

Appendix 16.1.1 Protocol and Protocol Amendments

16.1.1.1	Protocol Amendment Number 1 Summary of Changes (24 September 2013)
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16.1.1.2	Protocol Amendment Number 2 Summary of Changes (5 November 2013)
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16.1.1.3	Revised Protocol Number 1 (incorporates Amendment Numbers 1 and 2; 5 November 2013)
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CLINICAL STUDY PROTOCOL

Protocol Number: A-101-SEBK-201 Amendment Number 1

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, WITHIN SUBJECT COMPARISON STUDY OF THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF A-101 TOPICAL SOLUTION IN SUBJECTS WITH SEBORRHEIC KERATOSIS

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INVESTIGATOR/SPONSOR AGREEMENT

I have read this protocol amendment and agree to conduct this study in compliance with the protocol as amended and with any additional amendments.

Investigator Signature:

<Investigator Name>
Investigator

Date

Sponsor Signature:

Christopher Powala
Chief Operating Officer
Aclaris Therapeutics, Inc.

Date

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1. AMENDMENT HISTORY

Protocol date: 09-SEP-2013

Previous amendments: None

2. AMENDMENT SUMMARY

The following sections of the A-101-SEBK-201 protocol dated 09-SEP-2013, approved by Aclaris Therapeutics, Inc. on 09-SEP-2013, are amended:

- Section 2.1 Summary
- Section 4.3 Exclusion criteria
- Section 5.3.2 Visit 2 (Day1)
- Section 6.1.3 Lesion Dimensions.

3. AMENDMENT RATIONALE

These protocol changes are made to:

- Correct a misspelling in the Exclusion Criteria
- Clarify the Visit 2 procedures
- Correct typographical error in the Lesion Dimensions section.

4. PROTOCOL CHANGES

Section 2.1 Summary:

Previous paragraph 3, sentence 1:

Numerous treatment options exist, and include a plethora of destructive/ablative modalities such as liquid nitrogen cryotherapy, electrodesiccation, lasers...

Changed paragraph 3, sentence 1 (with corrected spelling highlighted):

Numerous treatment options exist, and include a plethora of destructive/ablative modalities such as liquid nitrogen cryotherapy, **electrodesiccation**, lasers...

Section 4.3 Exclusion Criteria:

Previous criterion 4:

Has used any of the following topical therapies on the treatment area within the specified period prior to Visit 1:

- Retinoids; 90 days
- Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-fluorouracil, or ingenol mebutate; 60 days
- Glucocortico-steroids or antibiotics; 14 days
- Moisturizers/emollients, sunscreens; 12 hours

Changed criterion 4 (with corrected spelling highlighted):

Has used any of the following topical therapies on the treatment area within the specified period prior to Visit 1:

- Retinoids; 90 days
- Liquid nitrogen, **electrodesiccation**, curettage, imiquimod, 5-fluorouracil, or ingenol mebutate; 60 days
- Glucocortico-steroids or antibiotics; 14 days
- Moisturizers/emollients, sunscreens; 12 hours

Section 5.3.2 Visit 2 (Day 1):

Previous item 14, Prior to randomization:

Have the subject perform a pre-application Local Skin Reaction assessment of the symptoms for each target lesion 20 (± 4) minutes after the study medication application to all target lesions is completed (Section 6.2.1)

Changed item 14, Prior to randomization:

Have the subject perform a pre-application Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)

Section 6.1.3 Lesion Dimensions:

Previous paragraph 3:

At Visit 1 and Visit 2 calculate and report the surface area (cm²) of each target lesion by multiplying the length of the longest axis in cm and the length of the longest axis perpendicular to the first measurement in cm and report to the nearest 1 cm.

Changed paragraph 3 (with typographical error correction highlighted):

At Visit 1 and Visit 2 calculate and report the surface area (cm²) of each target lesion by multiplying the length of the longest axis in cm and the length of the longest axis perpendicular to the first measurement in cm and report to the nearest **0.1cm**.

CLINICAL STUDY PROTOCOL

Protocol Number: A-101-SEBK-201 Amendment Number 2

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, WITHIN SUBJECT COMPARISON STUDY OF THE SAFETY, TOLERABILITY AND EFFECTIVENESS OF A-101 TOPICAL SOLUTION IN SUBJECTS WITH SEBORRHEIC KERATOSIS

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I have read this protocol amendment and agree to conduct this study in compliance with the protocol as amended and with any additional amendments.

Investigator Signature:

<Investigator Name>
Investigator

Date

Sponsor Signature:

Christopher Powala
Chief Operating Officer
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1. AMENDMENT HISTORY

Protocol footer date: 09-SEP-2013

Previous amendments

- Number 1; footer date 24-SEP-2013

2. AMENDMENT SUMMARY

The following sections of the A-101-SEBK-201 protocol with footer date 09-SEP-2013, approved by Aclaris Therapeutics, Inc. on 09-SEP-2013 are amended:

- Section 5.3.1 Visit 1 (Day -13 to 0)
- Section 5.3.2 Visit 2 (Day 1)
- Section 5.3.4 Visit 5 (Day 22)
- Section 5.4 Target Lesion Identification
- Section 5.7.6 Study medication applications
- Section 6 STUDY ASSESSMENTS
- Section 6.1.3 Lesion Dimensions
- Section 6.2.1 Local Skin Reactions (LSR)
- Section 7.1.1 Adverse Events (AE)
- Section 8 Pregnancy

The changes detailed in this amendment and the changes detailed in amendment 1 (footer date 24-SEP-2013), are incorporated in the attached A-101-SEBK-201 revised protocol number 1 dated 14-NOV-2013.

3. AMENDMENT RATIONALE

These protocol changes are made to:

- Respond to recommendations from the Food and Drug Administration; changes to sections 5.7.6, 6.2.1, 7.1.1 and 8
- Allow for enrollment of subjects with smaller seborrheic keratosis lesions without affecting the design or scientific rigor of the study; changes in sections 5.3.1, 5.3.2, 5.4 and 6.1.3
- Correct study instructions; changes in sections 5.3.4 and 6.

4. PROTOCOL CHANGES

Section 5.3.1 Visit 1 (Day -13 to 0):

Previous item 13:

Measure the dimensions of each target lesion; each target lesion must have a surface area of $\geq 1\text{cm}^2$ and $\leq 4\text{cm}^2$ and a thickness that is at least palpable and no greater than 3mm for the subject to continue in the study (Section 6.1.3).

Changed item 13:

Measure the dimensions of each target lesion; each target lesion must have a surface area of $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$ and a thickness that is at least palpable and no greater than 3mm for the subject to continue in the study (Section 6.1.3).

Section 5.3.2 Visit 2 (Day 1):

Previous item 13:

Measure the dimensions of each target lesion; each target lesion must have: a surface area of $\geq 1\text{cm}^2$ and $\leq 4\text{cm}^2$; a thickness that is at least palpable and no greater than 3mm for the subject to be randomized (Section 6.1.3).

