopardize the subject or require intervention to prevent one of the outcomes listed in the SAE definition above. These should also usually be considered serious.

SAEs will be reported from the time of informed consent until 30 days past last application of study medication, whether or not they are related to the study. SAEs will be documented on the Aclaris SAE report form and in the eCRF.

13.2.1.3. Unexpected adverse events

An AE is considered unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

13.3. Recording of Adverse Events

13.3.1. Adverse event reporting period

The investigator must start reporting non-serious AEs with the subject's first study medication application and continue reporting until the end of the subject's last study visit. Reporting for SAEs must start when the subject signs the ICF and continue until the end of the subject's last visit.

13.3.2. Severity

The investigator is to define the severity of each AE using the following definitions as a guideline. The investigator will consider the range of the possible severity of the event and identify the severity that is the most appropriate according to her/his medical judgment.

Mild – Awareness of signs or symptom, but easily tolerated.

Moderate – Discomfort, enough to cause interference with usual activity.

Severe – Incapacitating with inability to perform usual activity.

13.3.3. Relationship to study medication

The investigator will determine if there is a reasonable causal relationship between the study medication and an AE or not. The investigator will use her/his best medical judgment and consider all relevant factors (*e.g.*, temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies and concurrent conditions) to determine the relationship of the AE to the study medication. The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

Related – There is a reasonable causal relationship between the study medication and the AE.

Not Related – There is not a reasonable causal relationship between the study medication and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (International Conference on Harmonization [ICH] E2A).

13.3.4. Procedures for reporting adverse events

At each post-enrollment visit, the investigator will question the subject to elicit AEs using a non-directive question such as "Has there been any change in your health since the previous study visit?" If appropriate, based on the subject's response to non-directed questioning to elicit AEs, the investigator will follow-up with directed questions and appropriate evaluations.

Any AE noted during the reporting period must be reported in the source documents and on the appropriate AE eCRF. AEs that are defined as "Not Related" to the study medications will be followed until they are resolved or until the subject's last study visit. AEs that are defined as "Related" to the study medications will be followed until they are resolved or, if not resolved at the subject's last study visit, until in the opinion of the investigator, the AE reaches a clinically stable outcome with or without sequelae.

Should a pregnancy occur, it must be reported and recorded on Aclaris pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

13.3.5. Procedure for reporting a serious adverse event

Upon becoming aware of a SAE occurring during the AE reporting period, whether or not related to the study medications, the investigator must:

1. Take the appropriate medical action to ensure the subject's safety.
2. Immediately inform the Safety Monitor of the SAE by email, ensuring that the subject information is deidentified (only subject initials and subject number) to: **ProPharma, Email: clinicalsafety@propharmagroup.com.**
3. Print a copy of the email confirmation from ProPharma and place in the study file.
4. Within 24-hours complete, as fully as possible, an AE eCRF and an SAE form; e-mail the forms and any other relevant information (*e.g.*, concomitant medication eCRF, medical history eCRF, laboratory test results) to ProPharma.
5. Monitor and document the progress of the SAE until it resolves or, if not resolved after the subject's last study visit, until in the opinion of the investigator the AE reaches a clinically stable outcome with or without sequelae AND the investigator and Aclaris

Therapeutics, Inc. Safety and Medical Monitor agree that the SAE is satisfactorily resolved.

6. Inform the Aclaris Therapeutics, Inc. Safety Monitor of SAE updates, via telephone, followed by an SAE form update sent by e-mail.
7. Comply with the appropriate regulatory requirements and Aclaris Therapeutics, Inc. instructions regarding reporting of the SAE to the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

13.4. Pregnancy

13.4.1. Definition of Woman of Child Bearing Potential (WOCBP)

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (*e.g.*, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. WOCBP must have a negative serum pregnancy test at screening and a negative UPT at Baseline prior to randomization.

13.4.2. Highly Effective Methods of Birth Control

The Investigator or sub-investigator will discuss the potential risk factors associated with pregnancy and the importance of maintaining a highly effective method of contraception throughout the study with all WOCBP (for example, those which result in a low failure rate - i.e., less than 1% per year- when used consistently and correctly). All WOCBP must use a highly effective method of birth control during the study and for 30 days after the final dose of study medication in a manner such that risk of failure is minimized.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- obstruction of fallopian tubes via medical device (Essure™)
- intrauterine hormone-releasing system (IUS)
- vasectomized partner[1]
- sexual abstinence[2]

[1]Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual

abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

WOCBP must be on a highly effective method of birth control for the following timeframes prior to study entry:

- Implants (on a stable dose for ≥30 days)
- Injectables (on a stable dose for ≥30 days)
- Patches (on a stable dose for ≥30 days)
- Combined oral contraceptives (on a stable dose for ≥30 days)
- Intrauterine devices (inserted for ≥30 days).

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and of the potential risk factors associated with pregnancy while in the study. The subject must sign an informed consent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study medication administration, the study medication must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed, the subject must not receive study medication and must be discharged from the study.

