CLINICAL STUDY PROTOCOL

Protocol Number: A-101-SEBK-203

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL GROUP STUDY OF THE DOSE-RESPONSE PROFILE OF A-101 SOLUTION IN SUBJECTS WITH SEBORRHEIC KERATOSIS OF THE FACE

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INVESTIGATOR/SPONSOR AGREEMENT

I have read this protocol and I agree to conduct this study in compliance with the protocol and any applicable amendments.

Investigator Signature:

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1. SYNOPSIS

Title:
A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Dose-Response Profile of A-101 Topical Solution in Subjects with Seborrheic Keratosis of the face.

Objectives:
The main objective of this study is to evaluate the dose-response relationship of two concentrations of hydrogen peroxide (A-101) solution (32.5% and 40%) when applied to individual seborrheic keratosis (SK) lesions (target lesions) on the face compared with a matching A-101 Solution Vehicle.

Each subject will have one target lesion on the face.

A further objective is to evaluate the safety and efficacy of two concentrations of A-101 solution and its matching vehicle when applied to SK target lesions on the face.

Methodology/Study Design:
During this study, the investigator will identify 1 eligible SK target lesion on each subject's face. The target lesion will be treated a maximum of two times.

Approximately 108 subjects will be randomized to a study medication treatment group at multiple investigational centers.

The duration of study participation is anticipated to be a maximum of 124 days per subject. This includes a screening period of up to 14 days, a visit for the required first study medication application, a visit 21 days later for an optional retreatment study medication application and an 84-day no treatment follow-up period. The final study visit (Visit 8) has a maximum allowable visit window of 4 days. Study visits are:

- Visit 1 (Day -13 to 0) enrollment, start screening period
- Visit 2 (Day 1) randomization; study medication application
- Visit 3 (Day 8) no treatment follow-up
- Visit 4 (Day 22) follow-up visit where target lesions that meet the retreatment criteria will receive a second study medication application
- Visit 5 (Day 29) no treatment follow-up
- Visit 6 (Day 50) no treatment follow-up
- Visit 7 (Day 78) no treatment follow-up
- Visit 8 (Day 106) no treatment follow-up; end of study.

At Visit 1, the investigator will identify 1 SK target lesion on the face for each subject for treatment and evaluation. Subjects may have more than 1 SK lesion, but only the target lesion will be evaluated and treated. The investigator will also collect blood samples for clinical laboratory safety tests to determine the subject's eligibility for randomization.

At Visit 2, the investigator will randomize eligible subjects and perform an initial study medication application.

At Visit 3, subjects will be seen for a no treatment follow-up.

At Visit 4, subjects will be seen for follow-up and any SK target lesion that meets the re-treatment criteria (*e.g.*, Physician's Lesion Assessment [PLA] >0) will receive a second study medication application.

At Visits 5 through 7, subjects will be seen for a no treatment follow-up.

At Visit 8, subjects will be seen for a no treatment follow-up and will be discharged from the study.

Number of Subjects:
Approximately 108 subjects will be randomized in this study at multiple United States (US) investigational centers with a goal of 96 subjects completing the study. Each investigational center is expected to randomize approximately 36 subjects. Subject enrollment will be competitive.

Diagnosis and Main Criteria for Inclusion:
Subjects will be adult males and females with 1 clinically typical appearing SK target lesion on the face.

Study Medications, Application, and Mode of Administration:
There are 3 study medications:

- A-101 Solution 40%
- A-101 Solution 32.5%
- A-101 Solution Vehicle.

There are 3 treatment groups:

- A-101 Solution 40% applied a maximum of 2 times to the target lesion
- A-101 Solution 32.5% applied a maximum of 2 times to the target lesion
- A-101 Solution Vehicle applied a maximum of 2 times to the target lesion.

Subjects will be assigned to 1 of the 3 treatment groups in a random manner in a 1:1:1 ratio.

At Visit 2, after randomization, the investigator or designee, will perform, the study medication applications.

At Visit 4, any target lesion that meets the retreatment criteria will receive a second study medication application (Section 5.7.6).

Each subject will have the same study medication applied up to 2 times to the target lesion.

Duration of Treatment:
The planned treatment and study duration are:

- Enrollment period: approximately 42 days
- Subject participation period: up to 124 days
- Study duration (first subject first visit through last subject last visit): approximately 166 days.

Evaluations – Effectiveness:
The investigator will evaluate the average overall severity of each subject's SK target lesion using the Physician's Lesion Assessment (PLA) and the subject will evaluate the target lesion using the Subject's Self-Assessment (SSA). The investigator will measure the SK target lesion's Lesion Dimensions throughout the study.

Evaluations – Safety:
The investigator and subject, as indicated, will evaluate Local Skin Reactions (LSR) for the target lesion. In addition, clinical laboratory safety tests, vital sign readings, concomitant therapies, urine pregnancy tests and adverse events (AEs) information will be assessed throughout the study.

Evaluations – Other:
Standardized color photographs to document the status of the target lesion will be taken throughout the study at 1 selected investigational center.

Statistical Methods:
The primary effectiveness will consist of the mean change from baseline to Visit 8 PLA performed using Analysis of Covariance (ANCOVA) with baseline PLA as the covariate.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
°C	Degrees Centigrade
CMH	Cochran-Mantel-Haenszel
CR	Clinically Relevant
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
e.g.	for example (Latin; *exempla gratia*)
EC	Ethics Committee
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
H_2O_2	Hydrogen Peroxide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	that is (Latin; *id est*)
IPL	Intense Pulsed Laser
IRB	Institutional Review Board
ITT	Intent To Treat
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter

Abbreviation	Term
Mm	Millimeter
NCR	Not Clinically Relevant
OTC	Over-The-Counter
PDT	Photodynamic Therapy
PLA	Physician's Lesion Assessment
PP	Per Protocol
SAE	Serious Adverse Event
SK	Seborrheic Keratosis
SN	Subject Number
SOP	Standard Operation Procedure
SSA	Subject's Self-Assessment
US	United States
WOCBP	Women of childbearing potential

2. INTRODUCTION

2.1. Summary

Seborrheic keratosis (SK) is one of the most common skin tumors in man. These benign epithelial skin tumors are most commonly seen in older individuals, increasing in prevalence with increasing age, and affect men and women roughly equally. While the growths may be solitary, they often occur in large numbers and typically present as well demarcated, elevated or "stuck-on" appearing papules or plaques that may vary from flesh-colored, to shades of yellow, gray, brown, or black.

Though benign, SK lesions are often cosmetically worrisome to patients, must sometimes be distinguished from other benign or malignant skin tumors and may become pruritic, irritated, bleed, and may be painful when traumatized particularly when located in areas prone to friction and trauma such as belt-lines and brassiere-strap lines.

Patients often seek treatment of SK for cosmetic reasons, particularly if they are located in a highly visible ("cosmetically sensitive") area such as the face, and especially if they are large, pigmented, if multiple lesions are present, or simply because the lesions are commonly associated with "old age". Removal may be medically indicated, however, for lesions that become irritated, pruritic, inflamed, or painful, or for lesions that the clinician feels require histologic confirmation of the diagnosis.

Numerous treatment options exist, and include a plethora of destructive/ablative modalities such as liquid nitrogen cryotherapy, electrodesiccation, lasers of various wavelengths (ablative and non-ablative), radio-frequency ablation, and surgical removal by curettage or surgical excision. There is, however, a notable lack of well-controlled clinical trials comparing the efficacy, complications and complication rates of these treatments. There is great variability among practitioners in the methods employed using each of these techniques (*e.g.*, variability in contact time and method of freezing the lesions with liquid nitrogen) with great variability of the results. None of these treatments is, in fact, approved by the Food and Drug Administration (FDA) for the treatment of seborrheic keratosis. While these methods can be effective, many require specialized training and/or the use of expensive equipment, they are painful and may require anesthesia and/or analgesia, and they are often complicated by significant adverse outcomes. Both hypopigmentation and hyperpigmentation, which may be transient, but are often permanent, are common, as is scarring at the treatment site, and the typical post-surgical risks of bleeding and infection increase the risk that the result of the treatment of these lesions may be worse than the disease itself.