Changed item 13:

Measure the dimensions of each target lesion; each target lesion must have: a surface area of $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$; a thickness that is at least palpable and no greater than 3mm for the subject to be randomized (Section 6.1.3).

Section 5.3.4 Visit 5 (Day 22):

Previous paragraph 4 item 2:

Schedule Visit 5 for Day 22.

Changed paragraph 4 item 2:

Schedule Visit 6 for Day 28.

Section 5.4 Target Lesion Identification:

Previous paragraph 4 item 4:

Have a lesion area of $\geq 1\text{cm}^2$ and $\leq 4\text{cm}^2$ (Section 6.1.3).

Changed paragraph 4 item 4:

Have a lesion area of $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$ (Section 6.1.3)

Section 5.7.6 Study medication application:

Previous paragraphs 6:

At Visit 5 any target lesion that has a PLA grade of >0, and ONLY target lesions that have a PLA grade of >0, must receive a retreatment study medication application.

Changed paragraph 6:

At Visit 5 any target lesion that has a PLA grade of >0, and ONLY target lesions that have a PLA grade of >0, must receive a retreatment study medication application UNLESS the target lesion:

- Has a Visit 5 pre-application LSR grade of 3 (severe) for any sign or symptom
- Is, in the investigator's opinion, not appropriate for a retreatment study medication application.

Add a new paragraph 7 that reads:

All Visit 5 retreatment applications will be terminated for all subjects if 4 or more subjects discontinue from the study due to study medication related AEs.

Section 6 STUDY ASSESSMENTS:

Previous paragraphs 3:

The following evaluation must be performed with the subject prone with the plane of the target lesion horizontal:

Changed paragraph 3:

The following evaluation may be performed with the subject standing or prone:

Section 6.1.3 Lesion Dimensions:

Previous paragraphs 1:

The Lesion Dimensions must be measured with the subject prone.

Changed paragraph 4:

The Lesion Dimensions may be measured with the subject standing or prone.

Previous paragraphs 4:

The area of each target lesion must be $\geq 1\text{cm}^2$ and $\leq 4\text{cm}^2$ at Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized.

Changed paragraph 4:

The area of each target lesion must be $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$ at Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized.

Section 6.2.1 Local Skin Reactions (LSR):

Add a new final paragraph that reads:

The investigator must report any LSR that increases in severity, compared to the Visit 2 pre-application evaluation, by ≥ 1 grade AND persists for 2 or more successive visits, as an AE (Section 7.1).

Section 7.1.1 Adverse Events (AE):

Previous paragraph 3:

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.

Changed paragraph 3:

Except for Local Skin Reactions (see below) worsening of any of the target lesion assessments must 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. Any LSR that increases in severity, compared to the Visit 2 pre-application evaluation, by ≥ 1 grade AND persists for 2 or more successive visits must be reported as an AE.

Section 8 Pregnancy:

Previous paragraphs 1 and 2:

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). Even women who are using oral, implanted or injected contraceptive hormones (*i.e.*, using a stable dose for ≥ 90 days), an intrauterine device, barrier methods (*e.g.*, diaphragm, condoms, spermicides) to prevent pregnancy, practicing abstinence or where the partner is sterile (*e.g.*, vasectomy), should be considered to be of childbearing potential.

All WOCBP must use an active method of birth control during the course of the study, in a manner such that risk of failure is minimized. Abstinence or having a sterile partner is not an active method of birth control.

Changed paragraphs 1 and 2:

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as ≥ 12 months with no menses without an alternative medical cause). Women who 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
- Injectables
- Patch
- Combined oral contraceptives
- ParaGard® or Mirena® intrauterine devices
- Condom with spermicide; diaphragm with spermicide
- Vasectomized partner.

Aclaris Therapeutics, Inc.
Protocol Number: A-101-SEBK-201
Revised protocol number: 1

CLINICAL STUDY PROTOCOL

Protocol Number: A-101-SEBK-201
Revised Protocol Number: 1
Incorporates Amendments Number: 1 & 2

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Investigator

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Chief Operating Officer
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Date

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1. SYNOPSIS

Title:

A Randomized, Double-Blind, Vehicle-Controlled, Within Subject Comparison Study of the Safety, Tolerability and Effectiveness of A-101 Topical Solution in Subjects with Seborrheic Keratosis.

Objectives:

The main objective of this study is to evaluate the safety and effectiveness of A-101 (hydrogen peroxide) Solution 25%, 32.5% and 40% when applied to individual seborrheic keratosis (SK) target lesions on the back compared with a matching A-101 Solution Vehicle.

Methodology/Study Design:

The duration of study participation is anticipated to be a maximum of 95 days per subject. This includes the up to 14-day screening period, a visit for a required study medication application, a 21-day no treatment period, a visit for an optional study medication retreatment application, a 56-day no treatment follow-up period and a maximum allowable 4-day Visit 9 visit window. 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 15) no treatment follow-up
- Visit 5 (Day 22) follow-up visit where target lesions that meets the retreatment criteria will receive a second study medication application
- Visit 6 (Day 29) no treatment follow-up
- Visit 7 (Day 43) no treatment follow-up
- Visit 8 (Day 57) no treatment follow-up
- Visit 9 (Day 78) no treatment follow-up; end of study.

During Visit 1 the investigator will, for each subject, identify 4 individual SK lesions (target lesions) on the back for treatment, perform an electrocardiogram (ECG) and collect blood samples for clinical laboratory safety tests to determine the subject's eligibility for randomization. Subjects may have more than 4 SK lesions on the back, or on other body surfaces, but only the target lesions on the back will be evaluated and treated.

During Visit 2, eligible subject's target lesions will be randomized, each to receive 1 study medication (a unique study medication for each target lesion) and then the study medication applications will be performed. Every eligible subject will receive all 4 of the study medications.

At Visits 3 and 4, subjects will be seen for a no treatment follow-up.

At Visit 5, subjects will be seen for follow-up and any target lesion that meets the re-treatment criteria (*i.e.*, Physician's Lesion Assessment [PLA] >0) will receive a second study medication application.

At Visits 6-8, subjects will be seen for a no treatment follow-up.

At Visit 9, subjects will be seen for a no treatment follow-up and discharged from the study.

Number of Subjects:

Approximately 36 subjects will be enrolled in this study at one United States investigational center with the goal to have 32 subjects complete the study.

Diagnosis and Main Criteria for Inclusion:

Subjects will be adult males and females with 4 clinically typical appearing seborrheic keratosis target lesions on the back.

Study Medications, Application, and Mode of Administration:

There are 4 study medications for topical application:

- A-101 Solution 25%
- A-101 Solution 32.5%
- A-101 Solution 40%
- A-101 Solution Vehicle.

Study medications will be randomly assigned to the 4 target lesions on each subject's back; each subject will have all the 4 study medications applied, 1 study medication to each individual target lesion.

There are 16 treatment groups. Each treatment group consists of one of 8 randomly-selected permutations for applying each study medication to one of the four target lesions per subject.

At Visit 2, eligible subjects will be randomized to one of the treatment groups (determining the study medication that will be applied to each individual target lesion) in a blinded manner. After randomization an investigational center staff member other than the investigator, will perform, the study medication applications.

