A-101 (HYDROGEN PEROXIDE) TOPICAL SOLUTION, 40% (W/W)

AN OPEN-LABEL STUDY ASSESSING SUBJECT SATISFACTION WITH A-101 HYDROGEN PEROXIDE TOPICAL SOLUTION, 40% (W/W) TREATMENT FOR SEBORRHEIC KERATOSES OF THE FACE, NECK, AND DECOLLETAGE (SK-FAN)

Version 3.0

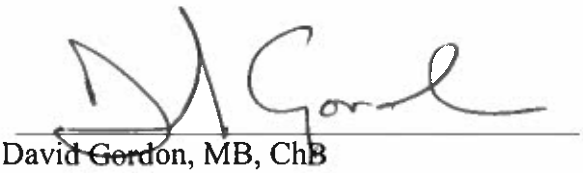
18 JUNE 2018

Protocol Number: A-101-SEBK-402

Version 3.0: 18 June 2018

Protocol Title: An Open-Label Study Assessing Subject Satisfaction with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) Treatment for Seborrheic Keratoses of the Face, Neck, and Décolletage.

Sponsor Signatures:



6|18|2018

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

Date

6-18-2018

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

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for A-101. I have read the A-101-SEBK-402 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Senior Director, Clinical Operations	Judy Schnyder	640 Lee Road Suite 200 Wayne, PA 19087 484-329-2144 jschnyder@aclaristx.com
Medical Monitor	Esther Estes, MD, MPH	640 Lee Road Suite 200 Wayne, PA 19087 484-321-2142 eestes@aclaristx.com
Serious Adverse Event (SAE) contact	Kenneth Kostenbader, MD	640 Lee Road Suite 200 Wayne, PA 19087 484-848-7012 kkostenbader@aclaristx.com SAE Fax: 484-324-2359

Amendment History:

This is the second amendment to the original protocol dated 13-Feb-2018.

Amendment Rationale:

The rationale for Amendment 2 dated 18-Jun-2018 is to increase the enrollment age to 75 years old.

Protocol Version	Date	Page/Section	Revision
1.0	13-Feb-2018	NA	NA
2.0	16-Apr-2018	1/Title Page	Updated version number and date
2.0	16-Apr-2018	2/Protocol Signature Page	Updated version number and date
2.0	16-Apr-2018	5-7/Amendment History and Rationale	Listed all changes to the current version of the protocol
2.0	16-Apr-2018	8/Methodology	Changed "Each SK must be treated by *the Principal Investigator or physician Sub-Investigator*" to "Each SK must be treated by *a study trained healthcare provider at the site*"
2.0	16-Apr-2018	9/Inclusion Criteria	#4d. and 5c. Changed "Be a discrete lesion *and the only SK present when centered in the area outlined by the provided circular template*" to "Be a discrete lesion *(no overlapping lesions)*"
2.0	16-Apr-2018	9/Inclusion Criteria	#6 Changed "Subjects must have had cryosurgery for SK removal within the last *3* months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)." to "Subjects must have had cryosurgery for SK removal within the last *6* months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)."
2.0	16-Apr-2018	11/ Reference therapy, dosage and mode of administration	Changed "Each SK must be treated by *the Principal Investigator or physician Sub-Investigator*" to "Each SK must be treated

Protocol Version	Date	Page/Section	Revision
			by *a study trained healthcare provider at the site*"
2.0	16-Apr-2018	25/Overall Study Design	Changed "Each SK must be treated by *the Principal Investigator or physician Sub-Investigator*" to "Each SK must be treated by *a study trained healthcare provider at the site*"
2.0	16-Apr-2018	28/Footnote 5	Updated typo "*Refer to Section 9.4*" to "*Refer to Section 8.4*"
2.0	16-Apr-2018	28/Footnote 12	Changed "A-101 40% will be applied to each target and non-target SK by *the Principal Investigator or physician Sub-Investigator*" to "A-101 40% will be applied to each target and non-target SK by *a study trained healthcare provider at the site.*"
2.0	16-Apr-2018	29/Inclusion Criteria	#4d. and 5c. Changed "Be a discrete lesion *and the only SK present when centered in the area outlined by the provided circular template*" to "Be a discrete lesion *(no overlapping lesions)*"
2.0	16-Apr-2018	29/Inclusion Criteria	#6 Changed "Subjects must have had cryosurgery for SK removal within the last *3* months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)." to "Subjects must have had cryosurgery for SK removal within the last *6* months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)."
2.0	16-Apr-2018	31/Withdrawal Procedures	Updated typo "*Visit 10*" to "*Visit 11*"
2.0	16-Apr-2018	33/Concomitant Medications	Removed typo "*Subjects should refrain from changing the use of any concomitant therapies during the study.*"

Protocol Version	Date	Page/Section	Revision
2.0	16-Apr-2018	33/Prohibited Therapies	Updated typo "*Starting with Visit 1*" to "*Starting with Visit 2*"
2.0	16-Apr-2018	33/Study Medication Treatment	Changed "*each target and non-target SK must be treated by the Principal Investigator or physician Sub-Investigator*" to "*each target and non-target SK must be treated by a study trained healthcare provider at the site.*"
2.0	16-Apr-2018	40/Target SK Identification	Changed "Be a discrete lesion *and the only SK present when centered in the area outlined by the provided circular template*" to "Be a discrete lesion *(no overlapping lesions)*"
2.0	16-Apr-2018	41/Target SK Identification	Changed "Be a discrete lesion *and the only SK present when centered in the area outlined by the provided circular template*" to "Be a discrete lesion *(no overlapping lesions)*"
2.0	16-Apr-2018	45/Vital Signs	Updated typo "*Section 12.4*" to "*Section 11.6*"
2.0	16-Apr-2018	54/Written Informed Consent	Removed typo "*urine pregnancy test*"
2.0	16-Apr-2018	75 & 76/Appendix 3	Added revised "End of Study Subject Satisfaction Assessment"
3.0	18-Jun-2018	1/Title Page	Updated version number and date
3.0	18-Jun-2018	2/Protocol Signature Page	Updated version number and date. Changed Sponsor Signature from Stuart Shanler, MD to David Gordon, MB, ChB.
3.0	18-Jun-2018	5-7/Amendment History and Rationale	Listed all changes to the current version of the protocol.
3.0	18-Jun-2018	9 & 29/Inclusion Criteria	Changed "Male or female between the ages of 30 and 65 years old." to "Male or female between the ages of 30 and 75 years old."

1. SYNOPSIS

Name of Sponsor/Company:
Aclaris Therapeutics, Inc.
640 Lee Road
Suite 200
Wayne, PA 19087

Name of Investigational Product:
A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)

Name of Active Ingredient:
Hydrogen Peroxide 40%

Title of Study:
(SK-FAN) An Open-Label Study Assessing Subject Satisfaction with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) Treatment for Seborrheic Keratoses of the Face, Neck, and Décolletage.

Study center(s): Up to 3 Investigational Sites

Studied period (months): 3 Estimated date first subject enrolled: March 5, 2018 Estimated date last subject completed: September 5, 2018	**Phase of development:** IV

Objectives: The main objective of this study is to assess subject satisfaction after treatment with A-101 40% on SKs of the face, neck, and décolletage.

Methodology:
Subjects will be naive to A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) treatment. Dermatologists will identify 3 eligible target SKs on each subject; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Up to 4 additional non-target SKs may be identified on the face, neck or décolletage. Each SK must be treated by a study trained healthcare provider at the site. Each target and non-target SK will be treated during up to 3 separate treatment visits: Visit 2, Visit 5 and Visit 7. Each treatment visit requires up to 4 applications of A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) to each eligible target and non-target SK. Each application will last up to 20 seconds with about 60 seconds between applications.

A total of 30 subjects will be enrolled. Subjects will be interviewed by the study staff prior to study medication application to assess their dermatological medical history. A trained photographer will document each subject's SKs at every visit, and during Visit 2, subjects will have photographs taken of each SK at specified post treatment timepoints.

Subjects will be assessed for adverse events related to study medication throughout the conduct of the study.

Number of subjects (planned): 30 subjects will be enrolled to the study

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

Subjects must meet all the following criteria to be considered for participation in this study:

1. Subject can comprehend and is willing to sign an informed consent for participation in this study.
2. Male or female between the ages of 30 and 75 years old.
3. Subject has a clinical diagnosis of stable clinically typical Seborrheic Keratosis.
4. Subject has 3 eligible Seborrheic Keratoses; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Each target SK must meet the following requirements:
   a. Have a clinically typical appearance
   b. Have a Physician's Lesion Assessment of ≥ 2
   c. Have a diameter between 5 to 15 mm
   d. Be a discrete lesion (no overlapping lesions)
   e. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
   f. Not be in an intertriginous fold
   g. Not be on the eyelids
   h. Not be within 5mm of the orbital rim
   i. Not be pedunculated
5. Subject may have up to 4 additional non-target Seborrheic Keratoses on the face, neck or décolletage treated. Each non-target SK must meet the following requirements:
   a. Have a clinically typical appearance
   b. Have a Physician's Lesion Assessment of ≥ 2
   c. Be a discrete lesion (no overlapping lesions)
   d. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
   e. Not be in an intertriginous fold
   f. Not be on the eyelids
   g. Not be within 5mm of the orbital rim
   h. Not be pedunculated
6. Subjects must have had cryosurgery for SK removal within the last 6 months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w).
7. Target and non-target SKs must not have been previously treated.
8. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair the evaluation of any

target or non-target SK or which exposes the subject to an unacceptable risk by study participation.

9. Subject is willing and able to follow all study instructions and to attend all study visits.

Exclusion Criteria:

Subjects are excluded from this study if any 1 or more of the following criteria is met:

1. Subject has clinically atypical and /or rapidly growing Seborrheic Keratoses.
2. Subject has presence of multiple eruptive Seborrheic Keratoses (Sign of Lesser - Trelat).
3. Subject has current systemic malignancy.
4. Subject has previously received A-101 (hydrogen peroxide) Topical Solution, 40% treatment.
5. Subject has used any of the following therapies within the specified period prior to Visit 2 on, or in a proximity to any target or non-target SK, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
   a. LASER, light or other energy-based therapy (*e.g.*, intense pulsed light [IPL], photo-dynamic therapy [PDT]; 30 days
   b. Imiquimod, 5-fluorouracil (5FU), or ingenol mebutate; 60 days
   c. Retinoids; 28 days
   d. Microdermabrasion or superficial chemical peels; 14 days
6. Subject would require the use of any topical treatment (*e.g.*, moisturizers, sunscreens) to any of the target or non-target SKs 12 hours prior to any study visit.
7. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any target or non-target SK that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
   a. Cutaneous malignancy; 180 days
   b. Sunburn; currently
   c. Pre-malignancy (*e.g.*, actinic keratosis); currently
   d. Body art (*e.g.*, tattoos, piercing, etc.); currently
   e. Excessive tan; use of self-tanning lotions/sprays is prohibited
8. Subject has a history of sensitivity to any of the ingredients in the study medications.
9. Subject has any current skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema, sun damage), or condition (*e.g.*, sunburn, excessive hair, open wounds) that, in the opinion of the investigator, might put the subject at undue risk by study participation or interfere with the study conduct or evaluations.
10. Participation in another therapeutic investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

Investigational product, dosage and mode of administration:

A-101 (hydrogen peroxide) Topical Solution, 40% (w/w); hereafter referred to as A-101, will be supplied as a single-use applicator to be applied topically to Seborrheic Keratoses.

The study drug, A-101 40%, is a clear, colorless solution that must be stored at room temperature (20-25º C or 68 -77 º F).

Duration of treatment:

The duration of the study participation is anticipated to be a maximum of 134 days per subject. The final visit, (Visit 11), has a maximum allowable visit window of 7 days.

Study visits are:

- Visit 1 (Day -13 - 0) Screening
- Visit 2 (Day 1) Study Medication Treatment
- Visit 3 (Day 2) Follow-up Visit
- Visit 4 (Day 8) Follow-up Visit
- Visit 5 (Day 15) Study Medication Treatment (if PLA ≥ 1)
- Visit 6 (Day 22) Follow-up Visit
- Visit 7 (Day 29) Study Medication Treatment (if PLA ≥ 1)
- Visit 8 (Day 36) Follow-up Visit
- Visit 9 (Day 57) Follow-up Visit
- Visit 10 (Day 85) Follow-up Visit
- Visit 11 (Day 113) Follow-up Visit; End of Study

Reference therapy, dosage and mode of administration:

Study drug medication will be applied to 3 target SKs and up to 4 non-target SKs during Visit 2, and for SKs that meet the criteria for retreatment, again on Day 15 (Visit 5) and Day 29 (Visit 7).

Each SK must be treated by a study trained healthcare provider at the site.

Study medication must be applied to each target and non-target SK for approximately 20 seconds. Each target and non-target SK may be treated up to 4 times with approximately 60 seconds between each application.

