

CLINICAL STUDY PROTOCOL

Protocol Number: A-101-SEBK-204

Amendment 2

Version 3.0

04 May 2017

A Phase 2 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Effectiveness of A-101 (hydrogen peroxide) Topical Solution in Subjects with Seborrheic Keratosis Lesions on the Trunk, Extremities and Face

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PROTOCOL APPROVAL SIGNATURE PAGE
Version 3.0

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05-04-2017

Chris Powala

Date

Chief Operating Officer

INVESTIGATOR SIGNATURE PAGE**Protocol Number:** A-101-SEBK-204**Protocol Title:** A Phase 2 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Effectiveness of A-101 (hydrogen peroxide) Topical Solution in Subjects with Seborrheic Keratosis Lesions on the Trunk, Extremities, and Face**Protocol Version** **Version 3.0: 04 MAY 2017**

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

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

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

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

I will notify the Sponsor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to the Sponsor as soon as possible, but no later than five days following the initial notification.

Investigator Name (print)

Investigator's Signature

Date

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1. SYNOPSIS

Protocol Number A-101-SEBK-204 Synopsis	
Protocol Number:	Protocol Title: A Phase 2 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study of the Safety and Effectiveness of A-101 (hydrogen peroxide) Topical Solution in Subjects with Seborrheic Keratosis Lesions on the Trunk, Extremities and Face
Sponsor: Aclaris	Phase of Development: Phase 2
Study Drug Description: A-101 Solution (40% and 45%) is a hydrogen peroxide solution that will be supplied in a glass ampule with an applicator to be applied to seborrheic keratosis lesions of the trunk, extremities and face.. The study drug, A-101 (hydrogen peroxide) 40% and 45% Topical Solution (hereafter referred to as A-101) is a colorless solution that must be stored at room temperature (20-25° C or 68 -77 ° F), protected from light.	
Study Objectives: Primary: The main objective of this study is to evaluate the effectiveness of A-101 40% and A-101 45% versus vehicle for the treatment of 4 seborrheic keratosis (SK) Target Lesions on the trunk, extremities and face. Secondary: The secondary objectives of this study include: <ul style="list-style-type: none"> • Duration of response • Safety 	
Study Design: This is a phase 2, multicenter, randomized study to evaluate the safety and efficacy of A101 40% and A101 45% versus vehicle. Subjects will be required to have a total of 4 target seborrheic keratosis (SK) lesions located on their trunk, extremities and face. At least one of the 4 target lesions must be on the face and at least one of the target lesions must be on the trunk or extremities. Subjects will be randomized to one of 3 treatment arms in a 1:2:2 ratio. Fifty subjects will be randomized to the Vehicle treatment arm and 100 subjects will be randomized to each A-101 active treatment arm. Subjects will receive a maximum of 2 treatments [Day 1 (Visit 2) and re-treatment on Day 22 (Visit 4) if a target lesion meets the criteria for re-treatment]. The duration of study participation is anticipated to be up to a maximum of 124 days per subject. Safety will be evaluated based on clinical laboratory studies (hematology and clinical chemistry), vital signs, assessment of local skin reactions (LSRs), assessment of adverse events (AEs), and concomitant medication review.	

Efficacy will be evaluated based on assessment of each Target Lesion according to the Physician's Lesion Assessment (PLA). Sites will be required to take standardized color photographs of each of the Target Lesions to assist with the documentation of the location of each of the Target Lesions throughout the study.

Number of Patients to be Enrolled:

A total of 250 evaluable subjects will be randomized to the study.

Number of Study Sites:

This study will be conducted in the US only at approximately 9 treatment centers.

Inclusion Criteria:

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

1. Subject is able to comprehend and is willing to sign an informed consent for participation in this study.
2. Male or female ≥ 18 years old.
3. Subject has a clinical diagnosis of stable clinically typical seborrheic keratosis.
4. Subject has 4 appropriate seborrheic keratosis Target Lesions on the trunk, extremities and face, with at least 1 Target lesion on the face and at least 1 Target Lesion on the trunk or extremities. The 4 identified Target Lesions must meet the requirements as defined below:
 - a. Have a clinically typical appearance
 - b. Have a Physician's Lesion Assessment of ≥ 2
 - c. Length that is ≥ 5 mm and ≤ 15 mm
 - d. Width that is ≥ 5 mm and ≤ 15 mm
 - e. Thickness that is ≤ 2 mm
 - f. Be a discrete lesion
 - g. Be the only SK lesion present when centered in the area outlined by the provided circular template
 - h. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
 - i. Not be in an intertriginous fold
 - j. Not be on the eyelids
 - k. Not be within 5mm of the orbital rim
 - l. Not be pedunculated
5. Subject chemistry and complete blood count results are within normal limits. If any of the laboratory values are outside normal range, the treating investigator must assess the value/s as NOT clinically significant and document this in the subject's medical chart in order for the subject to be eligible for randomization.
6. Woman of childbearing potential must have a negative urine pregnancy test within 14 days of the first application of study drug and agree to use an active method of birth control for the duration of the study.
7. Subject is non-pregnant and non-lactating.
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 Lesion 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 keratosis lesions.

2. Subject has presence of multiple eruptive seborrheic keratosis lesions (Sign of Lesser -Trelat).
3. Subject has current systemic malignancy.
4. Subject has used any of the following systemic therapies within the specified period prior to Visit 1:
 - Retinoids; 180 days
 - Corticosteroids; 28 days
 - Antimetabolites (e.g., methotrexate); 28 days
5. Subject has used any of the following topical therapies within the specified period prior to Visit 1 on, or in a proximity to any Target Lesion, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
 - LASER, light or other energy based therapy (e.g., intense pulsed light [IPL], photo-dynamic therapy [PDT]; 180 days
 - Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-fluorouracil (5FU), or ingenol mebutate; 60 days
 - Hydrogen peroxide; 90 days
 - Retinoids; 28 days
 - Microdermabrasion or superficial chemical peels; 14 days
 - Corticosteroids or antibiotics; 14 days.
6. 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 Lesion that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
 - Cutaneous malignancy; 180 days
 - Sunburn; currently
 - Pre-malignancy (e.g. actinic keratosis); currently
 - Body art (e.g. tattoos, piercing, etc.); currently
 - Excessive tan; currently. The use of self-tanning lotions/sprays are prohibited.
7. Subject has a history of sensitivity to any of the ingredients in the study medications.
8. 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.
9. Participation in another therapeutic investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

Duration of Treatment

The duration of the study participation is anticipated to be a maximum of 124 days per subject. The final visit (Visit 8) has a maximum allowable visit window of 14 days: Study visits are:

- Visit 1 (Day -13 to 0) screening
- Visit 2 (Day 1) randomization; study medication treatment
- Visit 3 (Day 8) follow up visit
- Visit 4 (Day 22) follow up visit; Target Lesions that meet the retreatment criteria will receive a second study medication treatment
- Visit 5 (Day 29) follow up visit
- Visit 6 (Day 50) follow up visit
- Visit 7 (Day 78) follow up visit
- Visit 8 (Day 106) follow up visit; end of study

Criteria for Evaluation

Efficacy:

The investigator will evaluate the severity of each SK Target lesion using the Physician's Lesion Assessment (PLA)

Safety:

Safety will be evaluated by following adverse events, clinical laboratory exams, vital signs, concomitant medications, as well as through skin examinations and general physical exams.