Hydrogen peroxide (H_2O_2) is a compound that is ubiquitous in the environment. It is the simplest peroxide and a potent oxidizing agent commonly used in innumerable household goods including chlorine-free bleaches, general-purpose cleaning products, and disinfectants. Additionally, H_2O_2 has been employed as the oxidizing component in hair dyes, and has been used in oral hygiene products and tooth-whitening systems for many years. In industry, it is employed in the treatment of wastewater. In high concentrations, it is used in bleaching paper, pulp, and textiles. Clinically, in addition to its use as an oral topical agent noted above, H_2O_2 is widely employed at low concentrations (*e.g.*, 3%-6%) as a wound irrigant and topical antiseptic/disinfectant, and has been in use medicinally since its introduction into clinical practice by Richardson in 1858.

H_2O_2 is an important oxidizing agent in biological systems. The local deleterious effects of reactive oxygen species on the skin are mitigated by the presence of a complex antioxidant defense system that includes, enzymes such as catalase, glutathione peroxidase, superoxide dismutase, thioredoxin reductase, lipoamine, lipid peroxidase and others, as well as non-enzymatic components including ascorbic acid, urates and uric acid, tocopherol, glutathione, ubiquinones, ubiquinol and other water soluble groups. The local application of supra-physiologic concentrations of H_2O_2 may overwhelm the antioxidant defense systems in the skin, allowing H_2O_2 to act not only through its direct oxidation of organic tissues, generation of reactive oxygen species, and local lipid peroxidation, but also by the generation of local concentrations of O_2 that are toxic to the abnormal lesional (seborrheic keratosis) cells.

Data from a proof of concept study (A-101-SEBK-201) suggests that the topical application of A-101 Solution 40% and 32.5% to SK lesions has the potential to safely and effectively resolve SK lesions without the need for analgesia and/or anesthesia, and with a minimal risk of hypopigmentation, hyperpigmentation, or scarring.

2.2. Study Rationale

Clinical information from a previous study (A-101-SEBK-201) suggests that A-101 Solution 40% and 32.5% may safely and effectively resolve SK lesions on the back. A second currently ongoing study (A-101-SEBK-202) is evaluating the safety and efficacy of A-101 Solution 40% and 32.5% to remove SK lesions on the trunk and extremities. The rationale for this study is to evaluate the safety and efficacy of 2 concentrations of A-101 Solution (*i.e.*, 40% and 32.5%) and it's matching A-101 Solution Vehicle when applied to SK target lesions on the face. This study is designed to provide data to provide an understanding of the safety and efficacy of A-101 Solution for the removal of SK lesions on the face.

3. STUDY OBJECTIVES

The main objective of this study is to evaluate the dose-response relationship of 2 concentrations of A-101 Solution and its matching A-101 Solution Vehicle when applied to SK target lesions on the face. A further objective is to evaluate the safety and efficacy of 2 concentrations of A-101 Solution and its matching A-101 Solution Vehicle when applied topically up to 2 times to SK target lesions on the face.

4. SELECTION AND DISPOSITION OF STUDY POPULATION

4.1. Number of Subjects

Approximately 108 subjects will be randomized in this study with approximately 36 subjects randomized in each of 3 treatment groups. Subjects will be enrolled at multiple US investigational centers and enrollment will be competitive.

4.2. Study Population Characteristics

Male and female subjects, 18 years of age or older, with a clinical diagnosis of SK and 1 clinically typical SK target lesion on the face, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible to enroll in this study.

4.3. Inclusion Criteria

In order to be eligible for the study, subjects must fulfill all of the following criteria:

1. Subject is at least 18 years of age
2. Subject has a Fitzpatrick skin type of 1-4
3. Subject has a clinical diagnosis of stable clinically typical seborrheic keratosis
4. Subject has 1 appropriate seborrheic keratosis target lesion, as defined below (Section 5.4), on the face:
    - Have a clinically typical appearance
    - Be treatment naïve
    - Have a PLA of ≥2 (Section 6.1.2)
    - Have a longest axis that is ≥7mm and ≤15mm (Section 5.4)
    - Have a longest dimension perpendicular to the longest axis that is ≥7mm and ≤15mm (Section 5.4)
    - Have a thickness that is ≤2mm
    - Be a discrete lesion
    - Be, when centered in the area outlined by the provided 3cm diameter circular template, the only seborrheic keratosis lesion present
    - Not be on the eyelids
    - Not be within 5mm of the orbital rim
    - Not be covered with hair which, in the investigator's opinion, would interfere with the study medication application or the study evaluations (NB: the study medication may bleach hair)
    - Not be in an intertriginous fold
    - Not be pedunculated.
5. If the subject is a woman of childbearing potential, she has a negative urine pregnancy test and agrees to use an approved effective method of birth control (Section 8) for the duration of the study
6. Subject is non-pregnant and non-lactating
7. Subject is 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 target lesion or which exposes the subject to an unacceptable risk by study participation
8. Subject is willing and able to follow all study instructions and to attend all study visits
9. Subject is able to comprehend and willing to sign an Informed Consent Form (ICF).

4.4. Exclusion Criteria

Any subject who meets one or more of the following criteria will not be included in this study:

1. Subject has clinically atypical and/or rapidly growing seborrheic keratosis lesions
2. Subject has presence of multiple eruptive seborrheic keratosis lesions (Sign of Lesser-Trelat)
3. Subject has a current systemic malignancy
4. Subject has a history of keloid formation or hypertrophic scarring
5. Subject has used any of the following systemic therapies within the specified period prior to Visit 1:
    - Retinoids; 180 days
    - Glucocortico-steroids; 28 days
    - Anti-metabolites (*e.g.*, methotrexate); 28 days
6. Subject has used any of the following topical therapies within the specified period prior to Visit 1 on, or in a proximity to the target lesion, which in the investigator's opinion, interferes with the application of the study medication or the study assessments:
    - LASER, light (*e.g.*, intense pulsed light [IPL], photo-dynamic therapy [PDT]) or other energy based therapy; 180 days
    - Retinoids; 28 days
    - Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-flurouracil, or ingenol mebutate; 60 days
    - Glucocortico-steroids or antibiotics; 14 days
7. Subject currently has or has had any of the following within the specified period prior to Visit 1 on, or in a proximity to the target lesion, which in the investigator's opinion, interferes with the application of the study medication or the study assessments :
    - A cutaneous malignancy; 180 days
    - Experienced a sunburn; 28 days
    - A pre-malignancy (*e.g.*, actinic keratosis); currently
    - Body art (*e.g.*, tattoos, piercing, etc.); currently
    - Excessive tan; currently
8. Subject has a history of sensitivity to any of the ingredients in the study medications
9. Subject has any current skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (*e.g.*, sunburn, excessive hair, open wounds) which, in the investigator's opinion, might put the subject at undue risk by study participation or interfere with the study conduct or evaluations

10. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

4.5. Previous and Concomitant Therapies

4.5.1. Previous therapies

At Visit 1, the investigator or designee will question the subject to ensure they have not used any excluded therapies (Section 4.4).

4.5.2. Concomitant therapies

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).

4.5.3. Prohibited therapies

During the course of this study, subjects are prohibited from using therapies listed in the exclusion criteria (Section 4.4). The investigator should notify the Aclaris Therapeutics, Inc. Medical Monitor (Section 7.2) immediately if any prohibited therapies are required to ensure subject safety.

Starting with Visit 2, subjects must:

- On study visit days, not apply any topical products (*e.g.*, moisturizers, makeup, sunscreens, etc.) to the target lesion within 12 hours prior to any study visit (Note: routine cleansing products are allowed)
- Not apply any topical products to the target lesion for at least 6 hours after any study medication application.

Starting 6 days prior to Visit 2, and for the remainder of the study, subjects must not use any peroxide containing products on her/his face or head.

4.6. Subject Discontinuation from the Study

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 criterion, occurrence of AEs, occurrence of pregnancy or use of a prohibited therapy. Immediately (within 24 hours) notify the Aclaris Therapeutics, Inc. study monitor of discontinuation.