At Visit 5, any lesion that meets the retreatment criteria (*i.e.*, PLA >0) will receive a second study medication application.

Duration of Treatment:

The planned treatment and study duration are:

- Enrollment period: approximately 35 days
- Subject participation period: up to 95 days
- Study duration (first subject first visit through last subject last visit): approximately 130 days.

Evaluations - Effectiveness:

The investigator will evaluate the average overall severity of each SK target lesion using the Physician's Lesion Assessment (PLA) and the subject will evaluate each target lesion using the Subject's Self-Assessment (SSA). The investigator will measure Lesion Dimensions (*i.e.*, surface area and thickness) throughout the study for each target lesion.

Evaluations - Safety:

Local Skin Reactions (LSR) for each target lesion, clinical laboratory safety tests, ECGs, vital sign readings, concomitant therapies, urine pregnancy tests and adverse events (AEs) will be monitored throughout the study.

Evaluations - Other:

The investigator will evaluate Signs of Seborrheic Keratosis (SSK) throughout the study and take standardized color photographs to document the status of the target lesions throughout the study.

Statistical Methods:

The primary effectiveness analyses will be comparisons between Vehicle and each active treatment, based on mean change from the Visit 2 PLA, using a repeated-measures Analysis of Covariance model suitable for the study design. For this purpose, the primary analysis visit will be Visit 9. Secondary effectiveness analyses will include a similar analysis of SSA and other effectiveness evaluations suitable for analysis as continuous variables. In addition, secondary analyses will be performed on proportion of PLA and SSA responders, where a subject will be considered a responder if the Visit 9 score is 0. A similar responder analysis will be done at Visit 5. Chi-square will be used to analyze difference in response rates.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
°C	Degrees Centigrade
cm	Centimeters
CR	Clinically Relevant
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
<i>e.g.</i>	for example (<i>Latin; exempla gratia</i>)
EC	Ethics Committee
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
<i>i.e.</i>	that is (<i>Latin; id est</i>)
IPL	Intense Pulsed Laser
IRB	Institutional Review Board
ITT	Intent To Treat
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
NCR	Not Clinically Relevant
OTC	Over-The-Counter
PDT	Photodynamic Therapy
PLA	Physician's Lesion Assessment
PP	Per Protocol
SAE	Serious Adverse Event

Abbreviation	Term
SK	Seborrheic Keratosis
SN	Subject Number
SOP	Standard Operation Procedure
SSA	Subject's Self-Assessment
SSK	Signs of Seborrheic Keratosis
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, they 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 may seek treatment of SK for cosmetic reasons, especially if they are large, pigmented, and/or 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 achieve cure rates, many require specialized training and the use of expensive equipment, they are painful and may require anesthesia and/or analgesia, and they are often complicated by significant adverse cosmetic 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, 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 and in high concentrations; it is used in bleaching vegetables, 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 preliminary clinical trial suggested that the topical application of H_2O_2 35% solution to SK lesions has the potential to safely and effectively resolve the SK lesions without the need for analgesia and/or anesthesia, and with a minimal risk of transient or permanent hypopigmentation, hyperpigmentation, or scarring.

2.2. Study Rationale

Preliminary clinical information, as discussed above, suggests that H_2O_2 35% solution applied topically may resolve SK lesions. This study is designed to provide initial safety, tolerability and effectiveness data for A-101 (H_2O_2) Solution when applied to target lesions of SK.

3. STUDY OBJECTIVES

The main objective of this study is to evaluate the effectiveness of A-101 Solution 25%, 32.5% and 40% when applied to SK target lesions on the back compared with a matching A-101 Solution Vehicle. Secondary objectives include evaluating the safety and tolerability of A-101 Solution when applied topically in subjects with SK.

4. SELECTION AND DISPOSITION OF STUDY POPULATION

4.1. Number of Subjects

Approximately 36 subjects will be enrolled in this study at one United States (US) investigational center with the goal to have 32 subjects complete the study.

4.2. Study Population Characteristics

Male and female subjects, 18 years of age or older, with a diagnosis of SK and at least 4 clinically typical SK target lesions on the back, 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. Is at least 18 years of age
2. Has a clinical diagnosis of stable clinically typical seborrheic keratosis
3. Has at least 4 appropriate seborrheic keratosis target lesions on the back
4. If subject is a women of childbearing potential, she must have a negative urine pregnancy test and must agree to use an active form of birth control for the duration of the study
5. Is non-pregnant and non-lactating
6. Is in good general health and free of any disease state or physical condition which, in the investigator's opinion, might impair evaluation of any target lesion or which exposes the subject to an unacceptable risk by study participation
7. Is willing and able to follow all study instructions and to attend all study visits
8. 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. Has clinically atypical and/or rapidly growing seborrheic keratosis lesions
2. Has presence of multiple eruptive seborrheic keratosis lesions (Sign of Lesser-Trelat)

3. 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
4. Has used any of the following topical therapies on the treatment area within the specified period prior to Visit 1:
 - Retinoids; 90 days
 - Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-fluorouracil, or ingenol mebutate; 60 days
 - Glucocortico-steroids or antibiotics; 14 days
 - Moisturizers/emollients, sunscreens; 12 hours
5. Has had any LASER, light (*e.g.*, intense pulsed light [IPL], photo-dynamic therapy [PDT]) or other energy based therapy on the treatment area within 180 days prior to Visit 1
6. Has a history of keloid formation or hypertrophic scarring
7. Has a current systemic malignancy
8. Has a history of, within the 180 days prior to Visit 1, or has a current cutaneous malignancy on the treatment area
9. Has a current pre-malignancy (*e.g.*, actinic keratosis) on the treatment area
10. Has had body art (*e.g.*, tattoos, piercing, sculpting, etc.) or any other invasive, non-therapeutic procedure performed on the treatment area that, in the opinion of the investigator, might put the subject at undue risk or interfere with the study conduct or evaluations
11. Has excessive tan on the treatment area that, in the opinion of the investigator, might put the subject at undue risk or interfere with the study conduct or evaluations
12. Has experienced a sunburn on the treatment area within the previous 4 weeks
13. Has a history of sensitivity to any of the ingredients in the study medications
14. Has any current skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (*e.g.*, sunburn, tattoos, excessive hair, open wounds on the back) that, in the opinion of the investigator, might put the subject at undue risk or interfere with the study conduct or evaluations
15. 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

During Visit 1, subjects will be questioned 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).

Subjects must avoid applying any topical product to the target lesions within 12 hours prior to any study visit, and for at least 6 hours after any study medication application.

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.

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. Notification of discontinuation will immediately (within 24 hours) be made to the Aclaris Therapeutics, Inc. study monitor.

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 the investigator or 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 or designee will assign a unique subject number (SN) to each subject at Visit 1.

The SN format will be 2 digits and must be assigned in ascending numerical order, without omitting or repeating any number, starting with 01. For example, the SN for the fifth subject enrolled in the study will be 05.