Study Drug Administration

Study drug medication will be applied to each of the four Target Lesions during Visit 2 by the treating physician or a member of the investigational site staff who is a trained healthcare professional.

Study medication must be applied to each of the Target Lesions for approximately 20 seconds. Each Target Lesion will be treated up to 4 times while waiting approximately 60 seconds between each application.

Study medication must be applied to a total of 4 SK Target Lesions. At least one of the SK Target Lesions must be on the face and at least one must be on the trunk or extremities.

Statistical Methods*Efficacy Analysis*

The primary effectiveness analysis will consist of pair-wise comparison between each active treatment group and the vehicle treatment group, and between the two active treatment groups, based on the mean of per-subject percentages of target lesions judged to be clear on the PLA (PLA = 0) at Visit 8. To conduct this analysis, the percentage of each subject's target lesions judged to be clear on the PLA at Visit 8 will first be calculated for each subject. Then the analysis will calculate the mean of this parameter for each treatment group (yielding an estimate of the mean percentage of clear lesions across subjects), and an analysis of variance (ANOVA) model will be used to perform all pair-wise comparisons among the treatment groups. Pair-wise comparisons will be conducted on the least-squares means using the overall pooled error term of the model. All efficacy analyses will be based on the per protocol (PP) population, defined as all randomized subjects who completed the study with no major protocol violation.

A secondary effectiveness analysis will be conducted using the same methodology as the primary efficacy analysis based on the mean of per-subject percentages of target lesions judged to be clear or near-clear on the PLA (PLA \leq 1) at Visit 8.

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, by relationship to study drug and discontinuation of patients from study due to AEs. Safety endpoints for AEs, clinical laboratory tests, vital signs, and physical examinations and local skin reactions will be specified in the statistical analysis plan (SAP). All safety endpoints will be summarized using descriptive statistics.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
°C	Degrees Centigrade
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
<i>e.g.</i>	for example, (Latin; <i>exempla gratia</i>)
EC	Ethics Committee
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
5FU	5 Fluorouracil
G	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
H ₂ O ₂	Hydrogen Peroxide
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
<i>i.e.</i>	that is (Latin; <i>id est</i>)
IPL	Intense Pulsed Laser
IRB	Institutional Review Board
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
LSR	Local Skin Reactions
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
Mm	Millimeter

Abbreviation	Term
NCS	Not Clinically Significant
OTC	Over-The-Counter
PDT	Photodynamic Therapy
PLA	Physician's Lesion Assessment
PP	Per Protocol
SAE	Serious Adverse Event
SI	Subject Identifier
SK	Seborrheic Keratosis
SOP	Standard Operating Procedure
US	United States
WOCBP	Women of childbearing potential

2. INTRODUCTION

2.1. Summary

Seborrheic keratosis (SK) is one of the most common skin tumors in man. These benign epithelial skin tumors are most commonly seen in older individuals, increasing in prevalence with increasing age, and affect men and women roughly equally. While the growths may be solitary, they often occur in large numbers and typically present as well demarcated, elevated or “stuck-on” appearing papules or plaques that may vary from flesh-colored, to shades of yellow, gray, brown, or black (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 (H₂O₂) 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, H₂O₂ 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, H₂O₂ 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).

H₂O₂ 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 H₂O₂ may overwhelm the antioxidant defense systems in the skin, allowing H₂O₂ 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 O₂ 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.

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

2.2.1. 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% 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.

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 8 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.

2.2.2. 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 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.

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.

2.2.3. A-101-SEBK-303

A-101-SEBK-303 was an 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.

3. STUDY RATIONALE AND OBJECTIVES

3.1. Rationale

The rationale for this study is to assess safety and efficacy of A-101 45% A-101 40% and Vehicle when applied to 4 Target Lesions on the trunk, extremities and face. For each subject, at least 1 Target Lesion must be on the face and at least 1 Target Lesion must be on the trunk or extremities.

Aclaris recently completed three phase 3 clinical studies (301, 302, and 303) that demonstrated that A-101 40% is both safe and effective in treating subjects with seborrheic keratosis lesions on the face, trunk and extremities. In addition, a randomized phase 2 study in subjects with common warts in which A-101 40% was compared to A-101 45% was completed. This study demonstrated that the higher concentration of A-101 45% was not only effective at treating subjects with a common wart but it also demonstrated that there was no increase in local skin reactions with the higher concentration. The results from these 4 clinical trials warrants further exploration of A-101 45% in subjects with SK lesions.

3.2. Study Objectives

3.2.1. Primary Objective

The primary objective of this study is to evaluate the safety and effectiveness of A-101 45% compared to A-101 40% and each active treatment arm to Vehicle for the treatment of 4 seborrheic keratosis (SK) Target Lesions on the trunk, extremities and face. For each subject, at least 1 Target Lesion must be on the face and at least 1 Target Lesion must be on the trunk or extremities.

3.2.2. Secondary Objective

The secondary objectives of this study include:

- Duration of response
- Safety of A-101

4. STUDY DESIGN

This is a phase 2, randomized, multi-center, study designed to evaluate the safety and efficacy of A-101 45% compared to A-101 40% and each active treatment arm to Vehicle in subjects with seborrheic keratosis lesions.

During the study, the investigator will identify 4 eligible SK Target Lesions on each subject on the trunk, extremities and face. For each subject, at least 1 SK Target Lesion must be on the face and at least 1 Target Lesion must be on the trunk or extremities. The Target Lesions will be treated at a maximum of two treatment visits.

Subjects will be required to complete a total of 8 study visits. The protocol defined study visits are:

- Visit 1 (Day -13 to 0) Screening
- Visit 2 (Day 1) Subject randomization and study drug application
- Visit 3 (Day 8) Target Lesion assessment
- Visit 4 (Day 22) Target Lesion assessment and if a Target Lesion meets the retreatment criteria the subject will receive a second study drug application
- Visit 5 (Day 29) Target Lesion assessment
- Visit 6 (Day 50) Target Lesion assessment
- Visit 7 (Day 78) Target Lesion assessment
- Visit 8 (Day 106) Target Lesion assessment and end of study visit

Refer to Section 6 or a complete list of protocol required study assessments.

A completed evaluable subject is a subject that completes all required treatment Visits (Visit 1 and Visit 4), completes Visit 8 (end of study visit), has had all Target Lesions assessed at these visits and has not had a protocol violation documented during the study

4.1. Number of Subjects and Study Centers

Approximately 250 evaluable subjects will be randomized to one of three treatment arms at approximately 9 investigational centers in the US.

4.2. Duration of Study

The anticipated time for study enrollment is 4 months. The duration of study participation is anticipated to be a maximum of 124 days per subject. Subjects will have a total of 8 study visits. The maximum anticipated duration for the study is approximately 8 months.