In case of premature discontinuation of study participation, efforts will be made to perform all final study day assessments. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's case report forms (CRFs). All withdrawn subjects with ongoing AEs will be followed as appropriate (Section 7.2.1).

The study may be discontinued at the discretion of Aclaris Therapeutics, Inc. Some examples of reasons for discontinuation are the occurrence of the following:

- Increased frequency, severity or duration of known AEs
- Medical, regulatory or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects.

4.7. Subject Number (SN)

The investigator will assign a unique four-digit subject number (SN) to each subject at Visit 1.

The SN format will be NN-NN where the first two digits are the investigational center site number (using leading zeroes as appropriate). The final two digits must be assigned in ascending numerical order, without omitting or repeating any number, starting with 01 at each investigational center. For example, the SN for the second subject that signs an informed consent at site number 01 would be 01-02.

The subject will be identified using the SN in all study documentation for the duration of the study.

4.8. Replacement Subjects

Subject enrollment will continue until approximately 108 subjects have been randomized. Subjects who are randomized and do not complete the study will not be replaced.

5. INVESTIGATIONAL PLAN

5.1. Study Design

This is a randomized, double-blind, vehicle-controlled, parallel group study of 2 concentrations of A-101 Solution (*i.e.*, 40% and 32.5%) and its matching A-101 Solution Vehicle in subjects with SK. Eligible subjects will have 1 appropriate SK target lesion on the face.

The study will be conducted at multiple US study centers. The study visit schedule is:

- Visit 1 (Day -13 to 0) enrollment; start screening period
- Visit 2 (Day 1) randomization; study medication application
- Visit 3 (Day 8) no treatment follow-up
- Visit 4 (Day 22) follow-up visit where target lesions that meet the retreatment criteria will receive a second study medication application
- Visit 5 (Day 29) no treatment follow-up
- Visit 6 (Day 50) no treatment follow-up
- Visit 7 (Day 78) no treatment follow-up
- Visit 8 (Day 106) no treatment follow-up; end of study.

At Visit 1, the investigator will identify 1 SK target lesion on the face for treatment for each subject. Subjects may have more than 1 SK lesion, but only the target lesion will be evaluated and treated. The investigator will also collect blood samples for clinical laboratory safety tests to determine the subject's eligibility for randomization.

At Visit 2, the investigator will randomize eligible subjects and perform an initial study medication application.

At Visit 3, subjects will be seen for a no treatment follow-up.

At Visit 4, subjects will be seen for follow-up and any target lesion that meets the re-treatment criteria (*e.g.*, PLA >0) will receive a retreatment study medication application.

At Visits 5 through 7, subjects will be seen for a no treatment follow-up.

At Visit 8, subjects will be seen for a no treatment follow-up and be discharged from the study.

5.2. Study Flow Chart

Visit	1	2	3	4	5	6	7	8	Protocol Section
Day	-13 to 0	1	8	22	29	50	78	106	
Informed consent	X								11.3
Subject number	X								4.7
Inclusion/exclusion criteria	X								4.3/4.4
Demographics & medical history	X								6.3.1
Vital signs	X	X[1]						X	6.2.2
Clinical laboratory sampling	X	X[1]						X	6.2.3
Urine pregnancy tests	X	X[1]						X	6.2.4
Target lesion identification	X								5.4
Subject's self-assessment		X[1]						X	6.1.1
Physician's lesion assessment	X	X[1]		X[1]		X	X	X	6.1.2
Lesion dimensions	X	X[1]		X[1]				X	6.1.3
Local skin reactions		X[2]	X	X[2]	X	X	X	X	6.2.1
Standardized photography (at 1 selected center only)	X	X[1]		X[1]				X	6.3.2
Subject randomization		X[1]							5.7.4
Study medication application		X		X[3]					5.7.6
Subject instructions	X	X	X	X	X	X	X	X	5.6
Concomitant therapies	X	X	X	X	X	X	X	X	4.5.2
Adverse events	X	X	X	X	X	X	X	X	7

[1] Performed prior to the study medication application
[2] Performed prior to and after the study medication application
[3] Only for Target Lesions that meet the retreatment criteria.

5.3. Study Visits Description and Procedures

A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedure (*i.e.*, prior to vital signs, clinical laboratory sampling, urine pregnancy test or photography).

5.3.1. Visit 1 (Day -13 to 0)

At this visit, the investigator or designee will:

1. Review and explain the nature of the study to the subject, obtain the subject's signature on the appropriate approved ICF and Health Insurance Portability and Accountability Act (HIPAA) authorization and provide a signed and dated copy to the subject (Section 11.3)
2. Assign a SN to the subject (Section 4.7)
3. Confirm the subject meets all inclusion criteria and no exclusion criteria (Section 4.3 and 4.4 respectively)
4. Collect demographic and medical history information (Section 6.3.1)
5. The investigator will determine the subject's Fitzpatrick skin type (Section 6.3.1)
6. Collect concomitant therapies information (Section 4.5.2)
7. Measure vital signs (Section 6.2.2)
8. Collect blood samples for clinical laboratory tests (Section 6.2.3)
9. Perform a urine pregnancy test for women of childbearing potential (WOCBP); results must be negative for the subject to continue in the study (Section 6.2.4)
10. Identify 1 appropriate seborrheic keratosis target lesion on the subject's face (Section 5.4)
11. Perform a PLA for the target lesion; a PLA grade of ≥2 is required for the target lesion for the subject to continue in the study (Section 6.1.2)
12. Measure the dimensions of the target lesion; the longest axis of the target lesion must be ≥7mm and ≤15mm and the longest dimension perpendicular to the longest axis must be ≥7mm and ≤15mm (Section 5.4)
13. AT ONE SELECTED CENTER ONLY take standardized color photographs of the target lesion (Section 6.3.2)
14. Review the study instructions and restrictions with the subject (Section 5.5)
15. Instruct the subject not to apply any topical products (*e.g.*, moisturizers, makeup, sunscreens, etc.), except routine cleansing products, to the target lesion within 12 hours prior to Visit 2 (Section 4.5.3)
16. Instruct the subject not to use any peroxide containing products on her/his face or head from at least 6 days prior to Visit 2 and for the remainder of the study (Section 4.5.3)
17. Dispense a Subject Instruction Sheet (Section 12)
18. Schedule Visit 2 within 14 days.

5.3.2. Visit 2 (Day 1)

This visit must occur within 14 days after Visit 1.

Subsequent study visit dates must be scheduled based on the date of Visit 2.

This visit may not occur before the investigator reviews the Visit 1 clinical laboratory test results. For the subject to continue in the study all required clinical laboratory test results must be within the range of normal for the laboratory or, if there are any abnormal results, they must be defined as not clinically relevant (NCR) by the investigator (Section 6.2.3).

At this visit, the investigator or designee will perform the following procedures PRIOR TO RANDOMIZATION:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions (Section 5.5)
4. Confirm the subject did not use any prohibited therapies (Section 4.5.3)
5. Measure vital signs (Section 6.2.2)
6. Collect concomitant therapies information (Section 4.5.2)
7. Collect blood samples for clinical laboratory tests (Section 6.2.3)
8. Perform a urine pregnancy test for women of childbearing potential (WOCBP); results must be negative for the subject to be randomized (Section 6.2.4)
9. Confirm the location of the target lesion (Section 5.4)
10. AT ONE SELECTED CENTER ONLY take standardized color photographs of the target lesion (Section 6.3.2)
11. Have the subject perform an SSA for the target lesion (Section 6.1.1)
12. Have the subject perform a pre-application Local Skin Reaction assessment of the symptoms for the target lesion (Section 6.2.1)
13. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for the target lesion; a PLA grade of ≥2 is required for the target lesion for the subject to be randomized (Section 6.1.2)
14. Perform a pre-application Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
15. Measure the dimensions of the target lesion; for the target lesion the longest axis must be ≥7mm and ≤15mm and the longest dimension perpendicular to the longest axis must be ≥7mm and ≤15mm (Section 5.4)
16. Confirm subject is eligible for randomization (Section 5.7.4)
17. Discharge from the study subjects who are not eligible for randomization (Section 4.6).