Criteria for evaluation:

Primary:

- Subject satisfaction after treatment with A-101 (Hydrogen Peroxide) topical solution, 40% (w/w) at Day 85 and Day 113.

Secondary:

- Effectiveness of treatment as measured by the PLA at Day 85 and Day 113.
- Comparison of the PLA score(s) to treatment satisfaction at Day 85 and Day 113.

Statistical methods:

Efficacy Analysis:

Descriptive statistics will be used to summarize the data. Descriptive statistics will be used to summarize the effectiveness for this study. The focus of the analyses will be the evaluation of the relationship between lesion outcomes and subject satisfaction scores from each of the subject satisfaction scales. Because satisfaction is assessed on a subject level and not for each individual lesion, it will be necessary to first summarize multiple lesion outcomes into one score for each subject visit. The analyses will then be implemented at each applicable visit by calculating separate Pearson correlations coefficients between (1) mean change from baseline in per-subject averaged PLA scores across all lesions, and (2) each subject satisfaction scale score at the visit. As a sensitivity analysis, the above statistics will also be calculated using Spearman's rank-order correlation. Exploratory analyses similar to the above will also be conducted between (1) per-subject averaged percent of treated lesions clear (PLA = 0) and (2) each subject satisfaction scale score. A similar exploratory analysis will also be conducted using per-subject averaged percent of lesions clear or near-clear (PLA < 2). Additional multiple regression models may be used across groups of subject satisfaction scales, depending on the pattern of individual subject satisfaction scale outcomes.

Safety Analysis:

Safety endpoints for adverse events (AEs) include the following: incidences of all treatment-emergent AEs (TEAEs), and all serious AEs (SAEs); by severity, and discontinuation of subjects from study due to AEs. Safety endpoints for AEs will be specified in the statistical analysis plan (SAP). All safety endpoints will be summarized using descriptive statistics.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
A-101 40%	A-101 Hydrogen Peroxide Topical Solution, 40% (w/w)
AE	Adverse event
ANCOVA	Analysis of Covariance
ºC	Degrees Centigrade
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
e.g.	For example, (Latin; *exempla gratia*)
EC	Ethics Committee
ºF	Degrees Fahrenheit
FDA	Food and Drug Administration
5FU	5 Fluorouracil
G	Gram
GCP	Good Clinical Practice
HCP	Healthcare Provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
H_2O_2	Hydrogen Peroxide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
i.e.	that is (Latin; *id est*)
IPL	Intense Pulsed Laser
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
ITT	Intent to Treat
LOCF	Last Observed Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
Mm	Millimeter
NB	Note Bene
NCS	Not Clinically Significant
OTC	Over the Counter
PDT	Photodynamic Therapy
PI	Principal Investigator
PLA	Physician's Lesion Assessment
PP	Per Protocol
SAE	Serious Adverse Event
SDV	Source Data Verification
SI	Subject Identifier
SK	Seborrheic Keratosis
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
US	United States
WOCBP	Woman of Childbearing Potential

4. INTRODUCTION

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 (Haffner C 2008).

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

Patients 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 be effective, many require specialized training and/or the use of expensive equipment, they are painful and may require anesthesia and/or analgesia, and they are often complicated by significant adverse outcomes. Both hypopigmentation and hyperpigmentation, which may be transient, but are often permanent, are common, as is scarring at the treatment site, and the typical post-surgical risks of bleeding and infection increase the risk that the result of the treatment of these lesions may be worse than the disease itself (Pierson DBC 2003) (Motley 2002) (McKee PH 2005).

Hydrogen peroxide (H_2O_2) is a compound that is ubiquitous in the environment. It is the simplest peroxide and a potent oxidizing agent commonly used in innumerable household goods including chlorine-free bleaches, general-purpose cleaning products, and disinfectants. Additionally, H_2O_2 has been employed as the oxidizing component in hair dyes, and has been used in oral hygiene products and tooth-whitening systems for many years. In industry, it is employed in the treatment of wastewater. In high concentrations, it is used in bleaching paper, pulp, and textiles. Clinically, in addition to its use as an oral topical agent noted above, H_2O_2 is widely employed at low concentrations (*e.g.*, 3%-6%) as a wound irrigant and topical antiseptic/disinfectant, and has been in use medicinally since its introduction into clinical practice by Richardson in 1858. (Schumb WC 1955) (Chan HP 2008) (Richardson, On Peroxide of Hydrogen, or Ozone, or Water as a Remedy: Continued from a Research Commenced in the

Year 1858 1891) (Richardson, On Peroxide of Hydrogen, or Ozone, or Water, as a Remedy: Continued from Research Commenced in the Year 1858 1891) (Richardson, On the Introduction of Peroxide of Hydrogen as a Medicine 1866) (Watt BE 2004) (Zonios 2007).

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

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

Further, data from two dose-ranging studies (A-101-SEBK-202 evaluating SK lesions on the trunk and extremities; A-101-SEBK-203 evaluating SK lesions on the face) demonstrated that topical treatment with A-101 Solution 40% is superior to both A-101 Solution Vehicle and A-101 Solution 32.5% for safely and effectively treating seborrheic keratosis lesions in adult subjects and has an acceptable safety profile.

Summary of Previous Clinical Trials with A-101 Solution in Seborrheic Keratosis

A-101-SEBK-301

A-101-SEBK-301 was a randomized, double-blind, vehicle-controlled, parallel-group study of A 101 and vehicle to investigate the effectiveness, safety, and tolerability in subjects with SK target lesions on the trunk, extremities, and face. Subjects randomized to the study were able to receive up to 2 applications of A-101 40% Solution or matching vehicle.

A total of 450 subjects were randomized and 435 (96.7%) completed the study. Among the 15 subjects who discontinued, the reasons were similar between the treatment groups with the most frequent being a protocol violation (2.6% vehicle, 2.2% A-101). Two subjects (0.4% vehicle, 0.4% A-101) discontinued due to an AE or SAE. The mean age was 68.7 years (range 42 to 90, 42.0% were at least 71 years old), 41.3% of subjects were male and 58.7% were female, and 97.8% were Caucasian. The most common Fitzpatrick skin types were 2 (46.9%) and 3 (27.3%).

Treatment with A-101 40% showed statistically significant efficacy compared to treatment with vehicle based on the primary analysis (supported by the sensitivity analyses) as well as the secondary and exploratory analyses.

For the primary endpoint, the proportion of ITT subjects who achieved clearance (PLA = 0) of all 4 target lesions at Visit 8 (Day 106) was 4.0% with A-101 compared to 0.0% with vehicle ($p = 0.0019$). For the secondary endpoint, the proportion of ITT subjects who achieved clearance of

at least 3 of the 4 target lesions at Visit 8 was 13.45% with A-101 compared to 0.0% with vehicle ($p < 0.0001$).

Treatment Emergent Adverse Events (TEAEs) were reported for 45 (19.8%) subjects in the vehicle group and 54 (24.2%) subjects in the A 101 group. The most frequently reported TEAEs were nasopharyngitis (3.1% vehicle, 1.3% A 101), bronchitis (0.4% vehicle, 1.3% A-101), and upper respiratory tract infection (1.3% vehicle, 0.4% A-101). Six (2.6%) subjects in the vehicle group had 7 SAEs and 4 (1.8%) subjects in the A 101 group had 4 SAEs. The SAEs were all considered not related to study medication. Two subjects, 1 in each treatment group, discontinued the study due to an SAE.

LSRs were few and predominantly mild. The LSRs of pruritus and stinging reported by subjects and crusting, edema, erythema, hyperpigmentation, scaling, and vesicles reported by the investigator following treatment and retreatment had generally resolved by Visit 8 (Day 106).

There were no clinically significant changes during the study in laboratory evaluations or vital signs.

A-101-SEBK-302

A-101-SEBK-302 was a randomized, double-blind, vehicle-controlled, parallel-group study of A 101 and vehicle to investigate the effectiveness, safety, and tolerability in subjects with SK target lesions on the trunk, extremities, and face. Subjects randomized to the study were up able to receive up to 2 applications of A-101 40% Solution or matching vehicle.

A total of 487 subjects were randomized and 461 (94.7%) completed the study. Among the 26 subjects who discontinued, the reasons were similar between the treatment groups with the most frequent being a protocol violation (2.9% vehicle, 4.5% A-101). No subject discontinued due to an AE or SAE. The mean age was 68.7 years (range 45 to 91, 41.5% were at least 71 years old), 41.7% of subjects were male and 58.3% were female, and 97.9% were Caucasian. The most common Fitzpatrick skin types were 2 (46.6%) and 3 (33.1%).

Treatment with A-101 showed statistically significant efficacy compared to treatment with vehicle based on the primary analysis (supported by the sensitivity analyses) as well as the secondary and exploratory analyses.

For the primary endpoint, the proportion of ITT subjects who achieved clearance (PLA = 0) of all 4 target lesions at Visit 8 (Day 106) was 7.8% with A-101 compared to 0.0% with vehicle ($p < 0.0001$). For the secondary endpoint, the proportion of ITT subjects who achieved clearance of at least 3 of the 4 target lesions at Visit 8 was 23.0% with A-101 compared to 0.0% with vehicle ($p < 0.0001$).

TEAEs were reported for 43 (17.7%) subjects in the vehicle group and 46 (18.9%) subjects in the A 101 group. The most frequently reported TEAEs were sinusitis (1.6% vehicle, 1.6% A 101), nasopharyngitis (1.2% vehicle, 0.4% A-101), and herpes zoster (0.0% vehicle, 1.2% A-101). Four (1.6%) subjects in the vehicle group had 4 SAEs and 6 (2.5%) subjects in the A 101 group had 10 SAEs. The SAEs were all considered not related to study medication. No subject discontinued the study due to a TEAE or SAE.

LSRs were predominantly mild. The LSRs of pruritus and stinging reported by subjects and edema, erythema, and scaling reported by the investigator following treatment and retreatment had generally resolved by Visit 8 (Day 106).

There were no clinically significant changes during the study in laboratory evaluations or vital signs.

A-101-SEBK-303

A-101-SEBK-303 was a large open-label safety study in which subjects received up to 4 applications of A-101 40% Solution to SK lesions on their face, trunk or extremities.

A total of 147 subjects were enrolled and treated and 139 subjects (94.6%) completed the study. Five subjects withdrew consent and 3 subjects were lost to follow-up. The mean age was 68.4 years (range 35 to 94, 40.1% were at least 71 years old), 32.0% of subjects were male and 68.0% were female, and 93.9% of subjects were Caucasian. The most common Fitzpatrick skin types were 2 (48.3%) and 3 (32.0%).

At Visit 12 (Day 148) in the ITT population, 10.9% of subjects had all 4 target lesions judged to be clear on the PLA (PLA = 0), 18.4% had at least 3 of 4 target lesions judged to be clear, and 27.9% had all 4 target lesions judged to be clear or near clear (PLA $\leq$ 1). In the PP population, the PLA average per-subject percent of target lesions judged to be clear at Visit 12 was 28.2%.

TEAEs were reported for 25 (17.0%) subjects. The most frequently reported TEAEs were cough, seasonal allergy, and sinusitis (2.0% each). No TEAEs were reported as severe, no SAEs were reported, and no subject discontinued the study due to an AE or SAE.

LSRs reported were predominantly mild and most commonly included transient pruritus, stinging, crusting, edema, erythema, and scaling post-treatment that usually resolved by the next visit. Few lesions had LSRs at Visit 12.

There were no clinically significant changes during the study in laboratory evaluations or vital signs.

All three of the phase 3 studies described above demonstrated that treatment with A-101 (hydrogen peroxide) Topical Solution 40% was both effective and well-tolerated for the treatment of subjects with multiple seborrheic keratosis lesions of the trunk, extremities, and face.

5. TRIAL OBJECTIVES AND PURPOSE

The rationale of this study is to understand a subject's experience and satisfaction after treatment with A-101 40% and how that correlates with a healthcare provider's assessment based on PLA score.

Aclaris Therapeutics, Inc. recently completed three phase III clinical studies (301, 302, and 303) that demonstrated the safety and efficacy of A-101 40% in treating Seborrheic Keratoses.

5.1. Objective

The objective of this study is to assess subject satisfaction after treatment with A-101 40% on SKs of the face, neck, and décolletage.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This study is an open-label study designed to evaluate subject's satisfaction after treatment of seborrheic keratoses with A-101 40%. The subject's treatment application will be documented via a series of photographs to aid in the assessment of the treated SK and to mimic real-world treatment environment.

Dermatologists (investigators) will identify 3 eligible target SKs on each subject; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Up to 4 additional non-target SKs may be identified on the face, neck or décolletage. Each target and non-target SK will be treated during up to 3 separate treatment visits: Visit 2, Visit 5, and Visit 7. Each SK must be treated by a study trained healthcare provider at the site. Retreatment of identified target and non-target SKs will be determined by the physician using the Physicians Lesion Assessment Scale (PLA). Target and non-target SKs that have been assigned a PLA of ≥ 1 will be treated on Day 15 and Day 29. Each treatment visit requires up to 4 applications of A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) to each eligible target and non-target SK. Each application will last up to 20 seconds with about 60 seconds between applications.