5. STUDY ENTRY CRITERIA

5.1. Inclusion Criteria

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

1. Subject is able to comprehend and is willing to sign an informed consent for participation in this study.
2. Male or female ≥ 18 years old.
3. Subject has a clinical diagnosis of stable clinically typical seborrheic keratosis.
4. Subject has 4 appropriate seborrheic keratosis Target Lesions on the trunk, extremities and face, with at least 1 Target Lesion on the face and at least 1 Target Lesion on the trunk or extremities. The 4 identified Target Lesions must meet the requirements as defined below:
 - a. Have a clinically typical appearance
 - b. Have a Physician's Lesion Assessment of ≥ 2
 - c. Length that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$
 - d. Width that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$
 - e. Thickness that is $\leq 2\text{mm}$

- f. Be a discrete lesion
 - g. Be the only SK lesion present when centered in the area outlined by the provided circular template
 - h. Not be covered with hair which, in the investigator's opinion, would interfere with the study medication treatment or the study evaluations
 - i. Not be in the intertriginous fold
 - j. Not be on the eyelids
 - k. Not be within 5mm of the orbital rim
 - l. Not be pedunculated
5. Subject chemistry and complete blood count results are within normal limits. If any of the laboratory values are outside normal range, the treating investigator must assess the value/s as NOT clinically significant and document this in the patient's medical chart in order for the subject to be eligible for randomization.
 6. Woman of childbearing potential must have a negative urine pregnancy test within 14 days of the first application of study drug and agree to use an active method of birth control for the duration of the study.
 7. Subject is non-pregnant and non-lactating.
 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 Lesion 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.

5.2. 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 keratosis lesions.
2. Subject has presence of multiple eruptive seborrheic keratosis lesions (Sign of Lesser - Trelat).
3. Subject has current systemic malignancy.
4. Subject has used any of the following systemic therapies within the specified period prior to Visit 1:
 - Retinoids; 180 days
 - Corticosteroids; 28 days
 - Anti-metabolites (e.g., methotrexate); 28 days
5. Subject has used any of the following topical therapies within the specified period prior to Visit 1 on, or in a proximity to any Target Lesion, that in the investigator's opinion interferes with the study medication treatment or the study assessments:
 - LASER, light or other energy based therapy (e.g., intense pulsed light [IPL], photo-dynamic therapy [PDT]; 180 days
 - Liquid nitrogen, electrodesiccation, curettage, imiquimod, 5-FU, or ingenol mebutate; 60 days
 - Hydrogen peroxide: 90 days
 - Retinoids; 28 days
 - Microdermabrasion or superficial chemical peels; 14 days
 - Corticosteroids or antibiotics; 14 days
6. Subject would require the use of any topical treatment (e.g. moisturizers, sunscreen) to any of the Target Lesions 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 Lesion that, in the investigator's opinion, interferes with the study medication treatment or the study assessments:
 - Cutaneous malignancy; 180 days
 - Sunburn; currently
 - Pre-malignancy (e.g. actinic keratosis); currently
 - Body art (e.g. tattoos, piercing, etc.); currently
 - Excessive tan; currently. The use of self-tanning lotions/sprays are 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 with 30 days prior to Visit 1.

5.3. Removal of Patients from Study Therapy

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 criteria
- Use of a prohibited medication during the treatment period (through Visit 5)
- Pregnancy
- 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.

5.4. Withdrawal Procedures

If a subject withdraws from the study prior to Visit 8, 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 or a clinically significant abnormal laboratory test result, monitoring of the subject will continue until the event has resolved or stabilized, until the patient 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.

5.5. Subject Replacement

If a subject is randomized to the study but does not receive a dose of study drug, then the subject will 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 randomized using the same subject identifier.

5.6. 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.

6. STUDY PROCEDURES

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 1. 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, urine pregnancy test or photography).

Table 1: Study Procedures

Visit	V1 Screening	V2	V3	V4	V5	V6	V7	V8
Treatment Day	-13 to 0	1	8	22	29	50	78	106
Treatment Window	N/A	N/A	+7 days	+ 4 days	+ 7 days	± 7days	± 7 days	± 7 days
Study Procedures								
Informed Consent	X							
Inclusion Criteria/Exclusion Criteria	X	X ¹						
Subject Identifier	X ²							
Medical history/demographics	X							
Fitzpatrick Skin Type Assessment	X ³							
Vital Signs	X ⁴	X						X
Prior Medications/Therapies	X ⁵							
Clinical Chemistry and CBC ⁶	X							X
Urine Pregnancy Test ⁷	X	X						X
Target Lesion Identification ⁸	X							
Physician's Lesion Assessment ⁹	X	X		X		X	X	X
Lesion Dimensions ¹⁰	X	X						
Standardized Photography ¹¹	X	X		X		X	X	X
Subject Randomization		X ¹²						
Local Skin Reactions		X ¹³	X	X ¹³	X	X	X	X
Study Medication Application		X		X ¹⁴				
Subject Instructions	X	X	X	X	X	X	X	X
Subject Satisfaction Questionnaire ¹⁵								X
Concomitant therapies ¹⁶		X	X	X	X	X	X	X
Adverse Events ¹⁷		X	X	X	X	X		

¹Subject inclusion/exclusion criteria will be re-assessed prior to randomization during Visit 2.

²Investigational sites will assign a unique five-digit subject identifier to each subject at Visit 1. This subject identifier will be used in all study documentation for the duration of the study.

³Each subject's skin must be assessed during Visit 1 using the Fitzpatrick Skin Type Assessment. Refer to Section 9.5.1 for the scale.

⁴Vital 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 prior to randomization, and at Visit 8.

⁵Prior medications/therapies will be collected for a time-period of 13 days prior to Visit 2. Refer to Section 7.8 for a list of permitted and restricted concomitant medications.

⁶A complete blood count (including hematocrit, hemoglobin, platelet count, red blood cell count and morphology, white blood cell count and differential (absolute and %) including basophils, eosinophils, lymphocytes, monocytes and neutrophils and a clinical chemistry panel including albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

⁷Woman of child bearing potential will be required to have a urine pregnancy test at Visit 1, at Visit 2 prior to randomization and at Visit 8.

⁸The treating investigator will identify 4 Target Lesions on the trunk, extremities, and face for each subject. Subjects must have at least 1 Target lesion on the face and at least 1 Target Lesion on the trunk or extremities.

⁹ The investigator will use the Physician's Lesion Assessment (PLA) to assess the severity of each Target Lesion. At Visit 2 and if applicable at Visit 4, the investigator must assess the Target Lesions prior to application of the study medication. In order to be eligible for randomization at Visit 2, the subject must have a PLA grade ≥ 2 .

¹⁰ The investigator will measure the dimensions of the Target Lesions at Visit 1 and prior to randomization at Visit 2. In order for the subject to be randomized at Visit each Target Lesion must have the following dimensions: length that is ≥ 5 mm and ≤ 15 mm and width that is ≥ 5 mm and ≤ 15 mm. Additional Target Lesion requirements are outlined in Section 8.1.3.

¹¹ At Visits 1, Visit 2 (prior to study medication application), Visit 4 prior to study medication application if applicable, Visit 6, Visit 7 and at Visit 8, a qualified investigational center staff member will take a photograph of each Target Lesion using the Aclaris supplied camera. All photographs will be sent to a central imaging laboratory.

¹² Subjects will be randomized at Visit 2 prior to application of study medication. Investigational study staff will re-confirm subject eligibility prior to randomization.

¹³ Both the investigator and the subject will assess each Target Lesion for symptoms associated with irritation. At Visit 2 and Visit 4, the investigator will assess the Target Lesions prior to application of the study medication and 20 (± 4) minutes after treatment with the study medication. At Visits 3 and 5-8, the investigator will assess each Target Lesion and report the severity for all signs. At Visit 2 and Visit 4, the subject will assess the Target Lesions prior to application of the study medication and 10 (± 4) minutes after the treatment of the study medication. At Visits 3 and 5-8, the subject will assess each Target Lesion and report the average severity over the previous 24 hours for all symptoms. Refer to Section 9.1 for the complete list of Local Skin Reaction signs and symptoms.