For subjects eligible for randomization the investigator or designee will perform the following procedures:

1. Randomize eligible subjects (Section 5.7.4)
2. Perform the initial study medication application for the target lesion (Section 5.7.6)
3. Monitor the subject for at least 20 minutes after the Application Completion Time to detect any adverse events (Section 7.2.1)
4. Have the subject perform a post-application Local Skin Reaction assessment of the symptoms for the target lesion 10 (±4) minutes after the Application Completion Time (Section 6.2.1)
5. Perform a post-application Local Skin Reaction assessment of the signs for the target lesion 20 (±4) minutes after the Application Completion Time (Section 6.2.1)
6. Review the study instructions and restrictions with the subject (Section 5.5)
7. Schedule Visit 3 for Day 8.

5.3.3. Visit 3 (Day 8)

This visit must occur 7 days (±4 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions (Section 5.5)
4. Confirm the location of the target lesion (Section 5.4)
5. Have the subject perform a Local Skin Reaction assessment for each of the symptoms for the target lesion (Section 6.2.1)
6. Perform an Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
7. Review the study instructions and restrictions with the subject (Section 5.5)
8. Schedule Visit 4 for Day 22.

5.3.4. Visit 4 (Day 22)

This visit must occur 21 days (±4 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures PRIOR TO ANY RETREATMENT STUDY MEDICATION APPLICATION:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions (Section 5.5)
4. Confirm the location of the target lesion (Section 5.4)
5. AT ONE SELECTED CENTER ONLY take standardized color photographs of the target lesion (Section 6.3.2)
6. Have the subject perform a Local Skin Reaction assessment of the symptoms for the target lesion (Section 6.2.1)
7. Perform a PLA for the target lesion (Section 6.1.2)
8. Perform a Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
9. Measure the dimensions of the target lesion (Section 6.1.3)
10. Determine if the target lesion requires a retreatment study medication application (Section 5.7.6).

ONLY for subjects who have a target lesion that requires a retreatment study medication application (*i.e.*, PLA>0), the investigator or designee will perform the following procedures:

1. Perform a retreatment study medication application for the target lesion (Section 5.7.6)
2. Monitor the subject for at least 20 minutes after the Application Completion Time to detect any adverse events (Section 7.2.1)
3. Have the subject perform a post-application Local Skin Reaction assessment of the symptoms for the target lesion that was retreated 10 (±4) minutes after the Application Completion Time (Section 6.2.1)
4. Perform a post-application Local Skin Reaction assessment of the signs for the target lesion that was retreated 20 (±4) minutes after the Application Completion Time (Section 6.2.1)

For all subjects the investigator or designee will perform the following procedures:

1. Review the study instructions and restrictions with the subject (Section 5.5)
2. Schedule Visit 5 for Day 29.

5.3.5. Visits 5 (Days 29)

This visit must occur 28 days (±4 days) after Visit.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions (Section 5.5)
4. Confirm the location of the target lesion (Section 5.4)
5. Have the subject perform a Local Skin Reaction assessment of the symptoms for the target lesion (Section 6.2.1)
6. Perform a Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
7. Review the study instructions and restrictions with the subject (Section 5.5)
8. Schedule Visit 6 for Day 50.

5.3.6. Visits 6 and 7 (Days 50 and 78)

These visits must occur within the following visit window after Visit 2:

- Visit 6, 49 days (±4 days)
  Visit 7, 77 days (±4 days).

At these visits, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions (Section 5.5)
4. Confirm the location of the target lesion (Section 5.4)
5. Have the subject perform a Local Skin Reaction assessment of the symptoms for the target lesion (Section 6.2.1)
6. Perform a PLA for the target lesion (Section 6.1.2)
7. Perform a Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
8. Review the study instructions and restrictions with the subject (Section 5.5)
9. Schedule the next study visit as appropriate.

5.3.7. Visit 8 (Day 106)

This visit must occur 105 days (±4 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs on the appropriate form (Section 7.2.1)
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes on the appropriate form (Section 4.5.2)
3. Confirm the subject continues to comply with all study restrictions and has followed all study instructions (Section 5.5)
4. Measure vital signs (Section 6.2.2)
5. Collect blood samples for clinical laboratory tests (Section 6.2.3)
6. Perform a urine pregnancy test for WOCBP (Section 6.2.4)
7. Confirm the location of the target lesion (Section 5.4)
8. AT ONE SELECTED CENTER ONLY take standardized color photographs of the target lesion (Section 6.3.2)
9. Have the subject perform an SSA for the target lesion (Section 6.1.1)
10. Have the subject perform a Local Skin Reaction assessment of the symptoms for the target lesion (Section 6.2.1)
11. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform PLA for the target lesion (Section 6.1.2)
12. Perform a Local Skin Reaction assessment of the signs for the target lesion (Section 6.2.1)
13. Measure the dimensions of the target lesion (Section 6.1.3)
14. Discharge the subject from the study.

5.4. Target Lesion Identification

At Visit 1, the investigator will identify 1 target lesion on the face for treatment and evaluation.

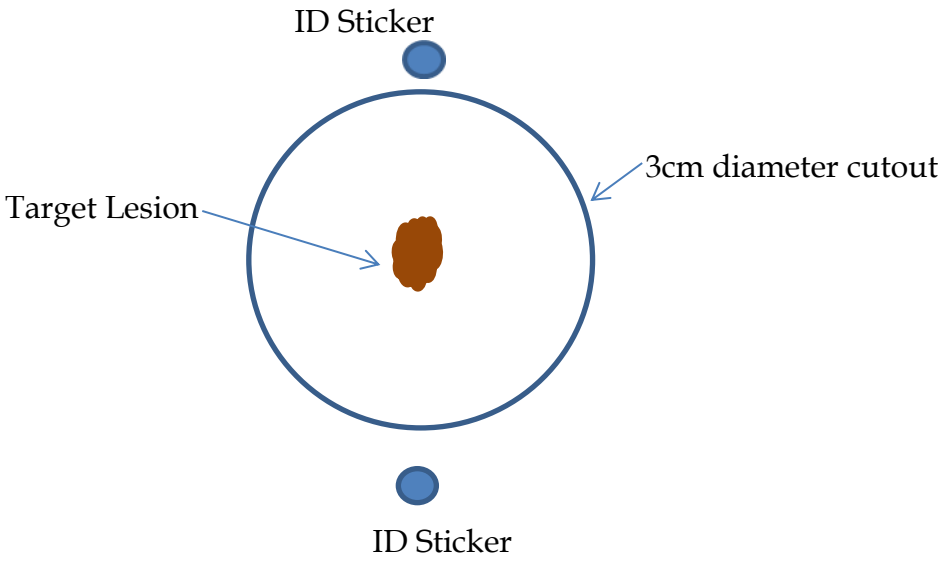
For this study, the face is defined vertically from the mandibular ridge to the hairline (for subjects with a receding hairline the hairline is defined by the vertical line drawn from tragus to tragus) and horizontally from tragus to tragus, excluding the eyelids and areas within 5mm of the orbital rim.

At Visit 1, the target lesion must:

- Have a clinically typical appearance
- Be treatment naïve
- Have a PLA of ≥2 (Section 6.1.2)
- Have a longest axis that is ≥7mm and ≤15mm (Section 5.4)
- Have a longest dimension perpendicular to the longest axis that is ≥7mm and ≤15mm (Section 5.4)
- Have a thickness that is ≤2mm
- Be a discrete lesion
- Be, when centered in the area outlined by the provided 3cm diameter circular template, the only visible seborrheic keratosis lesion
- Not be on the eyelids
- Not be within 5mm of the orbital rim
- Not be covered with hair which, in the investigator's opinion, would interfere with the study medication application or the study evaluations (NB: the study medication may bleach hair)
- Not be in an intertriginous fold
- Not be pedunculated.

Record the location of the target lesion on the face chart in the CRFs indicating landmarks and distances to assist with identifying the target lesion at subsequent visits.

At Visit 1, the investigator and an investigational staff member will identify the target lesion by placing 2 white identification (ID) stickers approximately 180 degrees opposite each other with the target lesion in the center of the area outlined by the provided circular template (diagram not to scale):



To help confirm the target lesion location at subsequent visits place one ID sticker above the target lesion and write an "x" on the sticker, place a second ID sticker below the target lesion.