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 36 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, within subject comparison study of A-101 Solution 25%, 32.5% and 40% and the A-101 Solution Vehicle to investigate the safety, tolerability and effectiveness in subjects with SK. Eligible subjects will have 4 appropriate SK target lesions on the back.

The duration of study participation is anticipated to be a maximum of 95 days per subject. This includes the up to 14-day screening period, a visit for a required study medication application, a 21-day no treatment period, a visit for an optional study medication retreatment application, a 56-day no treatment follow-up period and a maximum allowable 4-day Visit 9 visit window. Study visits are:

- Visit 1 (Day -13 to 0) enrollment; screening period
- Visit 2 (Day 1) randomization; study medication application
- Visit 3 (Day 8) no treatment follow-up
- Visit 4 (Day 15) no treatment follow-up
- Visit 5 (Day 22) follow-up visit where any target lesion that meets the retreatment criteria will receive a second study medication application
- Visit 6 (Day 29) no treatment follow-up
- Visit 7 (Day 43) no treatment follow-up
- Visit 8 (Day 57) no treatment follow-up
- Visit 9 (Day 78) no treatment follow-up; end of study.

During Visit 1 the investigator will, for each subject, identify 4 seborrheic keratosis lesions (target lesions) on the back for treatment, perform an electrocardiogram (ECG) and collect blood samples for clinical laboratory safety tests to determine the subject's eligibility for randomization. Subjects may have more than 4 lesions on the back, or on other body surfaces, but only the target lesions on the back will be evaluated and treated.

During Visit 2, eligible subjects will be randomized to study medication (a unique study medication for each target lesion) and then the study medication applications will be performed.

At Visits 3 and 4, subjects will be seen for a no treatment follow-up.

At Visit 5, subjects will be seen for follow-up and any lesion that meets the re-treatment criteria (Section [5.7.6](#)) will receive a second application of the assigned study medication.

At Visits 6-8, subjects will be seen for a no treatment follow-up.

At Visit 9, subjects will be seen for a no treatment follow-up and discharged from the study.

The study will be conducted at one US investigational center.

5.2. Study Flow Chart

Visit	1	2	3	4	5	6	7	8	9	Protocol
Day	-13 to 0	1	8	15	22	29	43	57	78	Section
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							X	6.2.2
Clinical laboratory sampling	X	X							X	6.2.4
Electrocardiogram	X	X							X	6.2.3
Urine pregnancy tests	X	X							X	6.2.5
Target lesion identification	X									5.4
Subject's self-assessment		X ¹	X	X	X ¹	X	X	X	X	6.1.1
Physician's lesion assessment	X	X ¹	X	X	X ¹	X	X	X	X	6.1.2
Signs of seborrheic keratosis		X ¹	X	X	X ¹	X	X	X	X	6.1.4
Lesion dimensions	X	X ¹	X	X	X ¹	X	X	X	X	6.1.3
Local skin reactions		X ²	X	X	X ²	X	X	X	X	6.2.1
Standardized photography	X	X ¹	X	X	X ¹	X	X	X	X	6.3.2
Subject randomization		X								5.7.4
Study medication application		X			X ³					5.7.6
Subject instructions	X	X	X	X	X	X	X	X	X	5.5
Concomitant therapies	X	X	X	X	X	X	X	X	X	4.5.2
Adverse events		X ²	X	X	X ²	X	X	X	X	7

¹ Performed prior to the study medication application

² Performed prior to and after completion of all study medication applications

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 procedures and/or evaluations.

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. Collect concomitant therapies information (Section 4.5.2)
6. Measure vital signs (Section 6.2.2)
7. Collect blood samples for clinical laboratory tests (Section 6.2.4)
8. Perform a urine pregnancy test for women of childbearing potential (WOCBP); results must be negative for the subject to continue in the study (Section 6.2.5)
9. Perform ECG (Section 6.2.3)
10. Identify 4 appropriate seborrheic keratosis target lesions on the subject's back (Section 5.4)
11. Take standardized color photographs of the target lesions (Section 6.3.2)
12. Perform a PLA for each target lesion; a PLA grade of ≥ 2 is required for each target lesion for the subject to continue in the study (Section 6.1.2)
13. Measure the dimensions of each target lesion; each target lesion must have a surface area of $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$ and a thickness that is at least palpable and no greater than 3mm for the subject to continue in the study (Section 6.1.3)
14. Review the study instructions with the subject and dispense a Subject Instruction Sheet (Section 5.5)
15. 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 this visit.

This visit may not occur before the investigator reviews the Visit 1 clinical laboratory test and ECG results. For the subject to continue in the study all 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 6.2.4). In addition, ECG results must be defined as normal for the subject to continue (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 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 6.2.4)
6. Perform a urine pregnancy test for WOCBP; results must be negative for the subject to be randomized (Section 6.2.5)
7. Perform ECG (Section 6.2.3)
8. Confirm the location of the 4 target lesions (Section 5.4)
9. Take standardized color photographs of the target lesions (Section 6.3.2)
10. Have the subject perform an SSA for each target lesion (Section 6.1.1)
11. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for each target lesion; a PLA grade of ≥ 2 is required for each target lesion for the subject to be randomized (Section 6.1.2)
12. Perform an SSK for each target lesion (Section 6.1.4)
13. Measure the dimensions of each target lesion; each target lesion must have: a surface area of $\geq 0.51\text{cm}^2$ and $\leq 4\text{cm}^2$; a thickness that is at least palpable and no greater than 3mm for the subject to be randomized (Section 6.1.3)
14. Have the subject perform a pre-application Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)
15. Perform a pre-application Local Skin Reaction assessment of the signs for each target lesion (Section 6.2.1)
16. Confirm subject is eligible for randomization, 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. An investigational center staff member, other than the investigator, will perform the initial study medication application for all 4 target lesions (Section 5.7.6)
3. Have the subject perform a post-application Local Skin Reaction assessment of the symptoms for each target lesion 10 (\pm 4) minutes after the study medication application to all target lesions is completed (Section 6.2.1)
4. Perform a post-application Local Skin Reaction assessment of the signs for each target lesion 20 (\pm 4) minutes after the study medication application to all target lesions is completed (Section 6.2.1)
5. Monitor the subject for at least 20 minutes after completion of the study medication applications to detect any adverse events (Section 7.2.1)
6. Review the study instructions and restrictions with the subject (Section 5.5)
7. Schedule Visit 3 for Day 8.

5.3.3. Visits 3 and 4 (Days 8 and 15)

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

- Visit 3, 7 days (\pm 4 days)
- Visit 4, 14 days (\pm 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 4 target lesions (Section 5.4)
5. Take standardized color photographs of the target lesions (Section 6.3.2)
6. Have the subject perform an SSA for each target lesion (Section 6.1.1)
7. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for each target lesion (Section 6.1.2)
8. Perform an SSK for each target lesion (Section 6.1.4)
9. Measure the dimensions of each target lesion (Section 6.1.3)
10. Have the subject perform a Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)
11. Perform a Local Skin Reaction assessment of the signs for each target lesion (Section 6.2.1)
12. Review the study instructions and restrictions with the subject (Section 5.5)
13. Schedule the next study visit.