A total of 30 subjects will be enrolled. A trained photographer will document each subject's target and non-target SKs at every visit. During Visit 2, subjects will have photographs taken of each SK at specified post treatment timepoints.

Subjects will be assessed for adverse events related to A-101 40% throughout the conduct of the study.

Subjects will be required to complete a total of 11 study visits. The protocol defined study visits are:

- Visit 1 (Day -13 - 0) Screening
- Visit 2 (Day 1) Study Medication Treatment
- Visit 3 (Day 2) Follow-up Visit
- Day 4 (Day 8) Follow-up Visit
- Visit 5 (Day 15) Study Medication Treatment (if PLA ≥ 1)
- Visit 6 (Day 22) Follow-up Visit
- Visit 7 (Day 29) Study Medication Treatment (if PLA ≥ 1)
- Visit 8 (Day 36) Follow-up Visit
- Visit 9 (Day 57) Follow-up Visit
- Visit 10 (Day 85) Follow-up Visit
- Visit 11 (Day 113) Follow-up Visit; End of Study

Refer to Table 3: Study Design and Schedule of Assessments for a complete list of protocol required study assessments.

6.2. Number of Subjects

A total of 30 subjects will be treated on the study at 3 investigational sites in the US.

6.3. Treatment Assignment

This is an open-label study.

6.4. Dose Adjustment Criteria

If a subject refuses the initial treatment or retreatment, the investigator must report the visit number, visit date, target SK number(s) that the subject refused to allow treatment for and the reason for the refusal in the subject's CRF.

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

The subject must have the Visit 2 initial study medication treatment to all target SKs to remain in the study.

The subject does not need to be removed from the study based solely on her/his refusal to have a study medication retreatment at Visit 5 or Visit 7.

Table 3: Study Design and Schedule of Assessments

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Treatment Day	**Day -13 - 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 57**	**Day 85**	**Day 113**
Visit Window	N/A	N/A	N/A	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 7 days	± 7 days	± 7 days
Informed Consent	X										
Inclusion/ Exclusion[1]	X	X									
Subject Identifier[2]	X										
Dermatological Medical History	X										
Demographics	X										
Fitzpatrick Skin Type Assessment[3]	X										
Vital Signs[4]	X	X			X		X			X	X
Prior Medications/Therapies[5]	X										
Target and Non-Target SK Identification[6]	X										
Physician's Lesion Assessment[7]	X	X	X	X	X		X			X	X
SK Dimensions[8]	X	X	X	X	X		X			X	X
SK Photography[9]	X	X[10]	X[11]	X	X[10]	X	X[10]	X	X	X	X
Study Medication Application[12]		X			X		X				
Subject Satisfaction Assessment[13]		X	X			X		X		X	X
Concomitant Therapies[14]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[15]		X	X	X	X	X	X	X	X	X	X

[1]Subject inclusion/exclusion criteria will be reassessed prior to enrollment during Visit 2.

[2]Investigational sites will assign a unique five-digit subject identifier to each subject at Visit 1, formatted as NN-NNN where the first 2 digits are the site number, and the final 3 digits are the subject number that must be assigned in ascending numerical order (using leading zeroes, as appropriate). This subject identifier will be used in all study documentation for the duration of the study.

[3]Each subject's skin must be assessed during Visit 1 using the Fitzpatrick Skin Type Assessment. Refer to Table 6 for the scale.

[4]Vital signs [including temperature, pulse, respiratory rate, blood pressure, height and weight (Visit 1 only)] will be measured by a qualified staff member at Visit 1, Visit 2, Visit 5, Visit 7 Visit 10, and Visit 11.

[5]Prior medications/therapies will be collected for a time-period of 13 days prior to Visit 1. Refer to Section 8.4 for a list of permitted and restricted concomitant medications.

[6]The treating investigator will identify 3 target SKs and up to 4 non-target SKs. Two (2) target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. The 4 non-target SKs may be located on the face, neck, or décolletage.

[7]The investigator will use the Physician's Lesion Assessment (PLA) to assess the severity of each target and non-target SKs at Visits 1, 2, 3, 4, 5, 7, 10, and 11. At Visit 2, Visit 5 and Visit 7, the investigator must assess each target and non-target SK prior to application of the study medication. In order to be eligible for enrollment to the study during Visit 2, the subject must have a PLA grade ≥ 2 for each target and non-target SK.

[8]The investigator will measure the dimensions of each target and non-target SK at Visits 1, 2, 3, 4, 5, 7, 10 and 11. At Visit 2, Visit 5 and Visit 7, the investigator must measure each target and non-target SK prior to application of the study medication. In order to be eligible for enrollment to the study during Visits 1 and 2, each target SK must have a diameter that is between ≥ 5 and ≤ 15 mm (inclusive) and be raised. In order to be eligible for enrollment to the study during Visits 1 and 2, each non-target SK must be a raised SK. At Visits 3, 4, 5, 7, and 10 the investigator must assess the thickness of each target and non-target SK above the surrounding skin. Additional target and non-target SK requirements are outlined in Section 10.1 .

[9]Each target and non-target SK will be photographed at all study visits using the Aclaris Therapeutics, Inc. supplied photography equipment.

[10]During Visit 2 each target and non-target SK will be photographed prior to the application of A-101 40%, 10 minutes post application (+2 minutes), and 1-hour post application (± 10 minutes). During Visit 5 and Visit 7, the target and non-target SKs will be photographed prior to the application of A-101 40%, if applicable.

[11]During Visit 3 each target and non-target SK will be photographed 24-hours post application during Visit 2 (± 2 hours).

[12] A-101 40% will be applied to each target and non-target SK by a study trained healthcare provider at the site. Each target and non-target SK will be treated with A-101 40% following confirmation of subject eligibility and study enrollment at Visit 2. If a target or non-target SK meets the criteria for retreatment as defined in Section 9.5, the SK will be retreated at Visit 5 and Visit 7. Following application of A-101 40%, subjects must NOT wash/submerge a target and non-target SK for at least 6 hours and they must NOT apply any topical products to any target or non-target SK for at least 6 hours.

[13]Subjects will be asked to assess how satisfied they are with the treatment experience they received for the target and non-target SKs at the specified visits. On Visit 2 the subject will complete the assessment prior to application of A-101 40%. On Visit 3 the subjects will complete the assessment approximately 24 hours after the treatment. On Visit 6 and Visit 8 the subjects will complete the assessment approximately 1 week after the treatment, only if the subject received treatment on Visit 5 or Visit 7. The subject will complete the assessment during the Visit 10 and Visit 11.

[14]All concomitant therapies including (topical and oral) prescription medications, over the counter medications, natural supplements and non-drug therapies including chiropractic, physical therapy, and energy-based therapy must be documented in the subject CRF. Subjects must not apply any topical products *(e.g.*, moisturizers, sunscreen, etc.) to their target and non-target SKs within 12 hours prior to any study visit.

[15]The reporting period for SAEs begins when the subject signs the informed consent form. Refer to Section 11.6 for instructions on the reporting of SAEs. Non-serious clinical adverse events will be collected following the application of the study medication at Visit 2 and continue through Visit 11. All safety reporting (AEs and SAEs) will conclude at Visit 11.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all the following criteria to be considered for participation in this study:

1. Subject can comprehend and is willing to sign an informed consent for participation in this study.
2. Male or female between the ages of 30 and 75 years old.
3. Subject has a clinical diagnosis of stable clinically typical Seborrheic Keratosis.
4. Subject has 3 eligible Seborrheic Keratoses; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Each target SK must meet the following requirements:
    a. Have a clinically typical appearance
    b. Have a Physician's Lesion Assessment of ≥ 2
    c. Have a diameter between 5 to 15 mm
    d. Be a discrete lesion (no overlapping lesions)
    e. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    f. Not be in an intertriginous fold
    g. Not be on the eyelids
    h. Not be within 5mm of the orbital rim
    i. Not be pedunculated
5. Subject may have up to 4 additional non-target Seborrheic Keratoses on the face, neck or décolletage treated. Each non-target SK must meet the following requirements:
    a. Have a clinically typical appearance
    b. Have a Physician's Lesion Assessment of ≥ 2
    c. Be a discrete lesion (no overlapping lesions)
    d. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
    e. Not be in an intertriginous fold
    f. Not be on the eyelids
    g. Not be within 5mm of the orbital rim
    h. Not be pedunculated
6. Subjects must have had cryosurgery for SK removal within the last 6 months and prior to first treatment with A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w).
7. Target and non-target SKs must not have been previously treated.
8. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, might impair the evaluation of any target or non-target SK or which exposes the subject to an unacceptable risk by study participation.
9. Subject is willing and able to follow all study instructions and to attend all study visits.

7.2. Subject Exclusion Criteria

Subjects are excluded from this study if any 1 or more of the following criteria is met:

1. Subject has clinically atypical and /or rapidly growing Seborrheic Keratoses.
2. Subject has presence of multiple eruptive Seborrheic Keratoses (Sign of Lesser -Trelat).
3. Subject has current systemic malignancy.
4. Subjects have previously received A-101 (hydrogen peroxide) Topical Solution, 40% treatment.
5. Subject has used any of the following therapies within the specified period prior to Visit 2 on, or in a proximity to any target or non-target SK, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
   a. LASER, light or other energy-based therapy (*e.g.*, intense pulsed light [IPL], photo-dynamic therapy [PDT]; 30 days
   b. Imiquimod, 5-fluorouracil (5FU), or ingenol mebutate; 60 days
   c. Retinoids; 28 days
   d. Microdermabrasion or superficial chemical peels; 14 days
6. Subject would require the use of any topical treatment (*e.g.*, moisturizers, sunscreens) to any of the target or non-target SKs 12 hours prior to any study visit.
7. Subject currently has or has had any of the following within the specified period prior to Visit 1 on or in a proximity to any target or non-target SK that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
   a. Cutaneous malignancy; 180 days
   b. Sunburn; currently
   c. Pre-malignancy (*e.g.*, actinic keratosis); currently
   d. Body art (*e.g.*, tattoos, piercing, etc.); currently
   e. Excessive tan; use of self-tanning lotions/sprays is prohibited
8. Subject has a history of sensitivity to any of the ingredients in the study medications.
9. Subject has any current skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema, sun damage), or condition (*e.g.*, sunburn, excessive hair, open wounds) that, in the opinion of the investigator, might put the subject at undue risk by study participation or interfere with the study conduct or evaluations.
10. Participation in another therapeutic investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

7.3. Subject Withdrawal Criteria

A subject may be removed from the study therapy for a variety of reasons, including:

- Unacceptable adverse event.
- Subject unwilling or refusal to continue with the protocol defined study visits and/or consent withdrawal for study participation.
- Change in compliance with an inclusion/exclusion criterion.

- Use of a prohibited medication during the treatment period.
- General or specific changes in the subject's condition that render the subject unacceptable for further treatment in this study in the judgement of the investigator.

If a subject is to be withdrawn from the study, the Aclaris Therapeutics, Inc. study monitor, or designee, must be informed with 24 hours of the decision to remove the subject from the study.

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

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

7.4. Withdrawal Procedures

If a subject withdraws from the study prior to Visit 11, the reason for and the date of withdrawal from the study must be recorded on the eCRF. If the reason for withdrawal is an adverse event, monitoring of the subject will continue until the event has resolved or stabilized, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

7.5. Subject Replacement

If a subject is enrolled to the study but does not receive a dose of study drug, then the subject may be replaced.

Subjects that are determined to be screen failures may be rescreened for the study and if determined to be eligible for the study they may be enrolled using the same subject identifier and must sign a new informed consent form.

7.6. Subject Identifier (SI)

The investigator or designee will assign a unique five-digit subject identifier (SI) to each subject at Visit 1.

The SI format will be NN-NNN where the first 2 digits are the investigational center site number (using leading zeroes, as appropriate). The final 3 digits are the subject number and must be assigned in ascending numerical order, without omitting or repeating any number, starting with 001 at each investigational center. For example, the SI for the second subject that signs an informed consent at site number 04 would be 04-002.

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

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Table 4: Investigational Product

	Investigational Product
Product Name:	A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w)
A-101 Concentration (%):	Hydrogen peroxide 40% (w/w)
Pharmaceutical Form	Solution
Route of Administration	Topical
Manufacturer	James Alexander Corporation, Blairstown NJ
Storage Conditions	Room temperature: 59ºF to 77ºF (15ºC to 25ºC) protected from excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area. Excursions from these conditions must be reported to Aclaris Therapeutics, Inc.
Application	Nitrile or vinyl examination gloves must be worn during the application process. Latex gloves are prohibited.
Duration of Administration	Apply study medication to each target and non-target SK for approximately 20 seconds, then allow each target and non-target SK to remain undisturbed for approximately 60 seconds. Repeat the application/waiting cycle until the A-101 40% has been applied to each target and non-target SK up to 4 times. Subjects may receive up to 3 treatments. (Visit 2, Visit 5 and Visit 7)
Activated Applicators	Activated applicators are stable for 4 hours at room temperature 59ºF to 77ºF (15ºC to 25ºC)

8.2. Previous Therapies

During Visit 1, the investigator or designee will question the subject to ensure they have not used any excluded therapies (Section 8.4).