At the selected investigational center where standardized photographs are taken, the identification stickers must be visible in the study photographs (Section 6.3.2).

At Visits 2-8, **an investigational staff member other than the investigator**, will confirm the location of the target lesion using an appropriate combination of the Visit 1 photographs and the face chart.

5.5. Subject Instructions

An investigational center staff member will dispense a Subject Instruction Sheet to each subject at Visit 1 (Section 12).

Throughout the study, the subjects should:

- Continue their routine cleansing regimen except they should avoid vigorous scrubbing of the target lesion (*e.g.*, abrasive cleansing pads, abrasive cleansers, etc.)
- Continue their routine cosmetics and skin care products
- Avoid exposing the target lesion to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the target lesion, if excessive exposure cannot be avoided
- Avoid or modify activities (*e.g.*, shaving, massages, etc.) that might irritate the target lesion
- Bring the subject instruction sheet with them to each visit.

Starting with Visit 2, subjects must:

- On study visit days, not apply any topical products (*e.g.*, moisturizers, makeup, sunscreens, etc.) to the target lesion within 12 hours prior to any study visit (Note: routine cleansing products are allowed)
- Not apply any topical products to the target lesion for at least 6 hours after any study medication application.

Starting 6 days prior to Visit 2, and for the remainder of the study, subjects must not use any peroxide containing products on her/his face or head.

After the completion of any study visit where a study medication application was performed DO NOT:

- Wash/submerge the target lesion for at least 6 hours
- Apply any topical products to the target lesions for at least 6 hours.

5.6. STUDY DURATION

The duration of study participation is anticipated to be a maximum of 124 days per subject. This includes the up to 14 day screening period, a visit for the required first study medication application, a visit 21 days later for an optional retreatment study medication application and an 84-day no treatment follow-up period. The final study visit (Visit 8) has a maximum allowable visit window of 4 days.

The total study duration is anticipated to be approximately 166 days from the first subject's first visit to the last subject's last visit.

The study end date is the date of the last subject's last visit.

5.7. STUDY MEDICATIONS

5.7.1. Study medication identity

The study medications are water-clear, colorless solutions that are indistinguishable in physical appearance. The study medications must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions.

Study Medication Information			
Study medication name	A-101 Solution 40%	A-101 Solution 32.5%	A-101 Solution Vehicle
Manufacturer	Pharmaceutical Manufacturing and Research Services, Horsham, PA, US		
A-101 concentration (%)	40	32.5	0
Pharmaceutical Form	Solution		
Storage Conditions	68°F to 77°F (20°C to 25°C) protected from light, excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area		
Dose regimen			
Route	Topical		
Frequency	1 application to the target lesion at Visit 2; a potential retreatment application to the target lesion at Visit 4		
Duration of administration	Up to 2 applications to the target lesion		

5.7.2. Study medication packaging and labeling

The study medications will be packaged in identical appearing, single-use, 2-dram (~7.4mL) amber glass, screw-top vials that each contains approximately 3mL of study medication.

One Subject Kit that contains 3 vials of study medication will be provided to each investigational center for each subject. Subject Kits will be labeled with a two-part, three-panel, double-blind label. One part (one-panel) of the label remains attached to the Subject Kit, the other part (two-panel tear-off) is separated and attached to the subject's Label Page CRF when the subject is randomized (Section 5.7.4).

The affixed part and the first panel of the tear-off part of the Subject Kit label show at least the following:

- Subject Kit number (randomization number)
- Protocol number
- Storage conditions
- Sponsor information
- Investigational drug warning
- Space to enter SN
- Space to enter the subject's initials
- Space to enter the date of randomization.

Each study medication vial will be labeled with a one-part label that remains attached to the vial and show at least the following:

- Subject Kit number (randomization number)
- Protocol number
- Vial number
- Investigational drug warning
- Space to enter SN
- Space to enter the date of application.

5.7.3. Method of treatment assignment

Prior to the start of the study, Aclaris Therapeutics, Inc. or a designated third party will generate a list of randomization numbers that shall be transmitted to the assigned clinical packaging organization for study medication labeling.

The randomization list will be stored with access limited to designated personnel for study medication labeling. The randomization list will be made available as appropriate to un-blind the database.

5.7.4. Subject randomization

At Visit 2, an investigational center staff member will assign study medication to eligible subjects by selecting an appropriate Subject Kit. The staff member must select Subject Kits in chronological sequence and in ascending numerical order starting with the lowest available Subject Kit number.

No Subject Kit number may be omitted or reused. The Subject Kit number is the randomization number.

The sequence of study medication assignments will be assigned in a random manner in a 1:1:1 ratio.

The investigational center staff member randomizing the subject will enter the SN, subject initials and date randomized on both parts of the Subject Kit label, remove the tear-off part, attach it to the subject's Label Page CRF and record the Subject Kit number in the subject's CRF.

5.7.5. Dispensing study medication

The study medications must be applied only to study subjects, only at the investigational center and only by authorized personnel as required by applicable regulations, guidelines and protocol.

At Visit 2, after a subject is randomized (Section 5.7.4), locate the appropriate Subject Kit and the study medication vial with the lowest vial number. Enter the SN and date of application on the vial label.

At Visit 4, perform a retreatment application if the target lesion meets the retreatment criteria (Section 5.7.6). Locate the appropriate Subject Kit and the unused study medication vial with the lowest number and enter the SN and date of application on the vial label. Use a different vial from the vial used for the Visit 2 applications.

5.7.6. Study medication application

The study medications are for external, topical use on the target lesions on the appropriate study subject only.

The investigational center staff member performing the study medication applications must comply with the study medication handling warnings (Section 5.7.1)

At Visit 2, the staff member will perform an initial study medication application for the target lesion.

At Visit 4, if the target lesion has a PLA grade of >0 it must receive a retreatment study medication application UNLESS either of the following criteria apply to the target lesion:

- The target lesion has a Visit 4 pre-application LSR grade of 3 (severe) for any sign or symptom AND the grade has increased compared to the Visit 3 grade
- The target lesion is, in the investigator's opinion, not appropriate for a retreatment (the investigator must note the reason on the subject's Comments CRF page).

The Visit 4 retreatment applications will be terminated for all subjects in the study if 3 or more subjects in a treatment group discontinue from the study due to study medication related AEs. The Aclaris Therapeutics Medical Monitor will inform each investigator if this situation occurs.

To perform a study medication application for a target lesion the staff member will select the appropriate vial of study medication (Section 5.7.5) then follow these application instructions:

- Wash her/his hands prior to, and after completing the study medication applications
- Wear latex, nitrile or vinyl examination gloves during the application
- DO NOT EVER pass the study medication vial or any study medication applicator over the subject's body or face even if the vial is closed and the applicator is dry.
- Do not apply the study medications to eyes, mouth, mucous membranes, open wounds
- Do not apply the study medication to the eyelids or within 5 mm of the orbital rim

- If, in the investigators opinion it is needed to ensure no study medication enters the eye:
    - Position the subject in the supine position with the head slightly elevated and angled such that any excess study medication will flow away from the eye.
    - Apply white petrolatum (100%) United States Pharmacopeia (USP) along the orbital rim and at the medial and lateral canthi; gently stretch the periorbital skin between the thumb and forefinger at the time of petrolatum application to distend any periorbital rhytides (*e.g.*, "crow's feet") and ensure full coverage of the skin at the base of the rhytides to decrease the likelihood of tracking of the study medication towards the eye
    - Have the subject hold an absorbent pad in the appropriate area of the eye to absorb any excess study medication that might track away from the target lesion
    - Instruct the subject to keep both eyes closed during the entire study medication application procedure
- After the subject is properly prepared and positioned, thoroughly cleanse the target lesion by firmly rubbing with a cotton-tipped swab or absorbent wipe wetted with 70% isopropyl alcohol
- Hold the study medication vial away from her/his face and from the subject's face when opening and at all times
- Using the supplied applicator:
    - Wet the applicator with a quantity of study medication sufficient to wet the target lesion with a thin film
    - Using firm pressure and an application technique that is appropriate for the target lesion size (*e.g.*, dab and roll the applicator on smaller lesions; rub using a circular motion on larger lesions) apply the study medication to the target lesion for approximately 20-30 seconds
    - Minimize exposure to the surrounding normal skin and sensitive areas; you may have the subject assist by holding absorbent material (*e.g.*, clean absorbent wipe, clean paper towel, etc.) to prevent the study medication from migrating from the target lesion
    - During the application process remove excess study medication from the surrounding skin using a clean absorbent wipe
    - Ensure the target lesion is wet with study medication at the end of the 20-30 seconds
    - Allow the target lesion to remain undisturbed for approximately 60 seconds
    - After approximately 60 seconds repeat the application process
    - Repeat the application/waiting cycle until the study medication has been applied to the target lesion 4 times.