5.3.4. Visit 5 (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 4 target lesions (Section 5.4)
5. Take standardized color photographs of the target lesions (Section 6.3.2)
6. Have the subject perform an SSA for each target lesion (Section 6.1.1)
7. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for each target lesion (Section 6.1.2)
8. Perform an SSK for each target lesion (Section 6.1.4)
9. Measure the dimensions of each target lesion (Section 6.1.3)
10. Have the subject perform a Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)
11. Perform a Local Skin Reaction assessment of the signs for each target lesion (Section 6.2.1)
12. Identify target lesions, if any, that require a retreatment study medication application (*i.e.*, target lesion has a PLA grade >0 ; Section 5.7.6)

ONLY for subjects that require a retreatment study medication application, the investigator or designee will perform the following procedures:

1. An investigational center staff member, other than the investigator, will perform a retreatment study medication application for the appropriate target lesion(s) (Section 5.7.6)
2. Have the subject perform a post-application Local Skin Reaction assessment of the symptoms for each target lesion that was retreated 10 (± 4) minutes after the study medication application(s) is(are) completed (Section 6.2.1)
3. Perform a post-application Local Skin Reaction assessment of the signs for each target lesion that was retreated 20 (± 4) minutes after the study medication application(s) is(are) completed (Section 6.2.1)
4. Monitor the subject for at least 20 minutes after completion of all retreatment study medication applications to detect any adverse events (Section 7.2.1)

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 6 for Day 28.

5.3.5. Visits 6, 7 and 8 (Days 29, 43 and 57)

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

- Visit 6, 28 days (± 4 days)
- Visit 7, 42 days (± 4 days)
- Visit 8, 56 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 4 target lesions (Section 5.4)
5. Take standardized color photographs of the target lesions (Section 6.3.2)
6. Have the subject perform an SSA for each target lesion (Section 6.1.1)
7. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for each target lesion (Section 6.1.2)
8. Perform an SSK for each target lesion (Section 6.1.4)
9. Measure the dimensions of each target lesion (Section 6.1.3)
10. Have the subject perform a Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)
11. Perform a Local Skin Reaction assessment of the signs for each target lesion (Section 6.2.1)
12. Review the study instructions and restrictions with the subject (Section 5.5)
13. Schedule the next study visit as appropriate.

5.3.6. Visit 9 (Day 78)

This visit must occur 77 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 6.2.4)
6. Perform a urine pregnancy test for WOCBP (Section 6.2.5)
7. Perform ECG (Section 6.2.3)
8. Confirm the location of the 4 target lesions (Section 5.4)

9. Take standardized color photographs of the target lesions (Section 6.3.2)
10. Have the subject perform an SSA for each target lesion (Section 6.1.1)
11. ONLY AFTER THE SUBJECT COMPLETES THE SSA perform a PLA for each target lesion (Section 6.1.2)
12. Perform an SSK for each target lesion (Section 6.1.4)
13. Measure the dimensions of each target lesion (Section 6.1.3)
14. Have the subject perform a Local Skin Reaction assessment of the symptoms for each target lesion (Section 6.2.1)
15. Perform a Local Skin Reaction assessment of the signs for each target lesion (Section 6.2.1)
16. Discharge the subject from the study.

5.4. Target Lesion Identification

At Visit 1, the investigator will identify 4 target lesions on the treatment area on each subject's back for treatment and evaluation.

For this study, the treatment area on the back is defined vertically from above the beltline to below the neck and horizontally from the left posterior axillary line to the right posterior axillary line.

Have the subject lie prone with the plane of the target lesions horizontal, except for the PLA, which must be performed with the subject standing (Section 6.1.2).

Each target lesion must:

- Have a clinically typical appearance
- Be treatment naïve
- Have a PLA of ≥ 2 (Section 6.1.2)
- Have a lesion area of $\geq 0.5\text{cm}^2$ and $\leq 4\text{cm}^2$ (Section 6.1.3)
- Have a thickness above the normal surrounding skin that is at least palpable and not greater than 3mm (Section 6.1.3)
- Be a discrete lesion
- Be separated from other target lesions, and from any confounding physical characteristic by at least 3cm
- Be able to be photographed
- Not be in an intertriginous fold
- Not be in an area where clothing, such as a bra, might cause physical irritation
- Not be pedunculated.

Number the target lesions 1-4. Place the appropriate identification sticker (provided) for each individual target lesion so it will be visible in the photographs.

Take a series of photographs as described in the photography instructions.

Detailed instructions for taking the study photographs will be provided to the site prior to the initiation of subject enrollment.

At Visits 2-9 use the photographs created at Visit 1 to confirm the location of the target lesions.

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 back (*e.g.*, loofah, back brushes, scrubbing straps, abrasive cleansing pads, etc.)
- Continue their routine cosmetics and skin care products
- Not apply any topical products to the target lesions (except sunscreens as described below)
- Avoid exposing their back to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the back, including on the target lesions, if excessive exposure cannot be avoided
- Avoid or modify activities (*e.g.*, vigorous exercise, carrying heavy backpacks, back massages, etc.) and clothing (*e.g.*, irritating bras, compression clothing, etc.) that might irritate the target lesions
- Bring the subject instruction sheet with them to each visit.

On study visit days, the subjects should:

- Wear a loose fitting blouse/shirt to the visit (Note: clothing that comes in contact with the study medication may be bleached)
- Not apply any topical products to their back within 12 hours prior to the visit (Note: routine cleansing products are allowed)
- After the completion of any study visit where a study medication application was performed do not:
 - Apply any topical products to the back for at least 6 hours
 - **Wash/submerge the target lesions for at least 6 hours.**

Contact the study staff immediately if you have any study related questions.

5.6. Study Duration

The duration of study participation is anticipated to be a maximum of 95 days per subject. This includes the up to 14-day screening period, a visit for a required study medication application, a 21-day no treatment period, a visit for an optional study medication retreatment application, a 56-day no treatment follow-up period and a maximum allowable 4-day Visit 9 visit window.

The total study duration is anticipated to be approximately 130 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 25%	A-101 Solution Vehicle
Manufacturer	Pharmaceutical Manufacturing and Research Services, Horsham, PA, US			
A-101 concentration (%)	40	32.5	25	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 each target lesion at Visit 2 with a possible retreatment application at Visit 5			
Duration of administration	Up to 2 applications to each 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 each of the 4 study medications (12 vials total) will be provided to the 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 study medication is first dispensed for a subject.

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 randomized.

The second panel of the tear-off part is a blinded label (*e.g.*, sealed, tamper-evident envelope, a scratch-off panel or equivalent) which when opened identifies the contents of the vials. The blinded label should only be opened in a medical emergency (Section [5.10.2](#)).