8.3. Concomitant Medications

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

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

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

8.4. Prohibited Therapies

During the course of this study, subjects are prohibited from using the following treatment therapies to treat any of the target and non-target SKs:

- Retinoids (topical)
- Corticosteroids (topical)
- LASER, light or other energy-based therapy
- Liquid nitrogen, electrodesiccation, curettage, imiquimod, ingenol mebutate
- Microdermabrasion or superficial chemical peels
- Antibiotics (topical)
- Self-tanner lotions and sprays

The investigator should notify the Medical Monitor immediately if any prohibited therapies are required to ensure subject safety.

Starting with Visit 2, subjects must not apply any topical products (*e.g.*, moisturizers, sunscreens, etc.) to their target and non-target SK within 12 hours prior to any study visit (Note: routine cleansing products are allowed).

After the completion of any study visit where a study medication treatment was performed subjects must NOT wash/submerge the target or non-target SK for at least 6 hours and must not apply any topical products to the target or non-target SK for at least 6 hours.

8.5. Study Medication Treatment

A-101 40% is for external, topical use on the target or non-target SK on the appropriate study subject only.

The Principal Investigator or physician Sub-Investigator performing the A-101 40% treatments must comply with the A-101 40% storage conditions outlined in Section 8.1.

At Visit 2, and Visit 5 and Visit 7 if applicable, each target and non-target SK must be treated by a study trained healthcare provider at the site.

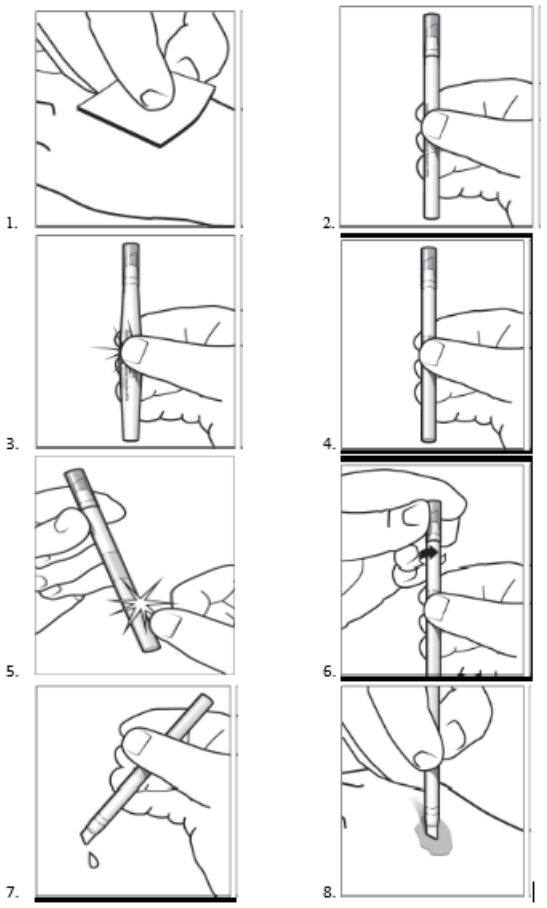
At Visit 5 and Visit 7, all identified target and non-target SKs that have a PLA grade of ≥ 1 will be re-treated with A-101 40%. If in the investigator's opinion, the lesion is not appropriate for re-treatment (e.g. cutaneous AE) treatment will be withheld. The reason for withholding treatment will documented in the comment section of the subject's CRF and the AE CRF if appropriate.

8.5.1. Preparing the Study Medication for Application

To perform a study medication treatment for a target or non-target SK a HCP at the site will select the appropriate A-101 40% applicator. The following instructions outline the procedure for application of A-101 40% to the target or non-target SK:

- Prepare for the treatment:
    - Wash your hands prior to, and after completing the A-101 40% treatments
    - Wear nitrile or vinyl examination gloves during the treatment; *latex gloves are prohibited*
    - Select the applicator
    - Visually inspect the applicator for damage:
        - If the applicator appears damaged do not use it for the treatment, contact the study monitor for return/disposal instructions and select an unused applicator for the treatment
        - If the applicator is intact, proceed with the treatment process as outlined in Figure 1

Figure 1: Diagram Showing the Process for Preparing and Applying A-101 40%



1. Each target and non-target SK should be cleaned using an alcohol wipe prior to application of A-101 40%.
2. Hold the A-101 40% applicator so that the applicator cap is pointing up.
3. Crush the ampule in the applicator by applying pressure to the center of the barrel of the applicator.
4. Remove the sleeve.
5. Tap the barrel of the applicator to ensure the solution is free of the crushed ampule.
6. Gently remove the cap by twisting while pulling away from the applicator.
7. Express a single drop of A-101 40% so that the tip of the applicator becomes wet.
8. Apply the solution to the target or non-target SK in a circular motion.

8.5.2. Applying A-101 40% to the Face, Neck or Décolletage

To apply A-101 40% to the target or non-target SK the HCP will follow these treatment instructions:

- Do not apply A-101 40% to eyes, mouth, mucous membranes, open wounds

- Do not apply A-101 40% to the eyelids or within 5 mm of the orbital rim
- If, in the investigator's opinion it is needed to ensure no A-101 40% enters the eye:
    - Position the subject in the supine position with the head slightly elevated and angled such that any excess study medication will flow away from the eye.
    - Apply white petrolatum (100%) United States Pharmacopeia (USP) that is to be applied along the orbital rim and at the medial and lateral canthi; gently stretch the periorbital skin between the thumb and forefinger at the time of petrolatum application to distend any periorbital rhytides (*e.g.*, "crow's feet") and ensure full coverage of the skin at the base of the rhytides to decrease the likelihood of tracking of the study medication towards the eye
    - Have the subject hold an absorbent pad in the appropriate area of the eye to absorb any excess study medication that might track away from the target or non-target SK
    - Instruct the subject to keep both eyes closed during the entire study medication treatment procedure
- After the subject is properly prepared and positioned, thoroughly cleanse the target or non-target SK by firmly rubbing with a swab/wipe wetted with 70% isopropyl alcohol
- Using firm pressure, squeezing in the middle of the applicator, apply one drop of study medication onto the target or non-target SK and then move applicator around in a circular motion to fully saturate the SK. Apply the study medication for approximately 20 seconds
- Minimize exposure to the surrounding normal skin
- During the treatment process remove excess study medication from the surrounding skin using a clean absorbent wipe
- Ensure the target or non-target SK is wet with study medication at the end of the approximately 20 second application
- Allow the target or non-target SK to remain undisturbed for approximately 60 seconds
- After approximately 60 seconds repeat the approximately 20 second application process

Repeat the application/waiting cycle until the study medication has been applied to each target or non-target SK up to 4 times. It is acceptable to treat the target and non-target SKs sequentially to minimize treatment time; such that, after treatment is applied to the 3rd SK, the 60 second wait time between applications would be met.

Record the time the final treatment is completed for the last treated target or non-target SK as the Treatment Completion Time.

8.6. Randomization and Blinding

8.6.1. Randomization

This is an open-label study and therefore randomization is not applicable.

8.6.2. Blinding

This is an open-label study and therefore the clinical drug supplies are not blinded.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The study medication is A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w). The study medication is a clear, colorless solution.

9.2. Study Drug Packaging and Labeling

A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) will be provided by Aclaris Therapeutics, Inc. and labeled according to the local law and legislation.

The study medication will be packaged in single use applicators. Each single-use applicator consists of a crushable glass ampoule that contains 2.2 milliliters (mL) of study medication that provides for at least 1.3 mL of study medication available for treatment. The ampoule is provided inside a sealed polyethylene tube with a flocked, doe foot applicator on one end.

9.3. Study Drug Storage

Investigational sites will be supplied with open-label stock of A-101 40%. Investigational study medication supplies are only to be used for subjects properly consented and enrolled to this study.

A-101 40% must be stored in a location where there is limited access to the investigational study medication at 59ºF to 77ºF (15ºC to 25ºC) excessive heat, open flame and combustibles, in a well-ventilated, dry area. Excursions from these temperature ranges must be reported to Aclaris Therapeutics, Inc.

9.4. Study Drug Preparation

Activated applicators are stable for 4 hours at room temperature (59ºF to 77ºF or 15ºC to 25ºC).

9.5. Administration

The subject will receive up to 4 applications to each target or non-target SK at Visit 2, and if the subject meets retreatment criteria, at Visit 5 and Visit 7.

Apply study medication to each target and non-target SK for approximately 20 seconds. Allow each target and non-target SK to remain undisturbed for approximately 60 seconds. Repeat the application/waiting cycle until the study medication has been applied to each target and non-target SK up to 4 times. Subjects may receive up to 3 treatments (Visit 2, Visit 5 and Visit 7).

9.6. Study Drug 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.

Final drug accountability will be completed by the study monitor at the completion of the study and all unused study medication will be returned to Aclaris Therapeutics, Inc. drug depot for disposal per Aclaris Therapeutics, Inc. (or designee's) written instructions.

9.7. Study Drug Handling and Disposal

Nitrile or vinyl examination gloves must be worn during the application process. *Latex gloves are prohibited.*

10. ASSESSMENT OF EFFICACY

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

10.1. Target SK Identification

At Visit 1, the investigator will identify up to 7 Seborrheic Keratoses on each subject for treatment and evaluation. Three (3) target lesion must be identified, and up to 4 non-target lesions may be identified. Two (2) target SKs must be on the face, and the additional 1 target SK must be on the neck, or décolletage. Up to 4 additional non-target lesions may be on the face, neck, or décolletage.

Face:

- Vertically from the mandibular ridge vertically up to the hairline (for subjects with a receded hairline the hairline is defined by the vertical line drawn coronally from tragus to tragus)
- Horizontally from tragus to tragus, excluding the eyelids and areas within 5mm of the orbital rim.

Neck:

- Vertically from the mandibular ridge vertically down to the top of the collar bone

Décolletage:

- From the collar bone down including the shoulders and cleavage area

At Visit 1, each target SK must:

- Have a clinically typical appearance
- Have a PLA of ≥2
- Have a diameter between 5 to 15 mm
- Be a discrete lesion (no overlapping lesions)
- Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations (NB: the study medication may bleach hair)
- Not be in an intertriginous fold
- Not be on the eyelids
- Not be within 5mm of the orbital rim
- Not be pedunculated.

At Visit 1, each non-target SK must:

- Have a clinically typical appearance

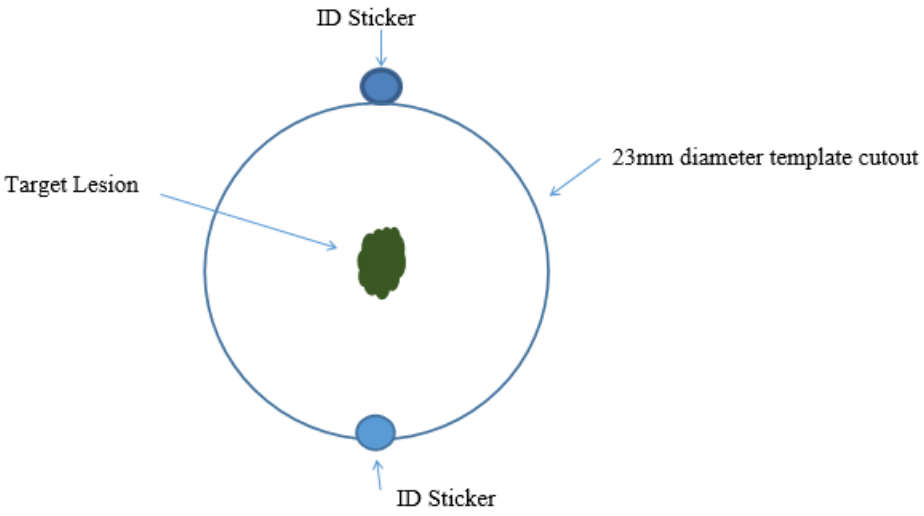
- Have a PLA of ≥2
- Be a discrete lesion (no overlapping lesions)
- Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations (NB: the study medication may bleach hair)
- Not be in an intertriginous fold
- Not be on the eyelids
- Not be within 5mm of the orbital rim
- Not be pedunculated.

Record the approximate location of each target and non-target SK on the body chart in the CRFs. Number the target SK starting with 1 and proceeding up to 3 with no number omitted or reused. The target SKs on the face should be numbered 1 and 2, and the additional 1 SK on the neck and/or décolletage should be numbered 3. The non-target SKs should be numbered 4-7 starting with 4 and proceeding up to 7 with no number omitted or reused.