If, following study medication administration, it is determined that the subject or partner of a male subject may have been or was pregnant at the time of study medication exposure (including at least 2 days after study medication administration) the investigator must immediately notify the Aclaris Therapeutics, Inc. Medical Monitor and record the event on a pregnancy surveillance form. While not an AE or SAE, the investigator must report every pregnancy using a pregnancy surveillance form and follow the reporting procedures described for SAE reporting.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (*e.g.*, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to Aclaris Therapeutics, Inc.'s Medical Monitor on the pregnancy surveillance form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of six weeks.

14. STATISTICS

14.1. Statistical Methods

Safety and efficacy results will be summarized and presented by visit, with no inferential statistics presented. Parameters related to safety and tolerability will be treated as primary analysis variables. Efficacy parameters will be treated as secondary endpoints.

All data will be summarized by visit, with presentations based on the nature of the parameter. For binary data such as presence or absence of treatment-emergent adverse events, the incidence will be presented along with the overall number of subjects and percentages. External clinical laboratory and similar externally sourced data will be summarized as binary outcomes based on the determination of values beyond applicable normal ranges, and in some cases the assessment of clinical significance of deviations from normal ranges. For ordinal categorical data including efficacy data from PGA, EASI, SPA and SAD scores, and continuous data such as affected body surface area, summary statistics will be presented including N, mean, median, standard deviation, and standard error, by visit. Where applicable, the mean changes from baseline for ordinal categorical and continuous parameters will be presented by visit, along with N, median, standard deviation and standard error.

14.2. Analysis of Efficacy Outcome Measures

Subject responder analyses will be conducted, by visit, based on the following criteria:

- The proportion of subjects whose active-treated lesions are judged to be clear or near clear on the PGA (PGA = ≤ 1) with a 2 grade or greater improvement from baseline;
- The proportion of subjects whose active-treated lesions are judged to be clear on the PGA (PGA = 0);
- The proportion of subjects who had an improvement from baseline of at least 75% in EASI score (EASI – 75).

Other subject responder criteria will be established as appropriate from data observation and the results will be presented as above.

15. TRAINING, DATA HANDLING AND RECORDKEEPING

15.1. Training

For each investigational center, there will be an initiation visit prior to enrolling any study subjects. It is strongly recommended that all investigators, other evaluators, study nurses, study coordinators or other applicable personnel attend this visit. During this visit, participants will be trained to the protocol, study specific procedures, and the eCRFs. Those unable to attend the initiation visit must receive on-site training from an appropriately trained individual prior to participating in any of the procedures and evaluations in this study.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOPs), the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

Aclaris Therapeutics, Inc. will provide an investigational center file to each center.

15.2. Data Collection

The Investigator must maintain required records for all study subjects. Data for this study will be recorded in the subject's source document and on the eCRFs. All data on these eCRFs should be recorded completely and promptly. A copy of the completed eCRFs for each subject will be retained by the investigational center.

Records of the subject's participation in this study will be held confidential except as disclosure is required by law. The study doctor, the sponsor, persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration and the Institutional Review Board will be able to inspect and copy confidential study-related records that identify subjects by name. Therefore, absolute subject confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject's identity will not be revealed.

15.3. Protocol Violations and Deviations

A *protocol deviation* is defined as an accidental or unintentional change to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's right, safety, or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher or research staff. A protocol deviation does not involve inclusion/exclusion criteria.

A *protocol violation* is defined as an accidental or unintentional change to, or non-compliance with the IRB approved protocol without prior sponsor approval. Protocol violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data.

15.4. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Aclaris Therapeutics, Inc. will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Aclaris Therapeutics, Inc. or its representatives. This will be documented in a Clinical Study Agreement between Aclaris Therapeutics, Inc. and the investigator.

During the study, a monitor from Aclaris Therapeutics, Inc. or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Aclaris Therapeutics, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Aclaris Therapeutics, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.5. Source Documentation

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' visits that include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in this clinical study and have provided written informed consent. Any AEs must be completely documented. Source documentation includes results of any diagnostic tests conducted during the study.

15.6. Inspection of Records

Aclaris will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study medication stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.7. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Aclaris or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The study is conducted under the sponsorship of Aclaris Therapeutics, Inc. in compliance with the applicable regulatory requirements as well as applicable ICH guidelines, Declaration of Helsinki, and in respect of the Aclaris Therapeutics, Inc. and/or sub-contractor SOPs for study conduct and monitoring.

Audits may be carried out by Aclaris Therapeutics, Inc. or Aclaris Therapeutics, Inc.'s representatives, and inspections may be performed by regulatory authorities or IRB/ECs before, during or after the study. The investigator will provide the auditing/inspecting group direct access to all study records (e.g., eCRFs, subject medical records, study medication dispensing records) and the investigational center study facilities. The investigator and study staff will be available and will assist the auditing/inspecting groups as appropriate.