Each study medication vial will be labeled with a one-part label that shows at least the following:

- Subject Kit number (randomization number)
- Protocol number
- Target lesion number
- Vial number
- Investigational drug warning
- Space to enter SN
- Space to enter 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 other than the investigator will assign study medication to eligible subjects by selecting Subject Kits in chronological sequence and in ascending numerical order starting with the lowest available Subject Kit number (the Subject Kit number is the randomization number). No Subject Kit number will be omitted or reused.

The sequence of study medications assignment will be randomly assigned.

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 and guidelines.

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

At Visit 5, perform application(s) for any target lesion that requires a retreatment (Section 5.7.6). Locate the appropriate Subject Kit and the unused study medication vial with the lowest number labeled for the appropriate target lesion number(s). Use a different vial from the vial used for the Visit 2 application. Enter the SN and date of application on each vial label.

5.7.6. Study medication application

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

An investigational center staff member other than the investigator will perform all study medication applications. The staff member 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 each target lesion (4 target lesions).

To perform a study medication application for a target lesion the investigational center staff member will select the appropriate vial of study medication (Section [5.7.5](#)). The staff member must follow these application instructions:

- Wash her/his hands prior to, and after completing the study medication applications; after completing the study medication applications wash her/his hands while still wearing the examination gloves then dispose of the gloves and wash her/his hands again
- Wear examination gloves during the application
- Hold the study medication vial away from her/his face and from the subject's face when opening
- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds
- Have the subject lie prone with the plane of the target lesion horizontal
- Thoroughly cleanse the target lesion by firmly rubbing with an alcohol swab/wipe to ensure it is clean
- Using the supplied applicator:
 - Firmly apply a quantity of study medication sufficient to cover the target lesion with a thin film
 - Minimize exposure to the surrounding normal skin (excess study medication may be removed from the surrounding skin using a clean absorbent wipe)
 - Use an application technique that is appropriate for the target lesion size and characteristics (*e.g.*, dabbing firmly, with moderate pressure, on small or smooth lesions; wiping firmly, with moderate pressure, onto large or rough lesions)
 - Repeat firm applications to the target lesion with the applicator approximately every 30 seconds, adding study medication to the applicator as needed to keep the target lesion wetted, for 5-6 minutes
 - Have the subject remain prone and avoid disturbing the target lesion until any visible reaction, if any, has stopped
 - Absorb any remaining study medication and dry the target lesion without wiping or rubbing the target lesion.

At Visit 2, repeat these steps to make the initial study medication applications to all 4 target lesions.

At Visit 5 any target lesion that has a PLA grade of >0, and ONLY target lesions that have a PLA grade of >0, must receive a retreatment study medication application UNLESS the target lesion:

- **Has a Visit 5 pre-application LSR grade of 3 (severe) for any sign or symptom**
- **Is, in the investigator's opinion, not appropriate for a retreatment study medication application.**

All Visit 5 retreatment applications will be terminated for all subjects if 4 or more subjects discontinue from the study due to study medication related AEs.

At Visit 5, for target lesions that require retreatment, a staff member, other than the investigator, will perform the application following the instructions above, using a different vial from the vial used for the Visit 2 application.

The investigator is prohibited from access to any study procedure or document that shows the study medication identity except in cases of a medical emergency (Section [5.10.2](#)).

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 5, by the investigational center staff at the direction of the investigator, no study medication will be dispensed to the study subjects.

If any subject refuses to allow a study medication retreatment application the investigator must report the visit number, visit date, target lesion number and the reason for the refusal in the subject's CRFs. 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 does not need to be removed from the study based solely on her/his refusal to have a study medication application on any individual target lesion(s).

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:

- Equipment, supplies and instructions for taking standardized photographs
- Appropriate equipment to assist the subject with the SSA
- Supplies for identifying, mapping and tracking the location of the target lesions
- An appropriate ruler, or other instrument, for measuring the Lesion Dimensions.

A third party will provide the supplies for collecting, labeling, shipping and result reporting for the clinical laboratory tests and urine pregnancy tests.

The investigational center will provide appropriate equipment and supplies required for collecting, documenting and assessing the study ECGs.

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 target lesion 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 (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. At the end of the study, the original Label Page CRFs will be returned to the Sponsor 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 subject whose blind has been broken must be discharged from the study (Section 4.6).

6. STUDY ASSESSMENTS

The study assessments will be performed according to the schedules noted below by the investigator or appropriately trained staff members as noted for each assessment. The same individual 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 the appropriate subject position (see below) should be used for all evaluations.

The following evaluations must be performed with the subject standing:

- SSA (Section 6.1.1)
- PLA (Section 6.1.2)
- SSK (Section 6.1.4)
- LSR (Section 6.2.1).

The following evaluation may be performed with the subject standing or prone:

- Lesion Dimensions (Section [6.1.3](#)).

6.1. Effectiveness Evaluations

The investigator and/or subject will evaluate the following for each target lesion.

6.1.1. Subject's Self-Assessment (SSA)

The SSA must be performed with the subject standing.

The SSA must be completed by the subject BEFORE the investigator performs the PLA.

The SSA is the subject's assessment of the average overall severity of each 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 2-9, each subject will assess each SK target lesion and report the one integer that best describes the average overall severity of each target lesion using the scale below. At Visit 2, and if appropriate Visit 5, the SSA must be completed prior to the study medication application.

An investigational center staff member must educate the subject on the SSA scale at every visit.

To perform the SSA assessment subjects must be provided with a handheld mirror, with both 1 power and 2 power magnification, and a full-length (*i.e.*, provides an unobstructed view of the target lesion being assessed) mirror. The subject must use the same handheld mirror magnification power for all SSA assessments.

To evaluate the target lesions:

- The subject should stand with her/his back to the full length mirror
- An investigational staff member will identify each target lesion to the subject in numerical order and direct the subject to assess each lesion sequentially
- The subject should view her/his back using the handheld mirror and full length mirror
- At Visit 2 the staff member will record the handheld mirror magnification power the subject used for the assessment (the subject must use the same magnification power for all SSA assessments)
- At Visits 3-9 the staff member will ensure the subject uses the same handheld mirror magnification as used for the Visit 2 assessment
- The staff member should not influence the subject's assessment.

The subject should indicate to the staff member the one integer that best describes the average overall severity of each target lesion using the following scale. The study staff member will report the SSA grade the subject indicates in the source document:

Subject's Self-Assessment	
Grade	Descriptor
0	Clear: no lesion is noticeable
1	Mild: lesion is barely noticeable on careful examination, but is not obvious
2	Moderate: lesion is obvious on routine examination
3	Severe: lesion is prominent

Both the subject and the study staff member must sign/initial and date the source document to indicate the SSA is reported accurately.

6.1.2. Physician's Lesion Assessment (PLA)

The PLA must be performed with the subject standing.

The investigator must perform the PLA evaluation ONLY AFTER the subject performs the SSA and PRIOR to the Signs of Seborrheic Keratosis (SSK). The subject and the investigator must not discuss the subject's SSA grade.

The PLA is the investigator's assessment of the average overall severity of seborrheic keratosis on each target lesion at a particular time point, and is based on the investigator's clinical experience evaluating SK lesions on subjects with similar skin types. The investigator should NOT refer to any other assessments to assist with this evaluation.