Aclaris Therapeutics, Inc. will provide the investigational site with standard circular templates and colored stickers that are to be used to identify the target and non-target SKs.

At Visit 1, the investigator and a HCP will identify the target and non-target SKs by placing 2 appropriately colored stickers approximately 180 degrees opposite each other with the target or non-target SK in the center of the area outlined by the provided circular template (Refer to Figure 2. Figure not to scale):

Figure 2: Target and Non-Target SK Identification



Write the target or non-target SK number on one of the identification (ID) stickers. The ID stickers must be visible in the study photographs. The target and non-target SK #/ID sticker color relationships are:

- Target SK on face#1/white ID stickers
- Target SK on face #2/yellow ID stickers
- Target SK on neck or décolletage #3/green ID stickers
- Non-Target SK on the face, neck or décolletage #4/pink ID stickers
- Non-Target SK on the face, neck or décolletage #5/grey ID stickers
- Non-Target SK on the face, neck or décolletage #6/purple ID stickers
- Non-Target SK on the face, neck or décolletage #7/orange ID stickers

At each study visit a HCP from the investigational staff will confirm the location of each target and non-target SK using an appropriate combination of the Visit 2 hard-copy reference prints and the body charts. The staff member will identify the target and non-target SKs by placing 2 appropriately colored ID stickers, with the target or non-target SK number written on one sticker, approximately 180 degrees opposite each other with the target or non-target SK in the center of area outlined by the provided circular template.

10.1.1. Standardized Photography

At each study visit a qualified investigational center staff member will take standardized color photographs of each target and non-target SK.

The photographs are to document the location of the target and non-target SK and to assist with relocating the target and non-target SK and the target and non-target SK ID stickers must be visible in the photographs. The subject's identity will not be revealed in the study photographs. These photographs will also be used to document the treatment effects of A-101 40% over time.

At Visit 2, the photographs must be taken prior to the study medication application, 10 minutes post application, and 1-hour post application of A-101 40%. At Visit 5 and Visit 7, the photographs will be taken prior to study medication application, if applicable. At Visit 3 photographs must be taken 24 hours post application of A-101 40% on Visit 2.

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

Sites will be provided with photography equipment and supplies necessary for obtaining the target and non-target SK photographs. Detailed instructions for obtaining and managing the photographs will be documented in the study specific Photography Manual and provided to the site at the study initiation visit.

10.1.2. Physician's Lesion Assessment (PLA)

The PLA is the investigator's assessment of the severity of the target and non-target SK at a particular time point. The investigator may refer to other evaluations (*e.g.,* prior photographs) to assist with these assessments.

At Visits 1, 2, 3, 4, 5, 7, 10, and 11 the investigator will assess the target and non-target SK using the scale below and report the one integer that best describes the severity of the target or non-target SK. At Visit 2 and if applicable at Visit 5 and Visit 7, the investigator must complete the PLA prior to the study medication treatment.

Table 5: Physician's Lesion Assessment Definitions

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

All investigational site staff will receive training on the PLA Assessment Scale and be provided with a PLA Assessment Manual (refer to Appendix 2) that will be used as a reference tool during the conduct of the study.

In order for a subject to be eligible for screening and enrollment to the study, each target and non-target SK must have a PLA grade of ≥ 2.

10.1.3. SK Dimensions

At Visit 1 and Visit 2 prior to study enrollment, the investigator will measure the diameter and thickness of each target and non-target SK using the ruler provided.

The investigator must measure the diameter of the longest axis of each target and non-target SK in millimeters (mm) as follows:

- Diameter (*i.e.*, the length of the longest axis)
- Thickness (height above the surrounding skin)

The PLA (the thickness) of the target and non-target SKs will be measured by the investigator at Visits 3, 4, 5, 7, 10, and 11. When the visit coincides with treatment (Visits 2, 5 and 7), the thickness must be measured prior to the application of study medication.

10.2. Subject Instructions

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

Throughout the study, the subjects should:

- Continue their routine cleansing regimen
- Continue their routine cosmetics and skin care products
- Avoid exposing the target and non-target SKs to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the target and non-target SKs, if excessive exposure cannot be avoided

- Avoid the use of self-tanning lotions and spray tans
- Bring the subject instruction sheet with them to each visit

On study visit days, the subjects should:

- When appropriate for the target and non-target SK locations, wear loose fitting clothing to the visit (Note: clothing that comes in contact with the study medication may be bleached)
- Starting with Visit 2, not apply any topical products to the target or non-target SKs within 12 hours prior to the visit (Note: routine cleansing products are allowed)
- After the completion of any study visit where a study medication treatment was performed DO NOT:
    - Wash/submerge the target or non-target SKs for at least 6 hours
    - Apply any topical products to the target or non-target SKs for at least 6 hours

10.3. Subject Satisfaction Assessment

Subjects will be asked to assess their level of satisfaction regarding the study medication treatment experience. The subject survey will be completed at Visits 2, 3, 6 (only if treated at Visit 5), 8 (only if treated at Visit 7), 10, and 11. (See Appendix 3)

10.4. Study Supplies

Aclaris Therapeutics, Inc. will provide:

- An appropriate ruler, or other instrument, for measuring the diameter and thickness of the target ad non-target SKs
- Templates for use when identifying target and non-target SKs
- Equipment, supplies and training for taking standardized photographs

11. ASSESSMENT OF SAFETY

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

11.1. Vital Signs

Vital signs will be measured by a qualified staff member at Visit 1, Visit 2, Visit 5, Visit 7 Visit 10, and Visit 11. The following items will be measured:

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

Any measure that is, in the opinion of the investigator, abnormal AND clinically significant (CS) must be recorded as history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins (Section 11.6).

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg is considered abnormal and therefore must be defined as CS or NCS on the CRFs.

11.2. Other Evaluations

11.2.1. Demographic/Medical History

At Visit 1, the investigator or designee will collect demographic information including date of birth, sex at birth, race, and ethnicity for each subject.

At Visit 1, the investigator must determine each subject's Fitzpatrick Skin Type and document appropriately on the subject's source document and CRF.

Table 6: Fitzpatrick Skin Type Scoring System

Skin Type Classification	Description
Type I	Always burns, never tans (pale white; blond or red hair; blue eyes; freckles)
Type II	Usually burns, tans minimally (white; fair; blond or red hair; blue, green, or hazel eyes)
Type III	Sometimes mild burn, tans uniformly (cream white; fair with any hair or eye color)
Type IV	Burns minimally, always tans well (moderate brown)
Type V	Very rarely burns, tans very easily (dark brown)

Skin Type Classification	Description
Type VI	Never burns, never tans (deeply pigmented dark brown to darkest brown)

11.3. Adverse and Serious Adverse Events

11.3.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to the study drug. An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study (or any concurrent disease), whether or not considered related to the study drug.

Accordingly, an adverse event could include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions.
- drug interactions
- events occurring during diagnostic procedures or any washout phase of the study
- laboratory or diagnostic test abnormalities occurring after the start of the study (i.e., after screening and once confirmed by repeat testing) that results in the withdrawal of the subject from the study, requires medical treatment or further diagnostic work up, or is considered by the study investigator to be clinically significant.

The investigator must, for any target or non-target SK related AE, 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.

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.

The investigator must start reporting non-serious AEs starting with the subject's first study medication treatment continuing through Visit 11.

11.3.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose results in one or more of the following:

- Results in death

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

The term "life threatening" refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it 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 elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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.

11.4. Relationship to Study Drug

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).

11.5. Severity

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

Intensity will be assessed according to the following scale:

- Mild - Awareness of sign or symptom, but easily tolerated
- Moderate - Discomfort sufficient to cause interference with normal activities
- Severe - Incapacitating, with inability to perform normal activities

11.6. Reporting Adverse Events

At each post enrollment visit, the investigator or designee 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 or designee will monitor the subject for at least 20 minutes after the Treatment Completion Time at Visit 2, and if applicable at Visit 5 and Visit 7 to elicit AEs in a similar manner.

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

Non-serious AEs should be recorded starting with the subject's first study medication treatment at Visit 2 and continuing through Visit 11.

All SAEs regardless of relationship to study medication must be collected and reported to Aclaris Therapeutics, Inc. from the time the Informed Consent is signed through Visit 11.

Upon becoming aware of a SAE the investigator must:

1. Take the appropriate medical action to ensure the subject's safety
2. Immediately inform the Safety Monitor of the SAE:

Ken Kostenbader, MD
Aclaris Therapeutics, Inc.
640 Lee Road, Suite 200
Wayne, PA 19087
Telephone: 484-848-7012
Serious Adverse Event Facsimile: 484-324-2359
Email: kkostenbader@aclaristx.com

3. Within 24-hours of becoming aware of the event, a SAE report form, an AE CRF and any other relevant information (*e.g.*, concomitant medication CRF, medical history CRF, laboratory test results) must be faxed to the SAE Fax line listed above.
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 SAE reaches a clinically stable outcome with or without sequelae AND the investigator and Safety Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Safety 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).

11.7. Withdrawal Due to an Adverse Event

Any subject who experiences an adverse event may be withdrawn from study drug at any time at the discretion of the investigator. If a subject is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time. The subject will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the subject is referred to the care of a local health care professional. The investigator must inform the medical monitor as soon as possible of all subjects who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

12. STATISTICS

Statistical Analysis of Efficacy

Descriptive statistics will be used to summarize the data for this study. The focus of the analyses will be the evaluation of the relationship between lesion outcomes and subject satisfaction scores from each of the subject satisfaction scales. Because satisfaction is assessed on a subject level and not for each individual lesion, it will be necessary to first summarize multiple lesion outcomes into one score for each subject visit. The analyses will then be implemented at each applicable visit by calculating separate Pearson correlations coefficients between (1) mean change from baseline in per-subject averaged PLA scores across all lesions, and (2) each subject satisfaction scale score at the visit. As a sensitivity analysis, the above statistics will also be calculated using Spearman's rank-order correlation. Exploratory analyses similar to the above will also be conducted between (1) per-subject averaged percent of treated lesions clear (PLA = 0) and (2) each subject satisfaction scale score. A similar exploratory analysis will also be conducted using per-subject averaged percent of lesions clear or near-clear (PLA < 2). Additional multiple regression models may be used across groups of subject satisfaction scales, depending on the pattern of individual subject satisfaction scale outcomes.

Statistical Analysis of Safety Data

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

Safety summaries will include listings 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 showing the proportion of subjects experiencing adverse events, both overall and by MedDRA System Organ Class.

Interim Analysis

An interim Analysis will not be conducted for this study.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The conduct of the study will be closely monitored by the Aclaris Therapeutics, Inc. study monitor /CRO to verify adherence to ICH Good Clinical Practice (GCP) guidelines, applicable SOPs, the protocol, other written instructions and regulatory guidelines.

The investigator will allow the Aclaris Therapeutics, Inc. representative, 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.

13.2. Audits and Inspections

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 Aclaris Therapeutics, Inc. or its 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.

The investigator should contact Aclaris Therapeutics, Inc. immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board (IRB)

This protocol and any accompanying material, including information that will be provided to prospective subjects (such as advertisements, subject information sheets, or study descriptions used to induce study participation or obtain informed consent) must be submitted to the IRB for approval. Approval of each such submission must be obtained from the committee before it may be used in the study and must be documented in a written notification to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval. In particular, each informed consent document must bear clear evidence (written, stamp, date of approval, etc.) of IRB approval before it may be presented to prospective (or ongoing, as appropriate) study subjects for signature.

Written evidence of the approval must be made available to the Sponsor. Any modifications made to the protocol and of correspondingly modified informed consent documents made after receipt of IRB approval must also be submitted to the committee for approval before implementation unless the modification is made on an emergency basis to protect the welfare of study subjects. In the latter case, the IRB must be notified promptly, and their written approval must be obtained as soon after the fact as possible.

Appropriate reports on the progress of the study will be made to the IRB and the Sponsor by the Investigator in accordance with applicable regulatory regulations and in conformity with policies established by both the IRB and the Sponsor. The shortest time interval between required reports required by either party or by regulations will prevail.

The Investigator at each investigative site, or his/her nominee, will be responsible for reporting any SAEs to the IRB as soon as possible, and in accordance with the guidelines of the IRB.

The Sponsor will be responsible for reporting all serious, life threatening or fatal adverse study drug events with a causal relationship to the study drug to appropriate regulatory agencies within their required timelines.

The Investigator is responsible for obtaining written, informed consent(s) from each prospective subject interested in participating in this study before performing any study-related procedures. Written informed consent must be obtained after adequate, thorough, and clear explanation of the aims, methods, objectives, and potential hazards of the study, as well as any use of the subject's genetic information from the study. The Investigator must use the most current Central IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject. The investigational site must retain the original signed consent and provide a copy to the subject.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

14.2. Protocol Deviations, Violations, and Exceptions

A protocol **deviation** is non-adherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol **violation** is defined as any divergence from the protocol-specific inclusion/exclusion criteria, subject is administered a prohibited medication during the active protocol treatment period, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study center personnel, on the CRF.