¹⁴Study medication will be applied by a member of the investigational study staff that has been trained on the protocol. All Target Lesions will be treated with study medication following randomization at Visit 2. If a Target Lesion meets the criteria for re-treatment as defined in Section 7.5 the lesion will be re-treated at Visit 4. Following application of study medication, subjects must NOT wash/submerge the Target Lesions for at least 6 hours and they must NOT apply any topical products to the Target Lesions for at least 6 hours.

¹⁵Subjects will be asked to assess how satisfied they are with the treatment they received to each Target Lesion. This questionnaire assessment will take place at Visit 8 only.

¹⁶All concomitant therapies including (topical and oral) prescription medications, over the counter medications and 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 Lesions within 12 hours prior to any study visit.

¹⁷The reporting period for Serious Adverse Events (SAEs) begins when the subject signs the informed consent and continues through Visit 6. Refer to Section 10.1.2 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. Non-serious adverse events that occur between the time of consent and study medication application will be documented as medical history. All safety reporting (AEs and SAEs) will conclude at Visit 6 (approximately 21 days after last study medication application) except for clinical adverse events related to local skin reactions. These events will be collected through V8.

7. STUDY TREATMENT

7.1. Investigational Study Medication

The study medications for the study are A-101 40%, A-101 45%, and matching Vehicle. All study medications are solutions that are water-clear, colorless solutions which are indistinguishable in physical appearance.

Table 2 Study Medication Information

Study Medication Name	A-101 40%	A-101 45%	Vehicle
Manufacturer	James Alexander Corporation, Blairstown NJ		
A-101 concentration (%)	40	45	0
Pharmaceutical Form	Solution		
Storage Conditions	59°F to 77°F (15°C to 25°C) protected from light, excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area*		
Dose Regimen			
Route	Topical		
Application	Safety glasses and 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 Lesion for approximately 20 seconds. Allow each Target Lesion to remain undisturbed for approximately 60 seconds. Repeat the application/waiting cycle until the study medication has been applied to each Target Lesion up to 4 times. Subjects may receive up to 2 treatments (Visit 2 and Visit 4)		
Activated Applicators	Activated applicators are stable for 4 hours at room temperature (59°F to 77°F or 15°C to 25°C)		

*Excursions from these temperature ranges must be reported to Aclaris.

7.2. Subject randomization

Prior to the start of the study, Aclaris Therapeutics, Inc./designee will generate a randomization list that will be provided to the assigned clinical packaging organization for study medication labeling.

The randomization list will be stored with limited access to designated personnel for study medication labeling.

Subjects will be randomized to the study in a 1:2:2 ratio. Subjects will be randomized at Visit 2 following re-confirmation of subject eligibility.

7.3. Study medication packaging, storage and dispensing

A-101 45%, A-101 40% and matching Vehicle will be provided by Aclaris Therapeutics, Inc. and labelled 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.

One subject kit box contains 3-single use study medication applicators. Each kit will be labelled with a two part, three panel, double blind label. One part (one-panel) of the label remains attached to the Subject Kit, the other part (two-panel tear-off) is separated and attached to the subject's Label Page CRF when the subject is randomized.

A-101 study medication must be stored in a location where there is limited access to the investigational study medication at 59°F to 77°F (15°C to 25°C) protected from light, excessive heat, open flame and combustibles, out of direct sunlight and in a well-ventilated, dry area.

Investigational study medication supplies are only to be used for subjects properly consented and enrolled to this study.

7.4. 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.

7.5. Study Medication Treatment

The study medications are for external, topical use on the Target Lesions on the appropriate study subject only.

The investigational center staff member performing the study medication treatments must comply with the study medication storage conditions outlined in Section 7.1. A trained healthcare professional may apply study medication to subjects randomized to the study.

At Visit 2, the staff member who has been trained on the application process for the A-101 solution medication will perform an initial study medication treatment for each Target Lesion.

At Visit 4, any Target Lesion that has a **PLA grade of >0** and **ONLY Target Lesions that have a PLA grade of >0**, must receive study medication treatment UNLESS either of the following criteria apply to the Target Lesion:

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

7.5.1. Preparing the Study Medication for Application

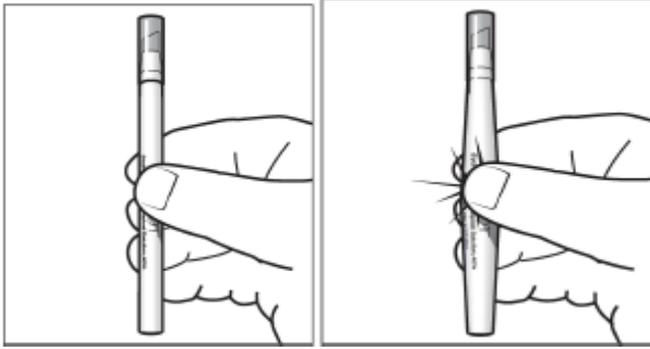
To perform a study medication treatment for a Target Lesion a staff member will select the appropriate study medication applicator. The following instructions outline the procedure for application of the study medication to the Target Lesions:

- Prepare for the treatment:
 - Wash your hands prior to, and after completing the study medication treatments
 - Wear safety glasses and nitrile or vinyl examination gloves during the treatment; **latex gloves are prohibited**
 - Select the applicator with the lowest available number
 - Complete the study medication applicator label as instructed
 - Visually inspect the applicator for damage:
 - If the applicator appears damaged do not use it for the treatment, contact the study monitor for disposal instructions and select an unused applicator with the next highest number for the treatment

If the applicator is intact, proceed with the treatment process as outlined in Figure 1.

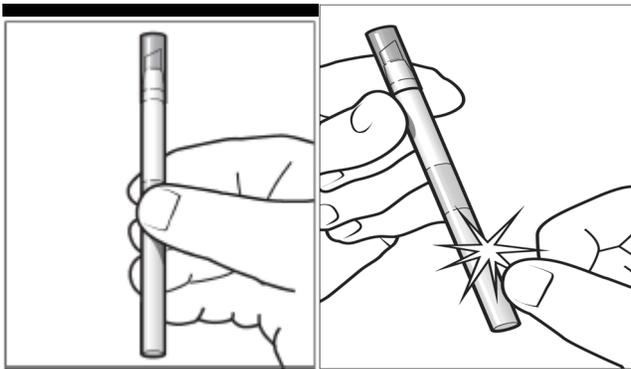
Seborrheic Keratosis Target Lesions should be cleaned using an alcohol wipe prior to application of A-101 Solution or matching Vehicle Solution.





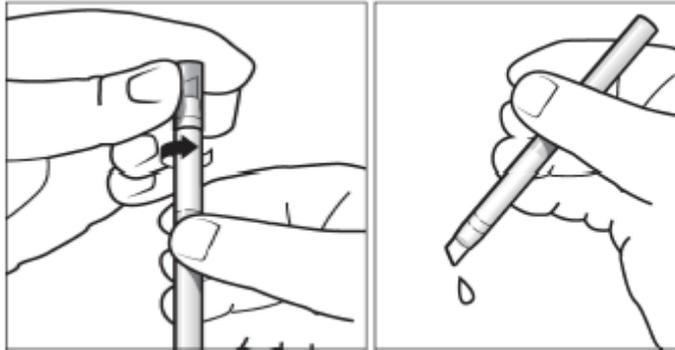
Step 1: Hold the Study Medication applicator so that the applicator cap is pointing up.