The PLA grade must be ≥ 2 at Visit 1 for the subject to be enrolled and must be ≥ 2 at Visit 2 for the subject to be randomized.

At every study visit, the investigator will assess each seborrheic keratosis target lesion and report the one integer that best describes the average overall severity of each using the following scale. For this evaluation the subject must stand in a position similar to the position used for the SSA (Section [6.1.1](#)). At Visit 2, and if appropriate Visit 5, the investigator must perform the PLA prior to the study medication application:

Physician's Lesion Assessment	
Grade	Descriptor
0	Clear: no lesion, normal skin
1	Mild: lesion is barely evident on examination
2	Moderate: obvious lesion
3	Severe: severe lesion, prominent

6.1.3. Lesion Dimensions

The Lesion Dimensions must be measured with the subject prone.

At every study visit the investigator or designee will measure the following dimensions of each target lesion using the ruler, or equivalent, provided:

- Surface area:
 - The length of the longest axis, in centimeters (cm) to the nearest 0.1cm
 - The length of the longest axis perpendicular to the first measurement, in cm to the nearest 0.1cm
- Thickness:
 - Height, at its highest point above the surrounding skin, in millimeters (mm) reported using the categories below.

At Visit 1 and Visit 2 calculate and report the surface area (cm²) of each target lesion by multiplying the length of the longest axis in cm and the length of the longest axis perpendicular to the first measurement in cm and report to the nearest 0.1cm.

The area of each target lesion must be $\geq 0.51\text{cm}^2$ and $\leq 4\text{cm}^2$ at Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized.

The lesion thickness of each target lesion must be at least palpable and no more than 3mm (grade 1-3) at Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized. Target lesion thickness will be reported by category:

- 0: No height above surrounding normal skin
- 1: Palpable to $\leq 1\text{mm}$
- 2: $>1\text{mm}$ and $\leq 2\text{mm}$
- 3: $>2\text{mm}$ and $\leq 3\text{mm}$
- 4: $>3\text{mm}$ and $\leq 4\text{mm}$
- 5: $>4\text{mm}$.

At Visit 2, and if appropriate Visit 5, the Lesion Dimensions must be measured prior to the study medication application.

6.1.4. Signs of Seborrheic Keratosis (SSK)

The SSK must be performed with the subject standing.

The investigator must perform the SSK evaluation ONLY after completing the PLA.

The SSK is the investigator's assessment of the average severity of two characteristic signs of seborrheic keratosis (pigmentation and surface characteristics) on each target lesion at a particular time point. The investigator should NOT refer to any other evaluations to assist with this evaluation.

At Visits 2-9, the investigator will evaluate each seborrheic keratosis target lesion and report the one integer that best describes the average severity of each sign of seborrheic keratosis for each target lesion using the following scales.

At Visit 2, and if appropriate Visit 5, the investigator must perform the SSK assessment prior to the study medication application:

Pigmentation	
Grade	Descriptor
0	Clear: no variation from normal skin pigmentation
1	Mild: mild, but obvious pigmentation
2	Moderate: marked pigmentation, may have variegated appearance
3	Severe: deeply pigmented lesion, may have variegated appearance

Surface Characteristics	
Grade	Descriptor
0	Clear: no variation from normal skin surface
1	Mild: slightly abnormal surface (<i>e.g.</i> , rough, waxy) evident with thin papular or plaque-like appearance
2	Moderate: abnormal surface (<i>e.g.</i> , rough, waxy), may have verrucous and/or cerebriform appearance
3	Severe: extremely abnormal surface (<i>e.g.</i> , rough, waxy) with verrucous and/or cerebriform surface

6.2. Safety Evaluations

6.2.1. Local Skin Reactions (LSR)

The investigator's portion of the LSR must be performed with the subject standing.

The LSR assessment is the investigator's and the subject's assessment of the average overall severity of the signs and symptoms, respectively, associated with irritation on a target lesion. 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
 - Erosion
 - Ulceration
 - Crusting
 - Induration
 - Vesicles/bullae
 - Scaling/dryness
 - Hyper-pigmentation
 - Hypo-pigmentation (a dermal effect; does not include superficial transient skin blanching/whitening that may be associated with the study medications)
 - Keloid/hypertrophic scarring
 - Atrophy

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

At Visits 2-9 the investigator and the subject will evaluate the LSR signs and symptoms respectively for each target lesion.

The subject will assess the LSR for symptoms as follows:

- At study visits where a study medication application is performed, report the average severity of the LSR for symptoms just prior to the start of the study medication applications and 10 (± 4) minutes after the study medication application to the target lesions is completed
- At study visit where no study medication application is performed, report the average severity of the LSR for symptoms over the previous 24 hours.

The investigator will assess the LSR for signs as follows using the scale below:

- At study visits where a study medication application is performed report the average severity of the LSR for signs prior to the start of the study medication applications and 20 (± 4) minutes after the study medication application to the target lesions is completed
- At study visit where no study medication application is performed report the average severity for each sign.

Both the subject and the study staff member will initial and date the source document to indicate the subject performed the LSR as instructed.

To perform the LSR assessment subjects must be provided with a handheld mirror and a full-length mirror.

To view the target lesions the subject should:

- Stand with her/his back to the provided full length mirror
- View her/his back using the handheld mirror and wall mirror
- An investigational staff member will identify each target lesion to the subject in numerical order and direct the subject to assess the lesion
- The subject will mark the LSR grade for each symptom on each target lesion on the appropriate source document
- The staff member should not influence the subject's assessment.

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

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

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

The investigator must report any LSR that increases in severity, compared to the Visit 2 pre-application evaluation, by ≥ 1 grade AND persists for 2 or more successive visits, as an AE (Section [7.1](#)).

6.2.2. Vital signs

A qualified staff member will measure the following vital signs at Visit 1, at Visit 2 prior to randomization and at Visit 9. At Visit 2 the vital signs should be measured prior to any study medication application:

- 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 CR must be recorded as history if found prior to the first study medication application at 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 >100mm Hg is considered abnormal and therefore must be defined as clinically relevant (CR) or 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. Electrocardiogram (ECG)

A standard 12-lead ECG will be performed by a qualified staff member at Visit 1, at Visit 2 prior to randomization and at Visit 9.

The ECGs must be obtained using a standard 12-lead ECG with a 10mm/mV amplitude, at 25mm/sec and 5-10 second duration. To ensure a steady heart rate the subject must rest quietly in the supine position for at least 5 minutes prior to performing the ECG.

A normal ECG is defined as:

- QTc \leq 450msec for males and \leq 460msec for females (use of the ECG algorithm is acceptable for this purpose)
- Heart rate that is \geq 50 and \leq 100 beats/minutes
- The tracing must not show any:
 - Rhythm disturbance other than a benign sinus dysrhythmia
 - Conduction disturbance including First Degree A-V Block (PR >200msec) and pre-excitation (PR <120msec)
 - Acute or chronic signs of ischemia.

Variations such as minor ST changes (*i.e.*, <0.5mm depression) and early re-polarization are considered normal.