As a matter of policy, sponsor/CRO will not grant **exceptions** to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from sponsor/CRO and the responsible IRB/IEC, in accordance with the Sponsor/CROs Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative center personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform sponsor/CRO. Such subjects will be discontinued from the study, except in a rare instance following review and written approval by sponsor/CRO and the responsible IRB/IEC, according to the applicable SOP

14.3. Training

For each investigational center, there will be an initiation visit prior to enrolling any study subjects.

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

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

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

15. ETHICS

15.1. Ethical Conduct of the Study

The Sponsor will use information developed in this clinical study in connection with the development of A-101 40% and, therefore, may disclose it as required to other clinical Investigators participating in other studies and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide all data produced during this study to the Sponsor.

The Sponsor considers that clinical data (complete or incomplete) constitute financially sensitive information. Consequently, the Sponsor requires that discussion of results in any form, electronic, verbal, or written before study completion and full reporting should only be undertaken with the Sponsor's prior written consent.

Individual subjects' medical information obtained as a result of this study is considered confidential. The Investigator and the study center will adhere to all applicable laws relating to the protection of subject information. To assure that subjects' confidentiality is maintained, subjects' data will be identified by a study-assigned number and date of birth only.

All Sponsor personnel will handle subjects' data in a confidential manner in accordance with applicable regulations governing clinical research. Subjects' records will be inspected only in connection with this research project. Information generated as a result of a subject's participation in this study may be disclosed to third parties for research and regulatory purposes in any country as determined by the Sponsor. However, subjects will not be individually identified but will be referred to only by the study assigned number and the subject's date of birth.

15.2. Written Informed Consent

The schedule of study activities (including assessments, tests, exams, disease assessments, and study drug administration) beginning with screening and continuing through the end of study are outlined in Table 3. A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedure (*e.g.*, vital signs, clinical laboratory sampling, or photography).

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

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

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

16.2. Data Management

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in US 21 Code of Federal Regulations (CFR) Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study specific training. After they are trained, users will be provided with individual system access rights.

The handling of data, including data quality assurance, will comply with regulatory guidelines, including ICH and GCP, and the sponsor/CRO SOPs and working instructions. Data management and control processes specific to this study will be described in a data management plan. At the end of the study, the database will be locked, and the data will be released for reporting and statistical analysis.

16.3. 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.

16.4. 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.

16.5. Retention of Records

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. /CRO/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 Aclaris Therapeutics, Inc., in writing, of the name and address of the new individual.

If the Investigator cannot guarantee this archiving requirement at the investigative site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers in an off-site storage location so that they can be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies will be made for off-site storage.

No trial document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the trial records to another party or move them to another location, the Investigator must notify the Sponsor in writing of the new responsible person and/or the new location

17. LIST OF REFERENCES

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18. APPENDICES

APPENDIX 1.

A-101-SEBK-402 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
- Continue your routine cosmetics and skin care products
- Avoid exposing your target and non-target SKs to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the target or non-target SKs, if excessive exposure cannot be avoided
- The use of the following therapies to treat any of the target or non-target lesions are prohibited
    - Retinoids (topical)
    - Corticosteroids (topical)
    - LASER, light or other energy-based therapy
    - Liquid nitrogen, electrodesiccation, curettage, imiquimod, ingenol mebutate
    - Microdermabrasion or superficial chemical peels
    - Antibiotics (topical)
- Use of self-tanner lotions/sprays are prohibited during the study
- Bring this subject instruction sheet with you to each visit

ON STUDY VISIT DAYS:

- When appropriate for the target lesion location wear loose fitting clothing to the visit (Note: clothing that comes in contact with the study medication may be bleached)
- Starting prior to Visit 2, do not apply any topical products to the target or non-target SKs, except for routine cleansing products, within 12 hours prior to the visit
- After any study visit where a study medication treatment was performed do not:
    - Wash/submerge the target or non-target SKs for at least 6 hours
    - Apply any topical products to the target or non-target SKs 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:
VISIT 10: Date: Time:	VISIT 11: Date: Time:
Thank you for following these instructions	

APPENDIX 2.

SK PLA Training Manual
January 12, 2016

Physician Lesion Assessment Scale
Training Manual

About the Physician Lesion Assessment Scale

The Physician Lesion Assessment (PLA) Scale is a rating scale used by a clinical investigator to assess the severity of individual Seborrheic keratosis (SK) lesions at a particular time point. The investigator should not refer to any other assessment or assessment guidelines when completing the PLA.

The PLA Scale defines severity as the presence and thickness in millimeters (mm) of an individual SK lesion. As the PLA Scale is meant to be used for all types of SK lesions the surface texture, size, shape, and color are not assessed by the PLA Scale.

The PLA Scale is presented in the table below:

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

Objective of the training manual

The objective of the training manual is to standardize the evaluation of the severity of an SK lesion by providing specific instructions and a photographic guide to the lesion grades in order to obtain an accurate PLA grade.

It is important for the clinician to follow these instructions to ensure the reliability of the evaluation over time and across investigators.

SK PLA Training Manual
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Content

The training manual contains:

- The instructions for evaluating the SK lesion
- A photo guide illustrating the different grades
- FAQ providing decision guidelines for difficult evaluations

Instructions

The PLA Scale has 2 assessment components:

- First, a determination of whether a clinically visible SK lesion is present
- Second, if a clinically visible SK lesion is present, a determination of the thickness of the visible SK lesion

The instructions below must be followed:

1. Determine if a clinically visible SK lesion exists

The identified area of the skin should be examined with a suitable non magnifying examination light to determine if a clinically visible SK lesion is present.

In the absence of a visible SK lesion (*i.e.*, a "stuck on," warty, well-circumscribed, often scaly lesion) the PLA grade should be "0" (Clear - no visible seborrheic keratosis lesion) even if the skin is not completely clear of other visible findings that are common on the normal, non-diseased skin of the subject such as signs of photo aging, pigmentary changes, erythema, roughness, scaling, etc. If there is uncertainty regarding the presence of an SK lesion, the treatment area may be palpated.

Please refer to the photo guide provided on the next pages for a PLA grade of "0".

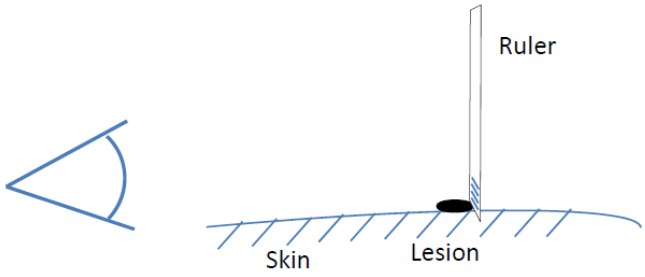
If the identified area of skin contains a visible SK lesion, regardless of the size of that lesion, the PLA grade is NOT "0" and the procedure below should be followed to evaluate the lesion.

2. Measure the thickness of the SK lesion

The SK lesion should be examined with a suitable non magnifying examination light. Cross lighting may be used.

Once it has been determined that a visible SK is present, the thickness of the SK lesion should be measured at its thickest point using the ruler provided as illustrated below. The ruler should be gently placed on the non-lesional skin behind the SK lesion, perpendicular to the skin without creating a depression on the skin.

Examine the visible SK lesion on a line parallel with the plane of the surrounding non-lesional skin and observe the ruler markings at the thickest point of the lesion.



PLA Grade 1:

The SK lesion should be assigned the PLA grade of "1" (Near Clear: a visible SK lesion with a surface appearance different from the surrounding skin (not elevated)) if:

- The SK lesion is macular (not palpable), and therefore has no elevation.
- The SK lesion has an elevation that is less than 0.5mm (*i.e.*, the 0.5mm mark is completely visible behind the SK lesion).

Please refer to the photo guide provided on the next pages for a PLA grade of "1".

PLA Grade 2:

If the SK lesion covers any part of the 0.5mm mark and does not completely cover the 1mm mark the SK lesion PLA grade should be: "2" (Thin: a visible seborrheic keratosis lesion (thickness ≤ 1 mm)).

PLA Grade 3:

If the SK lesion completely covers the 1mm mark the PLA grade should be: "3" (Thick: a visible seborrheic keratosis lesion (thickness > 1 mm)).

Please refer to the photo guide provided on the next pages for grades of "2" and "3".

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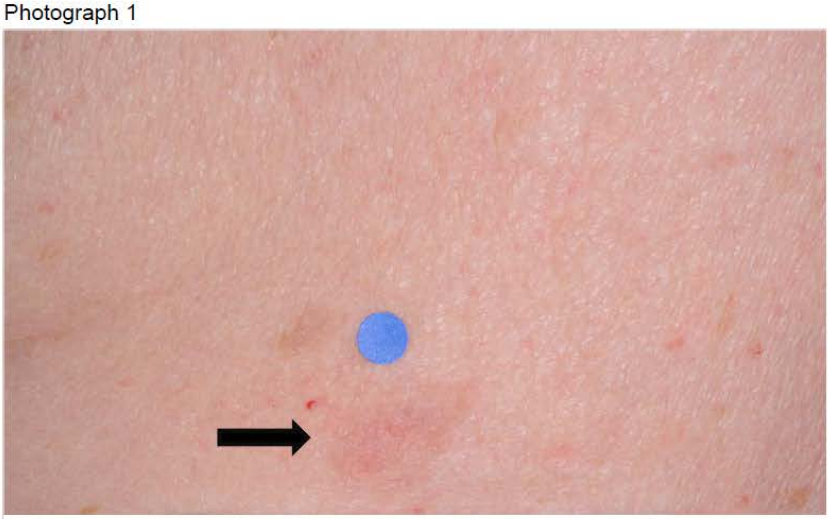
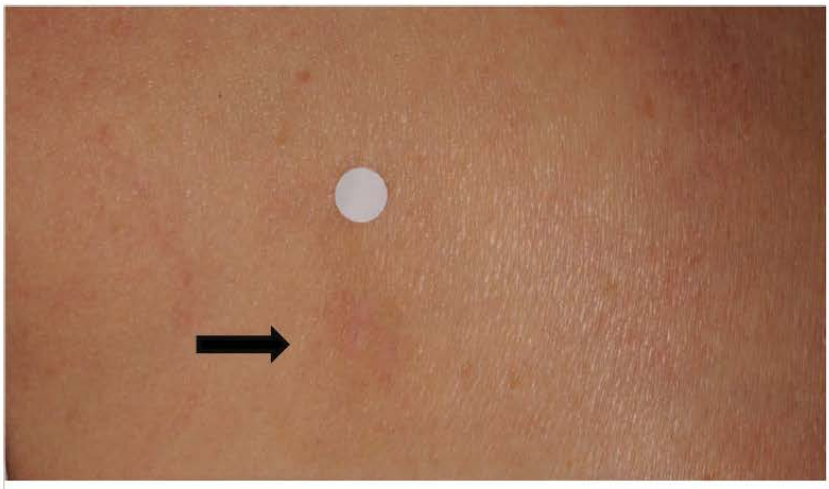
Photo guide