Step 2: Crush the ampule in the applicator by applying pressure at the center of the barrel of the applicator.



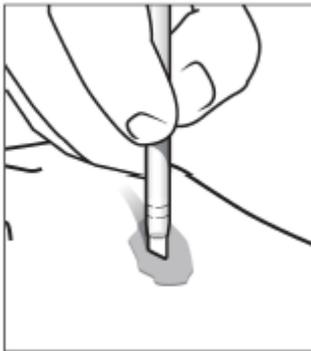
Step 3: Remove the sleeve.

Step 4: Tap the barrel of the applicator to ensure the solution is free of the crushed ampule.



Step 5: Gently remove the cap by twisting while pulling away from the applicator.

Step 6: Express a single drop of the Study Medication Topical Solution so that the tip of the applicator becomes wet.



Step 7: Apply the solution to the Lesion in a circular motion.

Figure 1: Diagram Showing the Process for Preparing and Applying A-101 Study Medication

7.5.2. Applying Study Medication to Trunk/Extremities

To apply the study medication to a Target Lesion on the **TRUNK AND EXTREMITIES** the staff member will follow these treatment instructions:

- Do not apply the study medications to eyes, nose, mouth, mucous membranes, or open wounds
- Position the subject with the plane of the Target Lesion to minimize exposure of the skin surrounding the Target Lesion to the study medication
- Thoroughly cleanse the Target Lesion 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 SK lesion and then move applicator around in a circular motion to fully saturate the lesion. 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 Lesion is fully saturated with study medication at the end of the ~20 second application
- Allow the Target Lesion to remain undisturbed for ~60 seconds
- After ~60 seconds repeat the ~20 second application process
- Repeat the application/waiting cycle until the study medication has been applied to the Target Lesion up to 4 times.

7.5.3. Applying Study Medication to the Face

To apply the study medication to Target Lesions on the **FACE** the staff member will follow these treatment instructions:

- Do not apply the study medications to eyes, mouth, mucous membranes, open wounds
- Do not apply the study medication to the eyelids or within 5 mm of the orbital rim
- If, in the investigator's opinion it is needed to ensure no study medication enters the eye:
 - Position the subject in the supine position with the head slightly elevated and angled such that any excess study medication will flow away from the eye.
 - Aclaris Therapeutics will supply sites supplies of 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 Lesion
 - 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 Lesion 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 SK lesion and then move applicator around in a circular motion to fully saturate the lesion. 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 Lesion is wet with study medication at the end of the ~20 second application
- Allow the Target Lesion to remain undisturbed for ~60 seconds
- After ~60 seconds repeat the ~20 second application process
- Repeat the application/waiting cycle until the study medication has been applied to the Target Lesion up to 4 times.

Repeat the treatment procedure that is appropriate for the body location (*i.e.*, trunk and extremities or face) until all Target Lesions that require treatment have been treated.

Record the time the final treatment is completed for the last treated Target Lesion as the Treatment Completion Time.

It is acceptable to treat multiple Target Lesions at the same time if, in the investigator's opinion, it is practical without exposing non-lesional skin to the study medication.

After completing the study medication treatment to the Target Lesion do not disturb the Target Lesion until just prior to the subject's post-treatment LSR evaluation.

Just prior to the subject's post-treatment LSR evaluation absorb any remaining study medication and gently dab or otherwise dry the Target Lesion with an absorbent pad or dry gauze without wiping or rubbing.

7.6. Video Recording of Study Medication Application

At one identified investigational site, a group of subjects will have the application of their A-101 study medication video recorded. The video recording will be performed during Visit 2 (Day 1) and will be done by a third-party imaging vendor. Up to 15 randomized subjects will be consented to allow for the video recording of the application of their A-101 study medication. Subjects will be de-identified by the imaging vendor and these video recordings will be stored by the third party vendor until the end of the study.

These video recordings will be used by Aclaris to develop a training video for physicians on the proper application technique utilizing the A-101 Topical Solution applicator.

7.7. Dose modification

If a subject refuses to allow a study medication initial treatment or retreatment the investigator must report the visit number, visit date, Target Lesion number(s) 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 Lesions 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 4.

7.8. Previous and Concomitant Therapies

7.8.1. Previous therapies

During Visit 1, the investigator or designee will question the subject to ensure they have not used any excluded therapies (Section 7.8.3).

7.8.2. Concomitant therapies

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

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

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

7.8.3. Prohibited therapies

During the course of this study, subjects are prohibited from using the following treatment therapies to treat any of the Target Lesions:

- Retinoids (systemic or topical)
- Corticosteroids (systemic or topical)
- Antimetabolites
- 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 Lesions 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 Lesions for at least **6 hours** and must not apply any topical products to the Target Lesions for at least **6 hours**.

7.9. Breaking the Blind

The blind may be broken ONLY in the event of a medical emergency, in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind the investigator should determine that the information is necessary. In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving an active study medication without the need for unblinding.

If deemed necessary to break the blind for a study subject, attempt to contact the Medical Monitor to obtain permission to break the blind of a particular subject. If it is not possible to contact the Medical Monitor beforehand, contact her/him as soon as possible after breaking the blind for a subject.

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

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

8. ASSESSMENTS OF CLINICAL EFFICACY

The investigator performing these evaluations must not participate in the study medication treatment for the subject being evaluated.

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

8.1. Target Lesion Identification

At Visit 1, the investigator will identify 4 Target Lesions on the trunk, extremities and face for each subject for treatment and evaluation. For each subject, at least 1 Target Lesion must be on the face and at least 1 Target Lesions must be on the trunk or extremities.

For this study, the trunk, extremities and face are defined as:

- Trunk:
 - The front and back of the torso, including the neck (below the mandibular ridge on the front of the torso and below the hairline on the back of the torso), vertically down to the beltline
- Extremities:
 - Arms:
 - From the shoulder to the tips of the fingers, including the back of the hands, excluding the palms
 - Legs:

- From the hip to the tips of the toes, including the top of the feet, excluding the soles.
- 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.

At Visit 1, each Target Lesion must:

- Have a clinically typical appearance
- Have a PLA of ≥ 2
- Have a length that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$
- Have a width that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$
- Have a thickness that is $\leq 2\text{mm}$
- Be a discrete lesion
- Be, when centered in the area outlined by the provided circular template, the only SK lesion present
- 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.

The groin areas and the inframammary fold, where, in the investigator's opinion, the Target Lesion might be occluded, are excluded from the treatment area.

Record the approximate location of each Target Lesion on the appropriate body chart in the CRFs. Also, identify the body area (*i.e.*, face, trunk, arm, leg) for each Target Lesion in the CRFs. Number the Target Lesions starting with 1 and proceeding up to 4 with no number omitted or reused.

Aclaris Therapeutics will provide the investigational site with standard circular templates and colored stickers that are to be used to identify the Target Lesions.