The ECG results must be interpreted by a qualified health professional (evaluator) and the interpretation reported either directly on the tracing or in a separate report. If an ECG result is abnormal, the evaluator should describe the abnormality and define the abnormality as CR or NCR. The evaluator will record this information directly on the ECG tracing/report and date and initial the tracing/report.

The evaluator must review the subject's Visit 1 ECG prior to Visit 2. The subject must not be randomized if the Visit 1 ECG is, in the evaluator's opinion, abnormal, regardless of the clinical relevance.

The evaluator must review all ECG tracings in a timely manner.

The investigator must report all ECG results that are BOTH abnormal AND, in the opinion of the evaluator, CR as medical history if found prior to the first study medication application at or as an AE if found after the first study medication application begins (Section 7.1).

6.2.4. 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 9. 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 subjects' Visit 1 laboratory reports 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 review all laboratory reports in a timely manner

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).

6.2.5. Urine pregnancy tests

The investigator or designee will perform a urine pregnancy test for subjects who are WOCBP (Section 8) at Visit 1, at Visit 2 prior to randomization and at Visit 9. The urine pregnancy test kits used must have a minimum sensitivity of 25-mIU β -HCG/milliliter (mL) of urine.

Subjects who are WOCBP must have a negative pregnancy test result at Visit 1 to be enrolled 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, skin type, race and, if appropriate, ethnicity.

Medical history information will be recorded including all medical conditions, all disease states that require concomitant therapy and other medical conditions and disease states that, in the opinion of the investigator, are relevant to the subject's study participation.

6.3.2. Standardized photography

At every study visit standardized color photographs of each target lesion will be taken. At Visit 2, and if appropriate Visit 5, 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 and detailed instructions for obtaining and managing the photographs will be provided to the investigational center prior to the initiation of subject enrollment.

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

At Visit 1, photographs will be taken as part of the target lesion identification (Section 5.4).

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.

Except for Local Skin Reactions, (see below) worsening of any of the target lesion assessments must 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. Any LSR that increases in severity, compared to the Visit 2 pre-application evaluation, by ≥ 1 grade AND persists for 2 or more successive visits must be reported as an AE.

The investigator must report the target lesion number(s) for any AE associated with a target lesion and should 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.

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) are 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

Non-serious AEs must be reported starting when the subject performs the first study medication application until the end of the subject’s last study visit. SAEs must be reported starting when the subject signs the ICF until the end of the subject’s last visit.

7.1.5. Severity

The investigator is to define the severity 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 will also question the subject in the same manner to elicit AEs during visits when study medication applications are conducted.

If appropriate, based on the subject's response, directed follow-up questions and appropriate evaluations should be conducted.

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 (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as ≥ 12 months with no menses without an alternative medical cause). Women who 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
- Injectables
- Patch
- Combined oral contraceptives
- ParaGard® or Mirena® intrauterine devices
- Condom with spermicide; diaphragm with spermicide
- Vasectomized partner.

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, every pregnancy must be reported 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 analyses will be pairwise comparisons between Vehicle and each active study medication, based on mean change from Visit 2 PLA, using a repeated-measures Analysis of Covariance model suitable for the study design. Study medication concentration is the within-subject independent variable. The Visit 2 score will be the covariate. The primary analysis visit will be Visit 9. An exploratory dose-response analysis may be conducted across concentrations to evaluate a concentration trend, as well as an exploratory longitudinal analysis across visits to evaluate trends over time.

Secondary efficacy analyses will include a similar analysis of SSA, SSK and other evaluations suitable for analysis as continuous variables. Separate primary and secondary effectiveness analyses at each post-baseline visit will be conducted. In addition, secondary analyses will be performed on proportion of PLA and SSA responders, where a subject will be considered a responder if the Visit 9 score is 0. A similar analysis will be done at Visit 5. Chi-square will be used to analyze differences in response rates under the assumption that lesions within a subject may be treated independently, along with a repeated-measures logistic regression model applied as an optional exploratory analysis method.

For all analyses two-tail alpha will be set at 0.05 with no adjustment for multiplicity due to the exploratory nature of the study. The Intent-to-Treat (ITT) population, defined as subjects with data for both Visit 2 and at least one post-Visit 2, will be the primary analysis population, supplanted by analyses of the Per-Protocol (PP) population defined as ITT subjects with no missing effectiveness data and no major protocol violations. ITT population analyses will use last-observation-carried-forward to impute missing post-Visit 2 data.

9.2. Statistical Analysis of Safety Data

Descriptive statistics will be calculated on the safety parameters using the intent-to-treat population, defined as those subjects who were randomized and received at least one study medication application. 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, clinically-relevant ECG results, LSR scores and clinically-relevant abnormal laboratory results will also be tabulated and presented by study medication and abrasion cohort. 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 completing this study was based on the estimated primary efficacy variable response rates for the most effective active medication and vehicle, which are expected to be approximately 60% and 10% respectively. This difference is expected to yield approximately 88% power using a standard chi-square test under the assumption of lesion independence.

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 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 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.

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 should dispense a copy of this instruction sheet to each subject at Visit 1 (Section [5.3.1](#)).

A-101-SEBK-201 SUBJECT INSTRUCTION SHEET

Please follow these instructions carefully. Contact the study staff at the telephone number noted below if you have any questions about the study:

Contact: _____ Telephone: _____

DURING THE STUDY:

- Continue your routine cleansing regimen except avoid vigorous scrubbing of the back (e.g., loofah, back brushes, scrubbing straps, abrasive cleansing pads, etc.)
- Continue your routine cosmetics and skin care products
- Do not apply any topical products to the target lesions (except sunscreens as described below)
- Avoid exposing your back to excessive natural or artificial ultraviolet radiation (e.g., sunlight, tanning beds) and use sunscreen on your back, including on the target lesions, if excessive exposure cannot be avoided
- Starting at Visit 1 and continuing until study completion, avoid or modify activities (e.g., vigorous exercise, carrying heavy backpacks, back massages) and clothing (e.g., bras, compression clothing) that might irritate the target lesions
- Bring this subject instruction sheet with you to each visit.

ON STUDY VISIT DAYS:

- Wear a loose fitting blouse/shirt as instructed by the study staff so it is easier for the investigator to examine the target lesions (NOTE: clothing that comes in contact with the study medication may be bleached)
- Do not apply any topical products to your back within 12 hours prior to the visit, routine cleansing products are allowed
- After visits when a study medication application is performed do not:
 - Apply any topical products to your back for at least 6 hours
 - **Wash/submerge your back for at least 6 hours.**

STUDY VISIT SCHEDULE:

VISIT 2: Date: _____ Time: _____	VISIT 3: Date: _____ Time: _____
VISIT 4: Date: _____ Time: _____	VISIT 5: Date: _____ Time: _____
VISIT 6: Date: _____ Time: _____	VISIT 7: Date: _____ Time: _____
VISIT 8: Date: _____ Time: _____	VISIT 9: Date: _____ Time: _____
Thank you for following these instructions	