Grade "0" Clear: no visible seborrheic keratosis lesion

Photograph 1

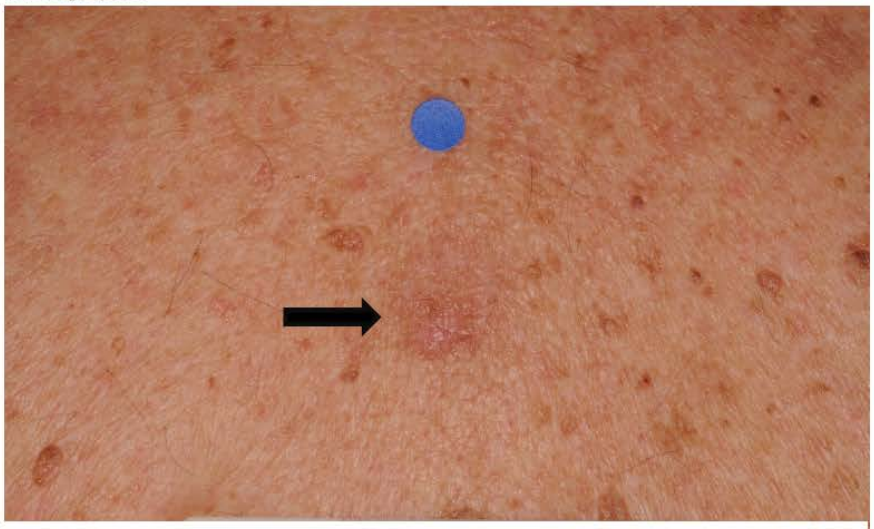


Photograph 2

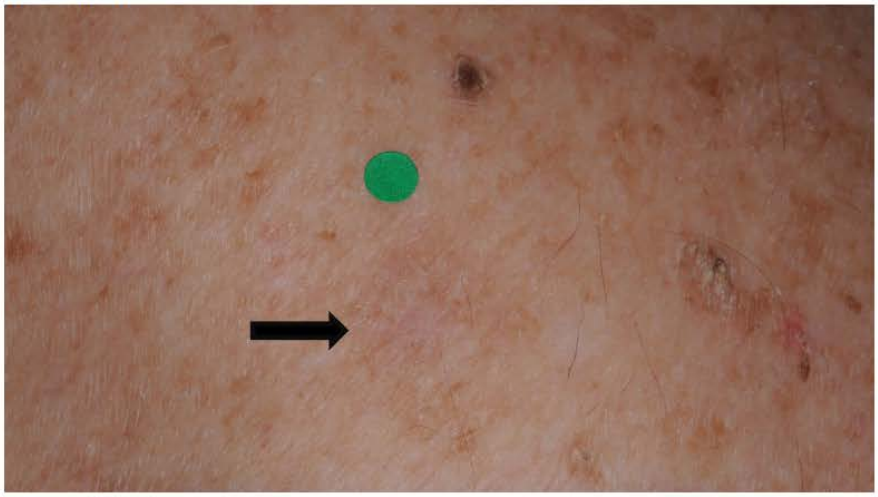


Grade "0" Clear: no visible seborrheic keratosis lesion

Photograph 3

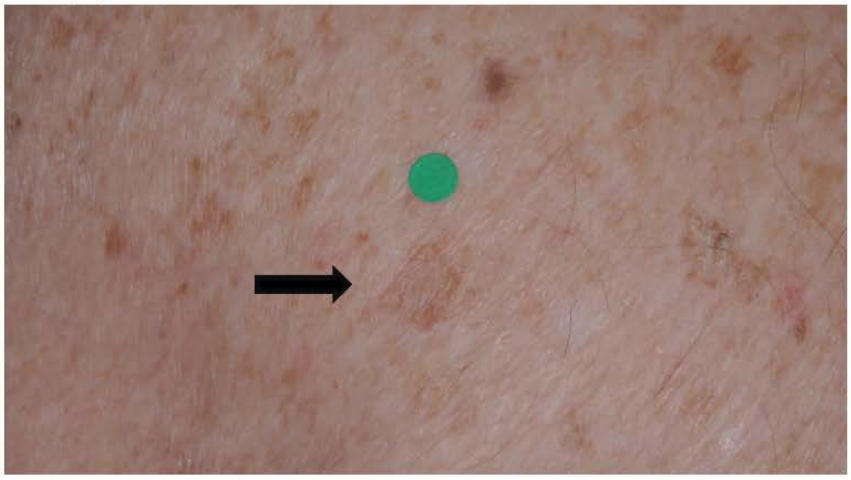


Photograph 4

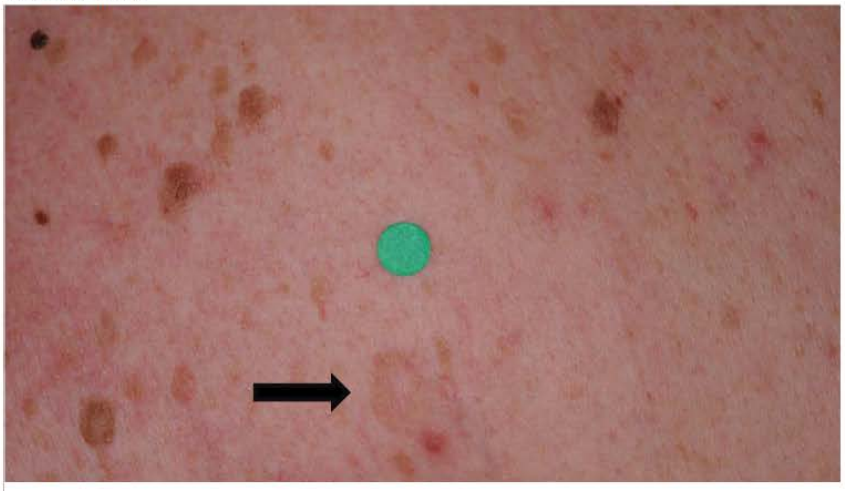


Grade "1" **Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)**

Photograph 1

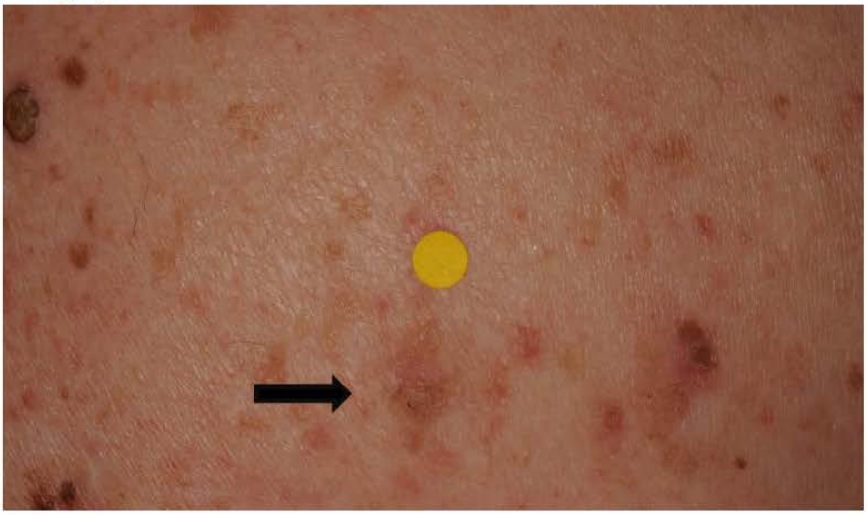


Photograph 2

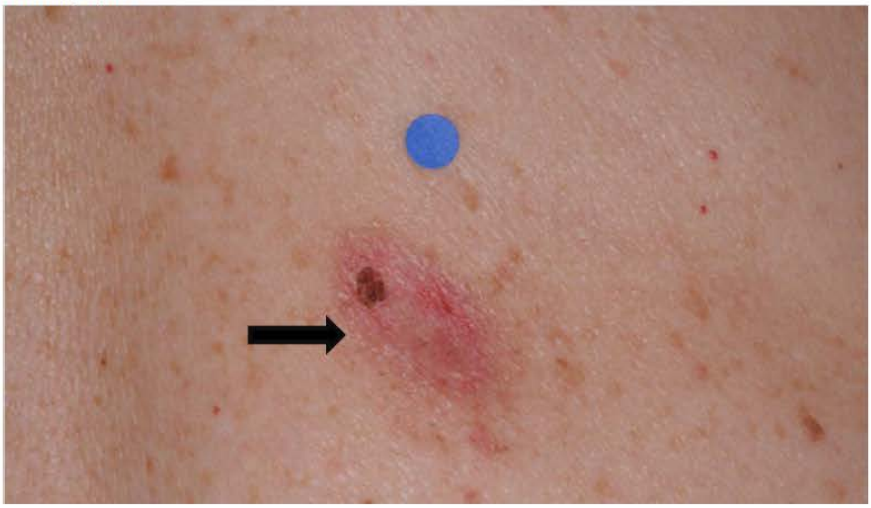


Grade "1" **Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)**

Photograph 3

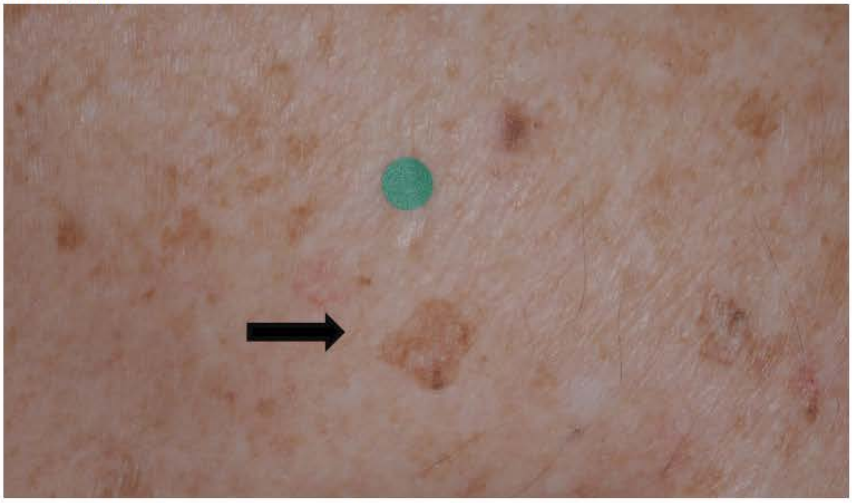


Photograph 4

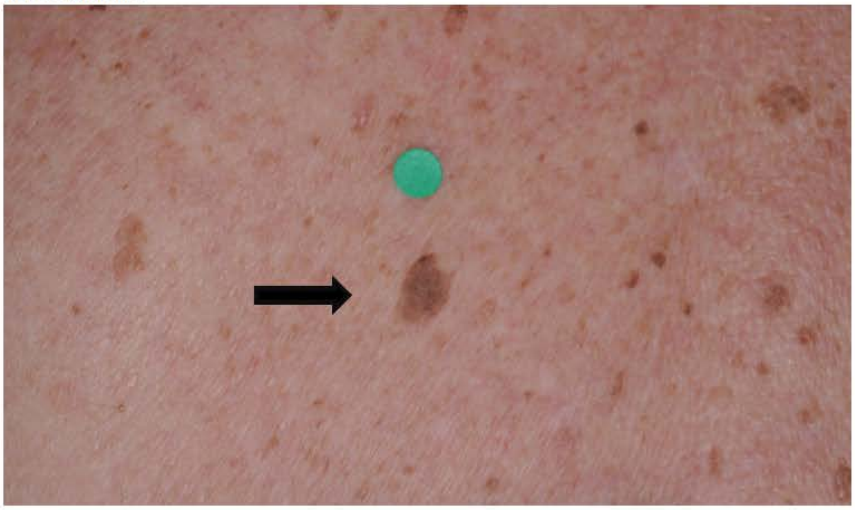


Grade "2" Thin: a visible seborrheic keratosis lesion (thickness ≤ 1 mm)

Photograph 1



Photograph 2



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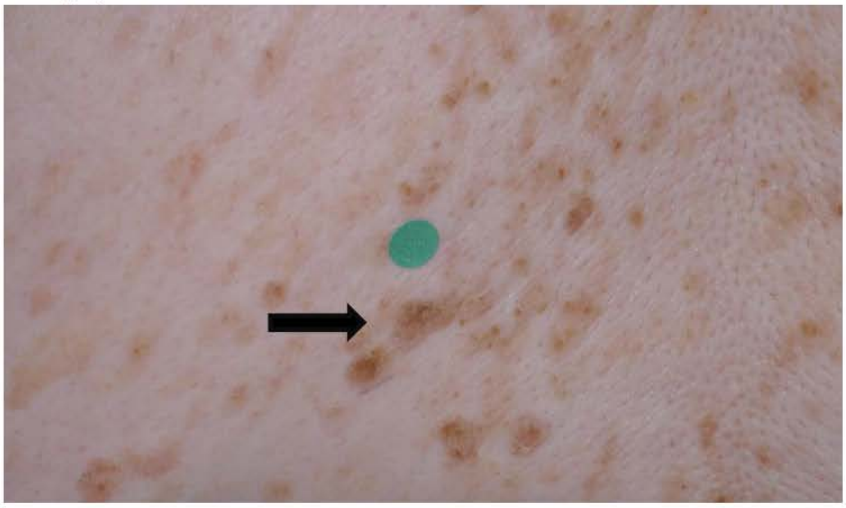
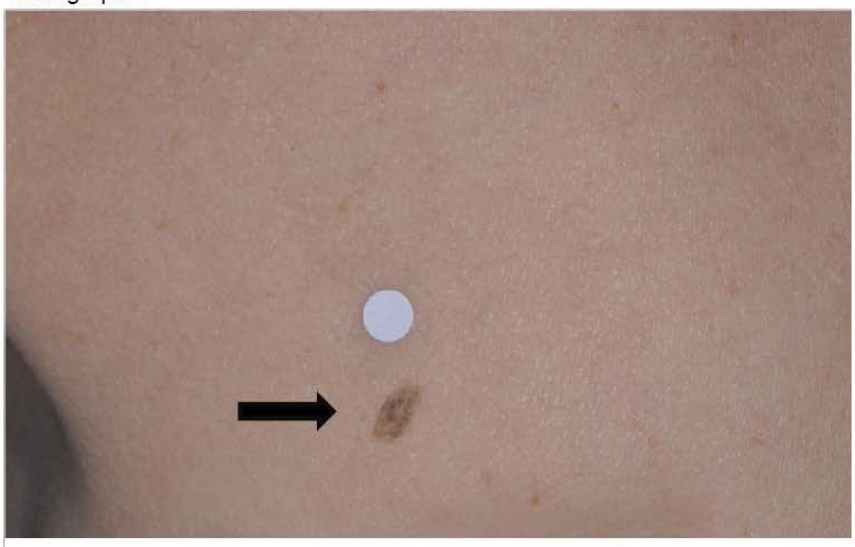
Grade "2" Thin: a visible seborrheic keratosis lesion (thickness ≤ 1 mm)