At Visit 1, the investigator and an investigational staff member will identify the Target Lesions by placing 2 appropriately colored stickers approximately 180 degrees opposite each other with the Target Lesion in the center of the area outlined by the provided circular template (Refer to Figure 2. Figure not to scale):

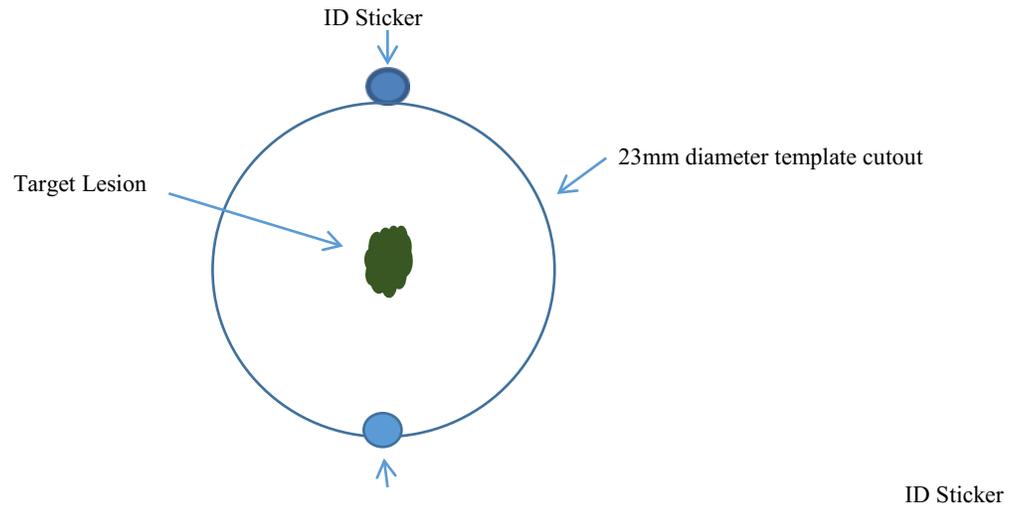


Figure 2 Target Lesion Identification

Write the Target Lesion number on one of the identification (ID) stickers. The ID stickers must be visible in the study photographs (Section 9.5.2). The Target Lesion #/ID sticker color relationships are:

- Target Lesion #1/white ID stickers
- Target Lesion #2/yellow ID stickers
- Target Lesion #3/green ID stickers
- Target Lesion #4/blue ID stickers.

At Visits 2-8, an investigational staff member will confirm the location of each Target Lesion using an appropriate combination of the Visit 1 hard-copy reference prints, Visit 2 photographs and the body charts. The staff member will identify the Target Lesion by placing 2 appropriately colored ID stickers, with the Target Lesion number written on one sticker, approximately 180 degrees opposite each other with the Target Lesion in the center of area outlined by the provided circular template.

8.1.1. Standardized photography

At Visits 1, 2, 4, 6, 7 and 8 qualified investigational center staff member will take standardized color photographs of each Target Lesion.

The photographs are to document the location of the Target Lesion and to assist with relocating the Target Lesion and the Target Lesion ID stickers must be visible in the photographs. The subject's identity will not be revealed in the study photographs.

At Visit 2, the photographs must be taken prior to the study medication treatment. 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 Lesion 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.

8.1.2. Physician's Lesion Assessment (PLA)

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

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

Table 3 Physician's Lesion Assessment Definitions

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

All investigational site staff will receive training on the PLA Assessment Scale and be provided with a PLA Assessment Manual (refer to Appendix 15.2) 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 randomization to the study, each Target Lesion must have a PLA grade of ≥ 2 .

8.1.3. Lesion Dimensions

At Visit 1 and at Visit 2 prior to randomization the investigator will measure the length and the width of each Target Lesion using the ruler provided.

The investigator must measure the length and width of each Target Lesion in millimeters (mm) as follows:

- Length (*i.e.*, the length of the longest axis) reported to the nearest mm
- Width (*i.e.*, the length of the longest axis perpendicular to the length) reported to the nearest mm.
- Thickness (height above the surrounding skin)

At Visit 1 for the subject to be enrolled and at Visit 2 for the subject to be randomized each Target Lesion must have:

- A Length that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$
- A Width that is $\geq 5\text{mm}$ and $\leq 15\text{mm}$.
- A Thickness that is $\leq 2\text{ mm}$.

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

At Visits 1, 2, 4, 6, 7 and 8 the investigator must measure the thickness (height) of each Target Lesion above the surrounding skin, in mm using the ruler provided as part of the PLA assessment.

At Visit 1 for the subject to be enrolled, each Target Lesion must have a thickness that is $\leq 2.0\text{mm}$.

8.2. Subject Instructions

An investigational center staff member will dispense a Subject Instruction Sheet to each subject at Visit 1 (Refer to Appendix 15.1).

Throughout the study, the subjects should:

- Continue their routine cleansing regimen except they should avoid vigorous scrubbing of the Target Lesions (*e.g.*, loofah, back brushes, scrubbing straps, abrasive washcloths, sponges and cleansing pads, etc.)
- Continue their routine cosmetics and skin care products
- Avoid exposing the Target Lesions to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the Target Lesions, 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 Lesion location 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 Lesions 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 Lesions for at least 6 hours
 - Apply any topical products to the Target Lesions for at least 6 hours.

8.3. Subject Satisfaction Survey

Subjects will be asked to assess their level of satisfaction regarding the study medication treatment. The subject survey will be completed at Visit 8 only. The subject will be asked to answer the following question in relation to the treatment of each Target Lesion:

Which of the following statements best reflects how your level of satisfaction with the outcome of your treatment to Target Lesion X?

1. Very Satisfied

2. Satisfied
3. Neutral
4. Dissatisfied
5. Very Dissatisfied

8.4. Other Study Supplies

Aclaris Therapeutics, Inc. will provide:

- An appropriate ruler, or other instrument, for measuring the thickness of the Target Lesions and the Lesion Dimensions
- 70% isopropyl alcohol for cleansing the SK Target Lesion during the study medication treatment process
- White Petrolatum USP for protecting sensitive areas during study medication treatments for Target Lesions on the face
- Templates for use when identifying Target Lesions
- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests and urine pregnancy tests from a third party
- Equipment, supplies and training for taking standardized photographs
- Eyewash kits.

9. ASSESSMENT OF SAFETY

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

The investigational staff member performing the LSR evaluations must not participate in the study medication treatment for the subject being evaluated.

9.1. Local Skin Reactions (LSR)

The LSR assessment is the investigator's assessment of the signs and the subject's assessment of the symptoms associated with irritation at each Target Lesion site, which includes the Target Lesion and the area immediately surrounding the Target Lesion. The investigator and subject may refer to other evaluations (photographs) to assist with these assessments. However, investigators may only refer to these evaluations after the PLA has been performed.

Local Skin Reactions:

- Signs (assessed by the investigator):
 - Erythema
 - Edema
 - Scaling/dryness
 - Vesicles/bullae
 - Crusting
 - Erosion
 - Ulceration
 - Post-inflammatory hyper-pigmentation

- Post-inflammatory hypo-pigmentation (does not include the superficial transient skin blanching/whitening related to the action of the study medications)
- Atrophy
- Scarring.

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

At Visits 2-8, the investigator and the subject will evaluate the LSR signs and the LSR symptoms at each Target Lesion site respectively.

The investigator will assess the LSR signs as follows:

- Visits 2 and 4:
 - For each Target Lesion site report the severity for all signs prior to any study medication treatment
 - For every treated Target Lesion site, 20 (± 4) minutes after the Treatment Completion Time, report the severity for the following signs:
 - Erythema
 - Edema
 - Scaling/dryness
 - Vesicles/bullae.
- Visits 3 and 5-8:
 - For each Target Lesion site, report the severity for all signs.