Record the time the final application to the target lesion is completed as the Application Completion Time.

After completing the study medication application to the target lesion do not disturb the target lesions until just prior to the subject's post-application LSR evaluation (Section 6.2.1). Just prior to the subject's post-application LSR evaluation (Section 6.2.1) absorb any remaining study medication, dry the target lesion without wiping or rubbing and after the target lesion and surrounding area are confirmed to be dry, remove, by gently wiping, any white petrolatum that may remain.

An eyewash kit is provided to use in the event that study medication comes in contact with a subject's eye. Follow the instructions on the eyewash kit to cleanse both of the subject's eyes. If you use the eyewash kit the event must be reported as an adverse event of "eye irritation" (Section 7.1.1).

5.7.7. Dose compliance record

At every study visit where a study medication application is performed, an investigational center staff member will document the study medication usage in the CRF.

5.7.8. Dose modification

Study medication applications will be performed at Visit 2, and if appropriate Visit 4, by the investigator or an investigational center staff member at the direction of the investigator. No study medication will be dispensed to the study subjects.

If any subject refuses to allow the initial study medication treatment or a retreatment application, the investigator must report the visit number, visit date and the reason for the refusal on the subject's Comments CRF page.

If the subject's refusal is associated with an AE, the investigator must report the event on the appropriate CRF (Section 7.2).

The subject must have the initial study medication application to the target lesion to remain in the study.

The subject does not need to be removed from the study based solely on her/his refusal to have a study medication retreatment application on the target lesion.

5.8. Study medication Management

5.8.1. Accountability

The investigator or designee will maintain an accurate record of the receipt of the study medications as shipped by Aclaris Therapeutics, Inc. (or designee), including the date received and the condition of the study medications. One copy of this receipt will be returned to Aclaris Therapeutics, Inc. (or designee) when the contents of the study medication shipment have been verified and one copy maintained in the study file. 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.

5.8.2. Return and disposition of study supplies

At the completion of the study, all used and unused study medication vials will be returned to Aclaris Therapeutics, Inc. (or designee) for disposal per Aclaris Therapeutics, Inc. (or designee's) written instructions.

5.9. Other Study Supplies

Aclaris Therapeutics, Inc. will provide:

- Handheld mirrors to assist the subject with the SSA
- An appropriate ruler, or other instrument, for measuring the lesion dimensions
- 70% isopropyl alcohol for cleansing the SK target lesions during the study medication application process
- White Petrolatum USP for protecting sensitive areas during the study medication application
- Templates for identifying target lesions
- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests and urine pregnancy tests from a third party
- For one selected investigational center only, equipment, supplies and training for taking standardized photographs from a third party
- Eyewash kits.

5.10. Blinding

5.10.1. Verification of blinding

Blinding of the study medications is important for validity of this study. This study uses a double-blind design. The study medications are indistinguishable in appearance, packaging and labeling.

5.10.2. Un-blinding during the study medication

Blinding is important for validity of this clinical study. However, the blind may be broken in the event of a medical emergency, in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind the investigator should determine that the information is necessary (*i.e.*, that it will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving an active study medication without the need for un-blinding.

If deemed necessary to break the blind for a study subject, attempt to contact the Aclaris Therapeutics, Inc. Medical Monitor (protocol page 1 and Section 7.2.2) to obtain concurrence. If it is not possible to contact the Medical Monitor beforehand, contact her/him as soon as possible after breaking the blind for a subject.

To identify a subject's study medication, locate the second panel of the tear-off label attached to the subject's Label Page CRF and follow the instructions on the label. Record the date of un-blinding, the reason for un-blinding and the initials of the investigational center staff member who performed the un-blinding on the subject's Label Page CRF.

Any subject whose blind has been broken must be discharged from the study (Section 4.6).

At the end of the study, the original Label Page CRFs will be returned to Aclaris Therapeutics with a photocopy placed in the investigator's study file. The original Label Page CRFs will be available, upon request, to the site if needed to respond to a regulatory audit.

Any event that requires the use of an eyewash kit the investigator is required to break the blind for the subject and take appropriate action (Section 7.1.1).

6. STUDY ASSESSMENTS

The investigator, a designated and appropriately trained staff member or the subject, will perform the study assessments according to the schedules noted below.

The same staff member should perform the assessments for a given subject throughout the study. If this becomes impossible, an appropriate designee with overlapping experience with the subject and study should perform the assessments.

The same lighting conditions and subject positioning should be used for all evaluations for a given subject.

6.1. Effectiveness Evaluations

6.1.1. Subject's Self-Assessment (SSA)

The SSA is the subject's assessment of the average overall severity of the target lesion at a particular time point and is not a comparison with the SSA at any other time point. The subject should NOT refer to any other evaluation to assist with these assessments.

At Visits 2 and 8, each subject will assess the target lesion using the scale below and report the one integer that best describes the average overall severity of the target lesion. At Visit 2, the subject must complete the SSA prior to the study medication application and prior to the PLA assessment. At Visit 8, the subject must complete the SSA prior to the PLA assessment.

An investigational center staff member other than the investigator must educate the subject on the SSA scale before each evaluation.

Subjects must be provided with a handheld mirror and/or a wall mirror (*i.e.*, a mirror that provides an unobstructed view of the target lesion).

To evaluate the target lesions an investigational staff member other than the investigator will identify the target lesion to the subject and direct the subject to assess the lesion. The staff member must not influence the subject's assessment.

Subject's Self-Assessment	
Grade	**Descriptor**
0	None: no visible seborrheic keratosis lesion
1	Mild: a slightly raised, light brown seborrheic keratosis lesion
2	Moderate: an obvious raised, brown seborrheic keratosis lesion
3	Severe: a prominent rough, dark seborrheic keratosis lesion

The study staff member will report the SSA grade the subject indicates in the source document. Both the subject and the study staff member must sign/initial the source document to indicate the subject performed the SSA as instructed.

The subject and the investigator must not discuss the subject's SSA grade and the subject must complete the assessment before the investigator performs the PLA (Section 6.1.2).

6.1.2. Physician's Lesion Assessment (PLA)

The PLA is the investigator's assessment of the average overall severity of the target lesion at a particular time point. The investigator should NOT refer to any other assessments to assist with these assessments.

At Visits 1, 2, 4, 6, 7 and 8, the investigator will assess the target lesion using the scale below and report the one integer that best describes the average overall severity of the target lesion. At Visit 2, and if appropriate Visit 4, the investigator must complete the PLA prior to the study medication application.

Physician's Lesion Assessment	
Grade	**Descriptor**
0	Clear: no visible seborrheic keratosis lesion
1	Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)
2	Thin: a visible seborrheic keratosis lesion (thickness ≤1mm)
3	Thick: a visible seborrheic keratosis lesion (thickness >1mm)

At Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized the target lesion must have a PLA grade ≥ 2.

At Visits 2 and 8, the subject must complete the SSA (Section 6.1.1) assessment prior to the investigator performing the PLA.

6.1.3. Lesion Dimensions

At Visit 1, at Visit 2 prior to randomization, at Visit 4 prior to any retreatment study medication application and at Visit 8 the investigator will measure the length, the width and, at Visit 1 ONLY, the thickness (height) of the target lesion using the ruler provided, or an equivalent.

The investigator must measure the length and width of the target lesion as follows:

- Length (*i.e.*, the length of the longest axis) measured in millimeters (mm) and reported to the nearest mm
- Width (*i.e.*, the length of the longest axis perpendicular to the length) measured in millimeters (mm) and reported to the nearest mm.

At Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized the target lesion must have:

- A length (longest axis) that is ≥7mm and ≤15mm
- A width (longest dimension perpendicular to the longest axis) that is ≥7mm and ≤15mm.

At Visit 2, and Visit 4, the length and width must be measured prior to any study medication application.

At Visit 1 ONLY, the investigator must measure the thickness (height) of the target lesion above the surrounding skin, in mm reported to the nearest 0.5mm.

At Visit 1 for the subject to be enrolled, the target lesion must have a thickness that is ≤2.0mm.

6.2. Safety Evaluations

In addition to reporting adverse events throughout the study the investigator, a designated and appropriately trained staff member or the subject, will perform study following safety assessments according to the schedules noted below.

6.2.1. Local Skin Reactions (LSR)

The LSR assessment is the investigator's assessment of the signs and the subject's assessment of the symptoms associated with irritation at the target lesion site (*i.e.*, the target lesion and the skin immediately surrounding the target lesion exposed to study medication). The investigator and subject must NOT refer to any other evaluation to assist with these assessments. This is not a comparison with the assessment at any other time point.

Local Skin Reactions:

- Signs (assessed by the investigator):
  - Erythema
  - Edema
  - Scaling/dryness
  - Vesicles/bullae
  - Crusting
  - Erosion
  - Ulceration
  - Post-inflammatory hyper-pigmentation
  - Post-inflammatory hypo-pigmentation (does not include the superficial transient skin blanching/whitening related to the action of the study medications)
  - Atrophy
  - Scarring.

- Symptoms (assessed by the subject):
  - Stinging/burning
  - Pruritus (itch).

At Visits 2-8, the investigator and the subject will evaluate the LSR signs and the LSR symptoms at the target lesion site respectively.

The investigator will assess the LSR signs for the target lesion site as follows:

- Visits 2 and 4:
  - Report the average severity for all signs prior to any study medication application
  - For the treated target lesion 20 (±4) minutes after the Application Completion Time, report the average severity for the following signs:
    - Erythema
    - Edema
    - Scaling/dryness
    - Vesicles/bullae.
- Visits 3 and 5-8:
  - Report the average severity for all signs.

The subject will assess the LSR symptoms for the target lesion site as follows:

- Visits 2 and 4:
  - Report the average severity over the previous 24 hours for all symptoms prior to any study medication application
  - For the treated target lesion, 10 (±4) minutes after the Application Completion Time, report the average severity of the LSR for all symptoms since completion of the study medication applications.
- Visits 3 and 5-8:
  - Report the average severity over the previous 24 hours for all symptoms.

The investigator should report the one integer that best describes average overall severity of each LSR sign for the target lesion site using the scale below.

An investigational staff member will identify the target lesion site being evaluated to the subject, educate the subject on the LSR scale before each evaluation and direct the subject to assess the site. The staff member should not influence the subject's assessment.

The study staff member will report the LSR grade the subject indicates in the source document. Both the subject and the study staff member must sign/initial the source document to indicate the subject performed the LSR as instructed.

The subject should report the one integer that best describes average overall severity of each LSR symptom for the target lesion site using the scale below:

Local Skin Reactions	
Grade	**Descriptor**
0	None
1	Mild
2	Moderate
3	Severe

6.2.2. Vital signs

Vital signs will be measured by a qualified staff member at Visit 1, Visit 2 prior to randomization, and at Visit 8. The following items will be measured:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 1 only)
- Weight (at Visit 1 only).

Any measure that is, in the opinion of the investigator, abnormal AND clinically relevant (CR) 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 (Section 7.1).

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg is considered abnormal and therefore must be defined as CR or not clinically relevant (NCR) on the comments page of the CRF.

A weight >300 lbs. is considered abnormal and therefore must be defined as CR or NCR on the comments page of the CRF.

6.2.3. Clinical laboratory sampling

Non-fasting samples for clinical laboratory analysis will be collected by a qualified staff member at Visit 1, at Visit 2 prior to randomization and at Visit 8. The following tests, at a minimum, will be conducted:

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	

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The investigator must note NCR or CR to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator must date and initial every laboratory report.

The investigator must review the Visit 1 laboratory results for each subject prior to Visit 2. The subject must not be randomized at Visit 2 if any of the Visit 1 results are outside normal range for the laboratory AND, in the opinion of the investigator, CR.

The investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CR as medical history if found prior to the first study medication application or as an AE if found after the first study medication application begins (Section 7.1). The investigator must review all laboratory reports in a timely manner

6.2.4. Urine pregnancy tests

The investigator or designee will perform a urine pregnancy test for subjects who are WOCBP (Section 6.2.4) at Visit 1, at Visit 2 prior to randomization and at Visit 8. The urine pregnancy test kits used must have a minimum sensitivity of 25-mIU ß-HCG/milliliter (mL) of urine.

Subjects who are WOCBP must have a negative pregnancy test result at Visit 1 to continue in the study and at Visit 2 to be randomized.

If the result of any post-randomization urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed (Section 8).

6.3. Other Evaluations

6.3.1. Demographics and medical history

At 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.

At Visit 1, the investigator must determine each subject's Fitzpatrick skin type.

The investigator or designee will interview each subject to obtain medical history information related to all medical conditions and disease states that, at Visit 1:

- Are ongoing
- Require concomitant therapy
- Are, in the opinion of the investigator, relevant to the subject's study participation.

6.3.2. Standardized photography

At Visits 1, 2, 4 and 8 an investigational center staff member other than the investigator, at one selected center ONLY, will take standardized color photographs of the target lesion.

Target lesion photographs will be digitally modified prior to any publication to ensure the subject's identity is not revealed.

The photographs are to document the appearance of the subjects' target lesion.

At study visits where a study medication application is performed (*i.e.*, Visit 2 and potentially Visit 4) the photographs must be taken prior to the study medication application.

Care must be taken to ensure the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph.

Equipment, supplies, training and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

7. ADVERSE EVENTS

Adverse events will be monitored throughout the study and immediately reported on the appropriate Aclaris Therapeutics, Inc. AE CRF.

7.1. Definitions

7.1.1. Adverse events (AE)

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

Thus any new, clinically relevant worsening of an existing sign, symptom or disease, should be considered an AE.

Worsening of any of the target lesion assessments should be reported as an AE ONLY if the use of the study medication is interrupted or discontinued or if therapy is required to manage the event.

The investigator must, for any AE associated with a target lesion, question the subject in detail to determine if there are any confounding factors (*e.g.*, irritation by clothing or activity, sunburn) for any such AE.

Report any event that requires use of the eyewash kit (Section 5.7.6) as an AE for "eye irritation". For all AEs of this type:

- **Contact the medical monitor (see contact information on Page 1, or in Section 7.2.2) immediately (within 24 hours)**
- **Unblind the study medication for the subject (Section 5.10.2)**
- **Arrange for the subject to be transported to the most appropriate hospital emergency room (ER) and provide the study medication identification information to the appropriate ER staff**
- **Follow the course of the AE**
- **Report the event as an SAE if appropriate (Section 7.1.2).**

Every new episode or clinically relevant worsening of a chronic condition (*e.g.*, headaches, seasonal allergies, depression, and hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history.

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

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

7.1.2. Serious adverse event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event.

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 was more severe.

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis, even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for a diagnostic test (even if related to an AE) or elective hospitalization that was planned before study enrollment (signing the ICF) is not themselves reasons for an event to be defined as a SAE.

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. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.

7.1.3. Unexpected adverse event

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

7.1.4. Adverse event reporting period

The investigator must start reporting non-serious AEs starting with the subject's first study medication application and continuing 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.

7.1.5. 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 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.

7.1.6. 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 possibility that there is a causal relationship between the study medication and the AE.

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

The term "reasonable causal relationship" means there are facts or arguments to suggest a causal relationship (International Conference on Harmonization (ICH) E2A).

7.2. Reporting Procedures

7.2.1. 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?"

The investigator/designee will monitor the subject for at least 20 minutes after the Application Completion Time at Visit 2 and at Visit 4 to elicit AEs in a similar manner.