17. ETHICS

17.1. Ethics Review

This protocol, informed consent form, any information provided to subjects, subject-recruiting advertisements, and any amendments to these items will receive IRB/EC approval prior to use.

The IRB/EC must receive a copy of the Investigator's Brochure, all protocol amendments, safety reports and other study related information as required by regulation or the IRB/EC procedures.

17.2. Ethical Conduct of the Study

The rights, safety and well-being of the subjects are the most important considerations in this study and take priority over the interests of society and science.

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, the ICH E6 GCP guideline, local regulatory requirements and, at US investigational centers, in compliance with the HIPAA. The study will be conducted in compliance with the IRB/EC approved version of the protocol and any applicable amendments.

17.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

17.4. Study Conduct and Protocol Amendments

With the exception of eliminating an immediate hazard to a subject, the investigator should not deviate from the protocol or implement any changes without prior written approval from the Aclaris Therapeutics, Inc.'s representative or designee and prior review and documented approval from the IRB/EC.

Changes that involve only logistical or administrative changes are allowed. The investigator should document and explain any deviation from the protocol. A protocol deviation is a non-adherence to protocol-specific study procedures or schedules that does not increase the risk to a study subject and does not affect the scientific integrity of the study.

A protocol violation is defined as any divergence from the protocol-specific study procedures or schedules that may result in an increased risk to a study subject or that affect the scientific integrity of the study. All protocol violations must be reviewed by the Medical Monitor and reported to the IRB by the Investigator, as directed by the IRB-specific procedures.

17.5. Regulatory Documents

The investigator must maintain a study file containing current and complete regulatory documentation in compliance with the current ICH E6 GCP guideline. This file will be reviewed as part of the routine monitoring for this study.

17.6. Contractual Requirements

A contractual agreement will be signed between Aclaris Therapeutics, Inc. and each investigator. This document will contain supplemental information, including financial terms, confidentiality, study schedule, third party responsibility, and publication rights.

18. REFERENCES

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4. Hanifin JM, et.al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp. Dermatology. 2001 FEB; 10(1): 11-8.
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19. APPENDICES

APPENDIX 1. SUBJECT INSTRUCTIONS

Preparation and General Instructions:

1. Gather a clean washcloth and towel, the study medication bottle, and disposable dropper.
2. Skin should be clean and dry before applying study medication.
3. Refrain from bathing, swimming and/or participating in strenuous exercise that would cause profuse sweating for 6 hours after application of study medication.
4. Refrain from applying moisturizers, emollients and sunscreen to AD treatment areas for the duration of protocol therapy. Moisturizers, emollients and sunscreens may be applied to non-AD treatment areas.
5. Wash your hands with soap and water before and after using this study medication.
6. Apply a thin layer of study medication to the identified AD target skin area as instructed by the study doctor or the study staff. Keep applying study medication to the area throughout the study, even if the skin begins to clear. If new areas of AD appear, study medication may be applied to these areas.
7. Avoid study medication contact with the eye.
8. You will apply study medication twice-a-day, approximately 12 hours apart.
9. Remember to bring your study medication bottles both used and unused to each study visit.

Study Medication Application:

1. Draw up exactly 1 mL of study medication into the dropper. The medication level should be at the 1mL line.
2. During study medication application, avoid any study medication running into your eyes.
3. Squeeze a few drops of study medication onto the center of the identified target AD area and gently rub the study medication into your skin. Keep applying a few drops and rubbing into your skin until **the entire area** is covered with a thin film of study medication.
4. Draw up additional medication - 1 mL at a time- to cover the entire AD area.
5. Replace the screw top cap and make sure it is closed tightly. Dispose of the used dropper(s).
6. It is important to continue to apply study medication to the target AD areas throughout the study, even if the skin begins to clear.
7. Wash your hands after using this product to prevent any residue being left on your hands.
8. If you missed a dose or doses, tell the study staff at your next visit.

Missed Doses: If you miss a dose of this study medicine, apply it as soon as possible. However, if it is almost time for your next dose, skip the missed dose, and go back to your regular dosing schedule.

Storage: Store the medicine in the original glass bottle in the carton provided at room temperature, away from heat, moisture, and direct light. Keep from freezing. Keep out of the reach of children.

APPENDIX 2. HANIFIN AND RAJKA DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

Hanifin and Rajka Diagnostic Criteria for Atopic Dermatitis (AD)

Major criteria: Must have three or more of:

1. Pruritus
2. Typical morphology and distribution
   - Flexural lichenification or linearity in adults
   - Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria: Should have three or more of:

1. Xerosis
2. Ichthyosis, palmar hyperlinearity, or keratosis pilaris
3. Immediate (type 1) skin-test reactivity
4. Raised serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (especially *S aureus* and herpes simplex) or impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor or facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental or emotional factors
23. White dermographism or delayed blanch

(Hanifin, 1980)