The subject will assess the LSR symptoms as follows:

- Visits 2 and 4:
 - For each Target Lesion site report the average of the severity over the previous 24 hours for all symptoms prior to any study medication treatment
 - For every treated Target Lesion site, 10 (± 4) minutes after the Treatment Completion Time, report the average of the severity of the LSR for all symptoms since completion of the study medication treatment.
- Visits 3 and 5-8:
 - For each Target Lesion site, report the average of the severity over the previous 24 hours for all symptoms.

Both the subject and the study staff member will initial and date the source document to indicate the subject performed the LSR for symptoms as instructed. The staff member must not influence the subject's assessment.

The investigator should report the one integer that best describes the severity of each LSR sign for each Target Lesion site using the scale below. Each subject should report the one integer that best describes the severity of each LSR symptom for each Target Lesion site using the scale below:

Table 4 Grading of Local Skin Reactions

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

9.2. Vital signs

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

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

Any measure that is, in the opinion of the investigator, abnormal AND clinically 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 10.1).

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg is considered abnormal and therefore must be defined as CS or not clinically significant (NCS) on the CRFs.

9.3. Clinical laboratory sampling

Non-fasting blood samples for clinical laboratory analysis will be collected by a qualified staff member at Visit 1 and at Visit 8. Approximately 2 mL of blood will be collected for each sample, a total of approximately 4 mL per subject. These blood samples will be sent to a central laboratory for analysis. Refer to the study specific laboratory manual for instructions regarding handling of the blood samples and shipping instructions.

The following tests, at a minimum, will be conducted:

Chemistry Panel	Complete Blood Count
Albumin	Hematocrit
Alkaline phosphatase	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Aspartate aminotransferase (AST)	Red blood cell morphology
Blood urea nitrogen (BUN)	Red blood cell count
Bicarbonate	White blood cell count
Calcium	White blood cell differential
Chloride	% & absolute
Creatinine	Basophils

Glucose	Eosinophils
Lactate dehydrogenase (LDH)	Lymphocytes
Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total bilirubin	
Total protein	
Uric acid	

The results of the clinical laboratory tests will be reported on the central laboratory's standard reports. These laboratory results will be sent to the investigator via fax. The investigator must review all laboratory reports in a timely manner and note NCS or CS to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator must date and initial every laboratory report.

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

The investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CS as medical history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins.

9.4. Urine pregnancy tests

The investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at Visit 1, at Visit 2 prior to randomization and at Visit 8.

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

If the result of any post-randomization urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed as outlined in Section 11.

9.5. Other Evaluations

9.5.1. Demographics and medical history

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

At Visit 1, the investigator must determine each subject's Fitzpatrick skin type and document appropriately on the subject's CRF.

Table 5 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)
Type VI	Never burns, never tans (deeply pigmented dark brown to darkest brown)

(Fitzpatrick 1988)

Medical history information will be recorded including all medical conditions and disease states that, at Visit 1:

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

9.5.2. Standardized photography

At Visits 1, 2, 4, 6, 7 and 8, a qualified investigational center staff member, other than the investigator, will take standardized color photographs of each Target Lesion.

The photographs are to document the location of the Target Lesion and to assist with relocating the Target Lesion and the Target Lesion ID stickers must be visible in the photographs (Section 8.1). The subject's identity will not be revealed in the study photographs.

At Visit 2, the photographs must be taken prior to the study medication treatment. Care must be taken to ensure the same lighting, background, subject positioning relative to the camera and camera settings are used for each photograph.

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

10. ADVERSE EVENTS

10.1. Definitions

10.1.1. Adverse events (AE)

- An adverse event (AE) is any untoward medical occurrence in a patient 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 pre-existing conditions. (NOTE: A condition, recorded as pre-existing, that is intermittently symptomatic [e.g., headache] and which occurs during the study should be recorded as an adverse event.)
- 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 patient from the study, requires medical treatment or further diagnostic work-up, or is considered by the study investigator to be clinically significant. NOTE: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events, but will be recorded to monitor data from patients who do not meet screening criteria.

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

The investigator must, for any Target Lesion 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.

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

10.1.2. Serious adverse event (SAE)

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

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

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

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis, even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for 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.

10.1.3. Adverse event reporting period

The investigator must start reporting non-serious AEs starting with the subject’s first study medication treatment continuing until Visit 5. Non-serious adverse events that occur between the time the subject was consented and the first application of study medication will be reported as medical history.

Reporting for SAEs begins after the subject signs the informed consent and continues until Visit 6 (regardless of relationship to study medication). If a subject experiences a SAE after Visit 6 that is deemed by the investigator to be related to study medication, the investigator must report this to the Sponsor using the study specific SAE report form.

10.1.4. 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.

Mild – Awareness of signs or symptom, but easily tolerated

Moderate – Discomfort, enough to cause interference with usual activity

Severe – Incapacitating with inability to perform usual activity.

10.1.5. Relationship to study medication

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

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

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

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

10.2. Reporting Procedures

10.2.1. Procedures for 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 at Visit 4 to elicit AEs in a similar manner.

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

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

AEs that are defined as “Not Related” to the study medications will be followed until they are resolved or until the subject’s last study visit. AEs that are defined as “Related” to the study medications will be followed until they are resolved or, if not resolved after the subject’s last study visit, until in the opinion of the investigator, the AE reaches a clinically stable outcome with or without sequelae.

10.2.2. Procedure for reporting a serious adverse event

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

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

Stuart D. Shanler, MD
Aclaris Therapeutics, Inc.
101 Lindenwood Drive
Suite 400
Malvern, PA 19355
Telephone: 484-321-5555
Serious Adverse Event Facsimile: 484-324-2359
Email: sshanler@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 AE reaches a clinically stable outcome with or without sequelae AND the investigator and Medical Monitor agree that the SAE is satisfactorily resolved.
5. Inform the Medical Monitor of SAE updates by telephone followed by an SAE form update sent by fax or by e-mail.
6. Comply with the appropriate regulatory requirements and Aclaris Therapeutics, Inc. instructions regarding reporting of the SAE to the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

10.2.3. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from study drug at any time at the discretion of the investigator. If a patient 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 patient 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 patient is referred to the care of a local health care professional. The investigator must inform

the medical monitor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

11. PREGNANCY

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

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

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

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

If, following study medication administration, it is determined that the subject may have been or was pregnant at the time of study medication exposure (including at least 2 days after study medication administration) the investigator must immediately notify the Medical Monitor and record the event on a pregnancy surveillance form. While not an AE or SAE, the investigator must report every pregnancy using a pregnancy surveillance form and follow the reporting procedures described for SAE reporting (Section 10.2.2).

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

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size and Power Consideration

Based on results from a previous study with similar design, the expected standard deviation for the primary efficacy parameter is approximately 23.7%. The mean difference between the two Active treatment groups is expected to be approximately 10 percentage points. With approximately 250 randomized subjects this study is expected to achieve approximately 85% power for the comparison between the two Active treatment groups, and more than 95% power for the pair-wise comparisons between each Active treatment group and the Vehicle group. Two-tail alpha will be set to 0.05 for all comparisons.