Photograph 3

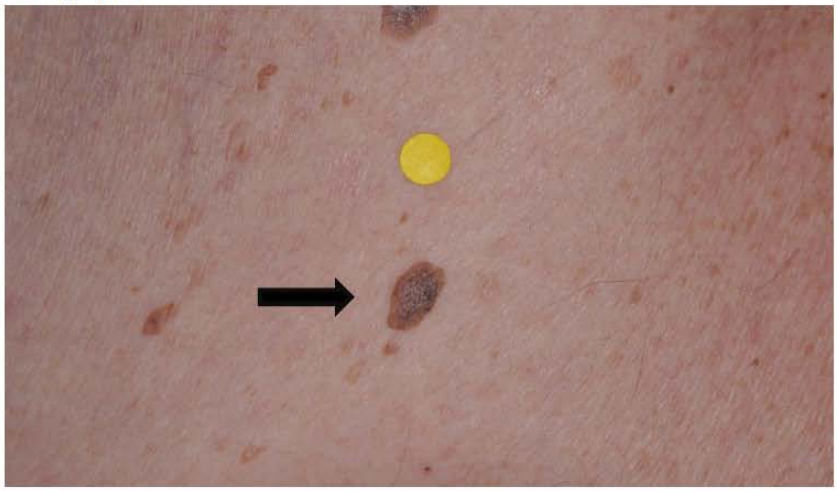


Photograph 4

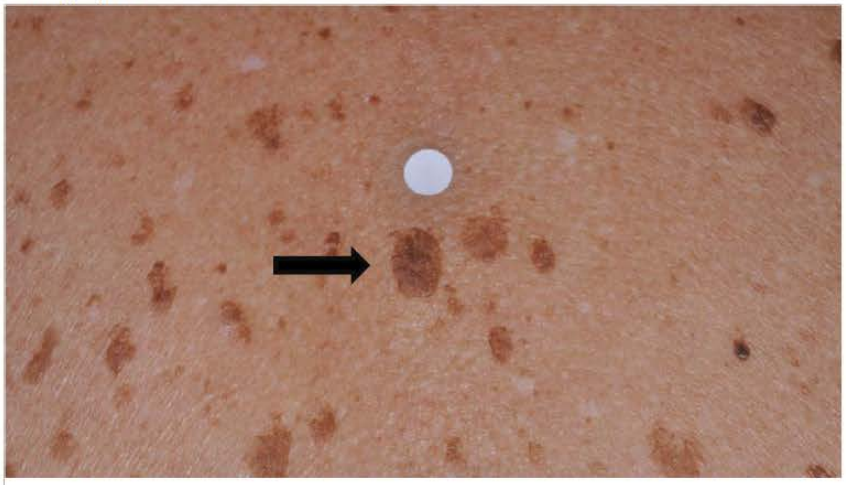


Grade "3" Thick: a visible seborrheic keratosis lesion (thickness > 1 mm)

Photograph 1

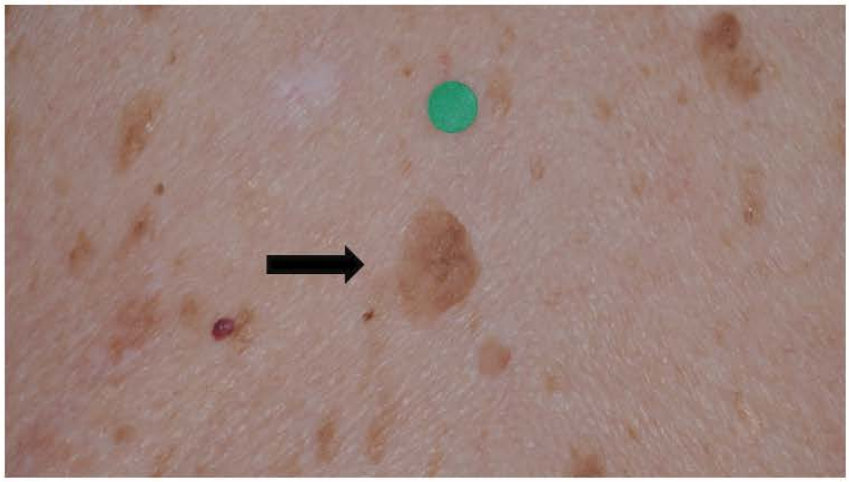


Photograph 2

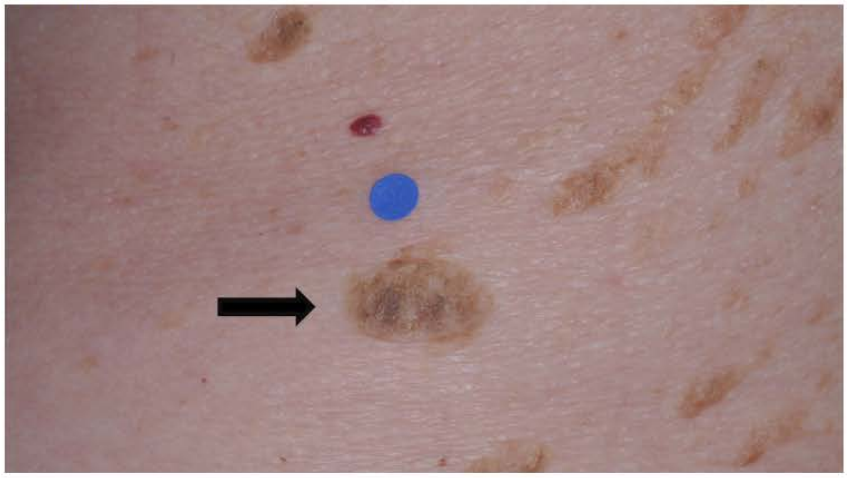


Grade "3" Thick: a visible seborrheic keratosis lesion (thickness > 1 mm)

Photograph 3



Photograph 4



APPENDIX 3.

A-101-SEBK-402 Pre-Dose Subject Satisfaction Assessment for Treatment Experience
(complete at Day 1/Visit 2 prior to treatment)

Subject Number: _____

Date: _____ Time: _____

1. a.	What prior treatments have you used/had performed for SK removal? *(Select all that apply)* ◯ Cryotherapy (freezing with liquid nitrogen) ◯ Curettage (scraping off tissue) ◯ Electrodesiccation (burning off with electricity) ◯ Laser therapy (burning off) ◯ Other (provide name) _____
2.	How bothered are you by the appearance of your face/hairline/neck SKs? ◯ 1 – Not bothered at all ◯ 2 – A little bit bothered ◯ 3 – Neutral ◯ 4 – Somewhat bothered ◯ 5 – Extremely bothered
3.	How do you feel about getting your SKs treated? *(Select all that apply)* ◯ Anxious/Nervous ◯ Concerned/Worried ◯ Unsure/Neutral ◯ Hopeful ◯ Excited
4.	What prior facial cosmetic treatment(s), excluding cryotherapy for SK removal, have you had for your face in a dermatology clinic or MedSpa? *(Select all that apply)* ◯ Botox injections ◯ Hyaluronic acid fillers *(e. g., Juvederm, Restylane, etc.)* ◯ Hair removal with laser or pulsed light ◯ Chemical peel ◯ Microdermabrasion ◯ Plastic surgery ◯ Other (provide name) _____ ◯ None, A-101 40% will be my first cosmetic treatment for my face at a medical clinic

Subject initials: _____

A-101-SEBK-402 Post-Dose Subject Satisfaction Assessment for Treatment Experience

(complete approximately 24 hours after treatment 1 at Day 2/Visit 3, and 1 week after treatments 2 and 3 (if applicable) Day 22/Visit 6 and Day 36/Visit 8)

Subject Number: _____

Visit: ◯ Day 2/Visit 3 ◯ Day 22/Visit 6 *(only if treated at Visit 5)* ◯ Day 36/Visit 8 *(only if treated at Visit 7)*

Date: _____ Time: _____

1.	During treatment, what was your level of discomfort? ◯ 1 – No discomfort ◯ 2 – Mild discomfort ◯ 3 – Moderate discomfort ◯ 4 – Severe discomfort ◯ 5 – Unbearable discomfort
2.	One hour after treatment, what was your level of discomfort? ◯ 1 – No discomfort ◯ 2 – Mild discomfort ◯ 3 – Moderate discomfort ◯ 4 – Severe discomfort ◯ 5 – Unbearable discomfort
3.	One day after treatment, what was your level of discomfort? ◯ 1 – No discomfort ◯ 2 – Mild discomfort ◯ 3 – Moderate discomfort ◯ 4 – Severe discomfort ◯ 5 – Unbearable discomfort
4.	Within 24 hours after treatment, were you comfortable enough with the appearance of your treated SKs to go out in public (with or without make-up)? ◯ Yes ◯ No
4. a.	How soon after your treatment were you comfortable enough with your appearance of your treated SKs to go out in public (with or without makeup)? ◯ Immediately after treatment ◯ 1-2 hours after treatment ◯ 2-4 hours after treatment ◯ 4-6 hours after treatment ◯ More than 6 hours after treatment

Subject initials: _____

A-101-SEBK-402 End of Study Subject Satisfaction Assessment for Treatment Experience
(complete at Day 85/Visit 10 and Day 113/Visit 11)

Subject Number: _____

Date: _____ Time: _____

1.	Please check prior treatments you have personally had for SKs (check mark all that apply). ◯ Cryotherapy (freezing with 196 °C liquid nitrogen) ◯ Curettage (scraping off tissue with a sharp instrument) ◯ Electrodesiccation (burning off with high-voltage electricity) ◯ Other (please describe)
2.	After your experience with A-101 40%, how likely will you pursue future treatment for other SKs on your face or body? ◯ 1 – Very unlikely ◯ 2 – Unlikely ◯ 3 – Neither unlikely or likely ◯ 4 – Likely ◯ 5 – Very likely
3.	On a scale of 1 – 5, rate your level of satisfaction of your **treatment experience** with 1 being not satisfied at all and 5 being completely satisfied? ◯ 1 – Not satisfied at all ◯ 2 – Slightly satisfied ◯ 3 – Moderately satisfied ◯ 4 – Satisfied ◯ 5 – Very satisfied
4.	On a scale of 1 – 5, rate your level of satisfaction with the **appearance of your skin** treated with A-101 40% with 1 being not satisfied at all and 5 being completely satisfied? ◯ 1 – Not satisfied at all ◯ 2 – Slightly satisfied ◯ 3 – Moderately satisfied ◯ 4 – Satisfied ◯ 5 – Very satisfied
5.	What is the likelihood you will get other SKs treated in the future with A-101 40%? ◯ 1 – Not likely at all ◯ 2 – Slightly likely ◯ 3 – Moderately likely ◯ 4 – Very likely ◯ 5 – Extremely likely
6.	What is the likelihood you will recommend A-101 40% to a friend/relative? ◯ 1 – Not likely at all ◯ 2 – Slightly likely ◯ 3 – Moderately likely ◯ 4 – Very likely ◯ 5 – Extremely likely

7.	For an SK you would like to treat in the future, please rank your preferred treatment method (1 – most preferred; 5 – least preferred). ◯ A-101 40% (topical application) ◯ Cryotherapy (freezing with 196 ˚C liquid nitrogen) ◯ Curettage (scraping off tissue with a sharp instrument) ◯ Electrodesiccation (burning off with high-voltage electricity) ◯ Other (please describe)
8.	After treatment with A-101 40%, how bothered are you by the appearance of your treated SKs today? ◯ 1 – Not bothered at all ◯ 2 – A little bit bothered ◯ 3 – Neutral ◯ 4 – Somewhat bothered ◯ 5 – Extremely bothered
9.	Since your treatment with A-101 40%, how do you feel about getting your untreated SKs treated in the future? ◯ Anxious/Nervous ◯ Concerned/Worried ◯ Unsure/Neutral ◯ Hopeful ◯ Excited
10.	Please indicate the level of agreement you have to the following statements: A) Since my treatment with A-101 40%, I feel more confident: ◯ Strongly disagree ◯ Disagree ◯ Neither disagree or agree ◯ Agree ◯ Strongly agree B) Since my treatment with A-101 40%, I feel more attractive: ◯ Strongly disagree ◯ Disagree ◯ Neither disagree or agree ◯ Agree ◯ Strongly agree C) Since my treatment with A-101 40%, I feel less embarrassed: ◯ Strongly disagree ◯ Disagree ◯ Neither disagree or agree ◯ Agree ◯ Strongly agree D) Since my treatment with A-101 40%, I feel more comfortable being photographed in pictures: ◯ Strongly disagree ◯ Disagree ◯ Neither disagree or agree ◯ Agree ◯ Strongly agree

Subject initials: _____