If appropriate, based on the subject's response to non-directed questioning regarding AEs, the investigator will follow-up with directed questions and appropriate evaluations.

Any AE noted during the reporting period (Section 7.1.4) must be reported in the source documents and on the appropriate AE CRF.

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 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.

7.2.2. 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 Medical Monitor of the SAE by telephone:

Stuart D. Shanler, M.D.
Aclaris Therapeutics, Inc.
101 Lindenwood Drive
Suite 400
Malvern, PA 19355
Office telephone: (484) 321-5555
Mobile telephone: (917) 841-9859
SAE facsimile: (484) 324-2359
E-mail: sshanler@aclaristx.com

3. Within 24-hours complete, as fully as possible, an AE CRF and an SAE form; fax or e-mail the forms and any other relevant information (*e.g.*, concomitant medication CRF, medical history CRF, laboratory test results) to the Aclaris Therapeutics, Inc. Medical Monitor.
4. 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. Medical Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Aclaris Therapeutics, Inc. Medical Monitor of SAE updates by telephone followed by an SAE form update sent by fax or by e-mail.

6. 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).

8. PREGNANCY

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (*e.g.*, hysterectomy, hysteroscopy, bilateral tubal ligation, bilateral oophorectomy or bilateral minilaparotomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. Women who are WOCBP and are using an active method of birth control, are practicing abstinence or where the partner is sterile (*e.g.*, vasectomy), should be considered to be WOCBP.

All WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Effective methods of birth control approved for use in this study are:

- Implants
- Injectable
- Patch
- Combined oral contraceptives
- Barrier methods (*e.g.*, condom, diaphragm) with spermicide
- ParaGard® and Mirena® intrauterine devices.

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for a pregnancy. 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 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 (Section 7.2.2).

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.

9. STATISTICAL ANALYSES

9.1. Statistical Analysis of Clinical Indices

The primary effectiveness analysis will consist of mean change from baseline to Visit 8 PLA performed using Analysis of Covariance (ANCOVA) with baseline PLA as the covariate. The analysis will be performed at each post-baseline visit with emphasis on Visit 8. Comparisons between vehicle and each active treatment group will be performed within the model using least-squares means and the common error term. The primary efficacy analyses will be based on the per protocol (PP) population, defined as all randomized subjects who completed the study with no major protocol violation.

A secondary efficacy analysis of a separate comparison between each active treatment group and the vehicle treatment group based on the proportion of subjects whose target lesion is judged to be clear on the PLA (PLA = 0) at Visit 8. A separate Cochran-Mantel-Haenszel (CMH) test stratified by Site will be used for each comparison. A secondary efficacy analysis will also be conducted using this same methodology, but based on SSA.

Secondary analyses will initially be performed on the PP population, but will also be performed on the intent-to-treat (ITT) population defined as all randomized subjects with non-missing data at baseline and at least one post-baseline visit. As a secondary analysis, the primary efficacy analysis will be performed using the ITT population. For all ITT-population analyses, missing efficacy data will be imputed from the last non-missing post-baseline visit carried forward to subsequent missing visits (LOCF).

For all analyses, two-tail alpha will be set to 0.05 with no adjustment for multiple comparisons. ANCOVAs will include Site in the model if doing so improves the sensitivity of the model for comparing treatment groups. As a sensitivity analysis, the primary efficacy analysis will also be run including Site and the Treatment-by-Site interaction. If the interaction term is associated with $p < 0.10$ then treatment group means for each Site will be examined individually to understand potential site differences. Sites with less than two completed blocks of subjects will be pooled with other such Sites to achieve new pooled analysis Sites that meet this criterion. Sites will

first be ranked by sample size and then pooled in that order until each new pooled analysis Site meets the two-block threshold.

9.2. Statistical Analysis of Safety Data

Descriptive statistics will be calculated on the safety parameters using the ITT population. The proportion of subjects with treatment-emergent adverse events will be tabulated and presented by treatment and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class. Vital signs, LSR scores and clinically relevant abnormal laboratory results will also be tabulated and presented by study medication. No inferential testing will be performed.

Data from all randomized subjects will be presented and summarized. Safety summaries by study medication group will include listings by study medication of adverse events incidences within each MedDRA System Organ Class, and changes from pre-application values in vital signs. Adverse event summaries will be presented by study medication showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

9.3. Sample Size

The sample size of 32 subjects per treatment group completing the study (as defined for the PP population) is based on previous data suggesting that the proportion of subjects with a clear lesion (PLA=0) at Visit 8 would be at least 0.325 for the highest active dose group with no more than 1 vehicle subject (a proportion of approximately 0.031) achieving a clear lesion at Visit 8. Under these assumptions this study would have approximately 87% power with two-tail alpha = 0.05, using the more conservative secondary efficacy endpoint. The ANCOVA analysis of the primary endpoint, mean change from baseline PLA for the PP population, is expected to be more sensitive than the above endpoint, with power greater than 90% under similar assumptions.

10. TRAINING, MONITORING, DATA MANAGEMENT AND QUALITY ASSURANCE

10.1. 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 CRFs. 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.

10.2. Monitoring

The conduct of the study will be closely monitored by representatives of Aclaris Therapeutics, Inc. to verify adherence to ICH Good Clinical Practice (GCP) guidelines and applicable SOPs. Reports of these verifications will be archived with the study report. The investigator will allow the Aclaris Therapeutics, Inc. representatives designee and/or and any regulatory agency to have direct access to all study records, CRFs, corresponding subject medical records, study medication dispensing records and study medication storage area, and any other documents considered source documentation. The investigator also agrees to assist the representative, if required.

10.3. Data Management

Data-management activities of this study will be sub-contracted.

Edit checks and review processes will be performed by the sub-contractor until all data clarifications are resolved. The data will be exported to be stored in SAS datasets (or equivalent) by the sub-contractor. After all data clarifications are resolved and subject's evaluability is determined, the database will be locked.

10.4. 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, Helsinki Declaration, and in respect of the Aclaris Therapeutics, Inc. and/or sub-contractor SOPs for study conduct and monitoring.

Audits may be carried out by the 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.*, CRFs, 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.

11. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

11.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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.

11.2. 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.

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. Subjects will provide voluntary informed consent prior to initiation of any study related procedures.

11.3. Subject Information and Consent

All subjects who participate in this study must be fully informed about the study in accordance with the GCPs, federal regulations, local regulations and, at US investigational centers, with HIPAA. The ICF will contain all the required elements in compliance with the current ICH E6 GCP guideline, local regulatory requirements and, at US investigational centers, in compliance with HIPAA.

The investigator must have a defined process for obtaining voluntary informed consent from every subject.

The ICF, approved by an IRB/EC, will be fully explained to the subject. Prior to any study related procedures, including washout from therapies, the subject will voluntarily sign and date the ICF. The investigator must maintain each subject's ICF in the investigational center's study file and must provide each subject with a copy of the signed and dated ICF.

11.4. 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. 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.

11.5. 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.

11.6. 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.

11.7. Data Collection and Archiving

11.7.1. 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 CRFs. All data on these CRFs should be recorded completely and promptly. A copy of the completed CRFs 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.

11.7.2. Source documentation

Investigators must keep accurate separate records (other than the CRFs) 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.

11.7.3. Archiving

All pertinent data, samples, photographs, correspondence, original or amended protocol, reports and all other material relating to the study will be maintained securely in Aclaris Therapeutics, Inc. /contract research organization/investigator archives for the legally required duration for archiving.

The investigator should maintain the essential study documents as specified in ICH GCP, and in compliance with all regulatory requirements. The investigator should ensure these documents are protected from accidental destruction or disposal.

If the Investigator needs to re-assign responsibility for maintaining these documents (*e.g.*, due to retirement) it must be transferred to a person willing to accept this responsibility. The investigator must notify the Aclaris Therapeutics, Inc., in writing, of the name and address of the new individual.

12. SUBJECT INSTRUCTION SHEET

The investigator or designee will dispense a copy of the subject instruction sheet to each subject at Visit 1.

Aclaris Therapeutics will provide a supply of the subject instruction sheet to each investigational center prior to the initiation of subject enrollment.