12.2. Statistical Analysis of Efficacy

The primary effectiveness analysis will consist of pair-wise comparison between each active treatment group and the vehicle treatment group, and between the two active treatment groups, based on the mean of per-subject percentages of target lesions judged to be clear on the PLA (PLA = 0) at Visit 8. To conduct this analysis, the percentage of each subject's target lesions judged to be clear on the PLA at Visit 8 will first be calculated for each subject. Then the analysis will calculate the mean of this parameter for each treatment group (yielding an estimate of the mean percentage of clear lesions across subjects), and an analysis of variance (ANOVA) model will be used to perform all pair-wise comparisons among the treatment groups. Pair-wise comparisons will be conducted on the least-squares means using the overall pooled error term of the model. All efficacy analyses will be based on the per protocol (PP) population, defined as all randomized subjects who completed the study with no major protocol violation.

A secondary effectiveness analysis will be conducted using the same methodology as the primary efficacy analysis based on the mean of per-subject percentages of target lesions judged to be clear or near-clear on the PLA (PLA \leq 1) at Visit 8. The primary and secondary analyses above will also be conducted separately for lesions in each body location, using the same methodology as specified above.

In addition to the above Visit 8 analyses, each of these analyses will be conducted at each other visit where PLA scores are collected, as exploratory analyses.

Three exploratory responder analyses will be conducted using the following criteria for classifying subjects as responders:

- Subjects with PLA = 0 for all 4 target lesions at Visit 8;
- Subjects with PLA = 0 for at least 3 target lesions at Visit 8; and
- Subjects with PLA \leq 1 for all 4 target lesions at Visit 8.

For each exploratory analysis, separate chi-square tests will be used to compare the percentage of responders between each active treatment group and the vehicle treatment group, and between the two active treatment groups. The chi-square analyses may be supplemented by one logistic regression model for each exploratory analysis that will allow all 3 pairwise comparisons to be performed within a single model.

Duration of response will be calculated on a lesion basis by determining the percentage of clear lesions (PLA=0) at Visit 8 which remain clear at Visit 13. This will be done for each treatment group separately.

For all analyses, two-tail alpha will be set to 0.05 with no adjustment for multiple comparisons. ANOVAs will include Site in the model if doing so improves the sensitivity of the model for comparing treatment groups.

12.3. Statistical Analysis of Safety Data

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

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

12.4. Interim Analysis

An interim Analysis will not be conducted for this study.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. 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 study subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

13.2. 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. Deviations include study procedures that occurred outside the treatment windows (except for treatment application days).

A **protocol violation** is defined as any divergence from the protocol-specific inclusion/exclusion criteria, subject is administered a prohibited medication, 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 patients to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular patient, prior approval from sponsor/CRO and the responsible IRB/IEC, in accordance with the Sponsor/CROs Standard Operating Procedure (SOP), is required before the patient will be allowed to enter the study. If investigative center personnel learn that a patient 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.

13.3. 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 investigational center file to each center.

13.4. 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. representatives designee and/or and any regulatory agency to have direct access to all study records, CRFs, corresponding subject medical records, study medication dispensing records and study medication storage area, and any other documents considered source documentation. The investigator also agrees to assist the representative, if required.

13.5. 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

13.6. Quality Assurance

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

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

13.7. Record Retention

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 patient, 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

14. ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

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

This protocol and any accompanying material, including information that will be provided to prospective patients (such as advertisements, patient information sheets, or study descriptions used to induce study participation or obtain informed consent) must be submitted to the Central 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 patients 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 Central 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 patients. In the latter case, the Central 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 Central IRB and the Sponsor by the Investigator in accordance with applicable regulatory regulations and in conformity with policies established by both the Central 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 Central IRB as soon as possible, and in accordance with the guidelines of the Central 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 patient 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 patient'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 patient and the person obtaining consent and each page not signed must be initialed and dated by the patient. The investigational site must retain the original signed consent and provide a copy to the patient.

14.2. Ethical Conduct of the Study

The Sponsor will use information developed in this clinical study in connection with the development of A-101 Solution 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 patients' 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 patient information. To assure that patients' confidentiality is maintained, patients' data will be identified by a study-assigned number.

All Sponsor personnel will handle patients' 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.

14.3. 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.

14.4. 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.

15. APPENDICES

15.1. Subject Instruction Sheet

A-101-SEBK-204 SUBJECT INSTRUCTION SHEET

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

Contact: _____ Telephone: _____

DURING THE STUDY:

- Continue your routine cleansing regimen except avoid vigorous scrubbing of the Target Lesions (*e.g.*, loofah, back brushes, scrubbing straps, abrasive washcloths, sponges and cleansing pads, etc.)
- Continue your routine cosmetics and skin care products
- Avoid exposing your Target Lesions to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the Target Lesion, if excessive exposure cannot be avoided
- The use of the following therapies to treat any of the Target Lesions are prohibited
 - Retinoids (oral or topical)
 - Corticosteroids (oral or topical)
 - Antimetabolites
 - LASER, light or other energy based therapy
 - Liquid nitrogen, electrodesiccation, curettage, imiquimod, ingenol mebutate
 - Microdermabrasion or superficial chemical peels
 - Antibiotics (oral or 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 Lesions, 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 Lesions for at least 6 hours
 - Apply any topical products to the Target Lesions for at least 6 hours.

STUDY VISIT SCHEDULE:

VISIT 2:		VISIT 3:	
Date:	Time:	Date:	Time:

VISIT 4: Date: Time:	VISIT 5: Date: Time:
VISIT 6: Date: Time:	VISIT 7: Date: Time:
VISIT 8: Date: Time:	Thank you for following these instructions

15.2. Physician Lesion Assessment Scale-Training Manual (12JAN2016)

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 \leq 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.

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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.

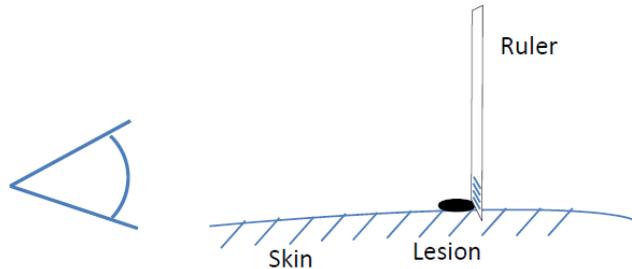
2. Measure the thickness of the SK lesion

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.

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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 \leq 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)).

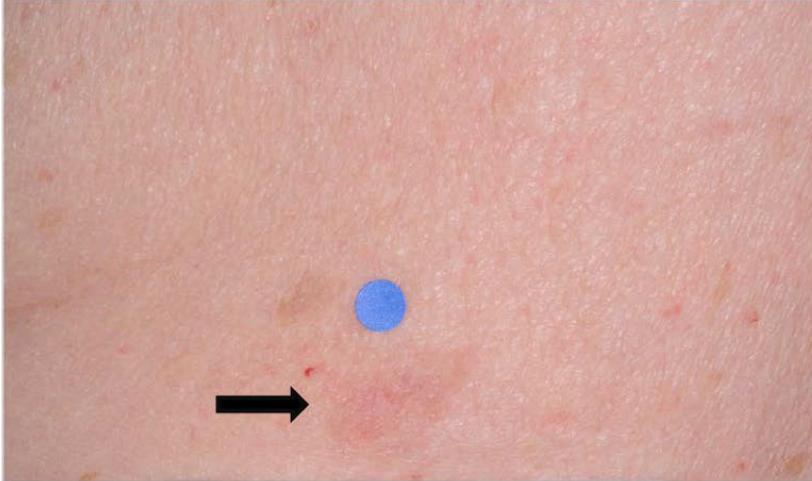
Please refer to the photo guide provided on the next pages for grades of “2” and “3”.

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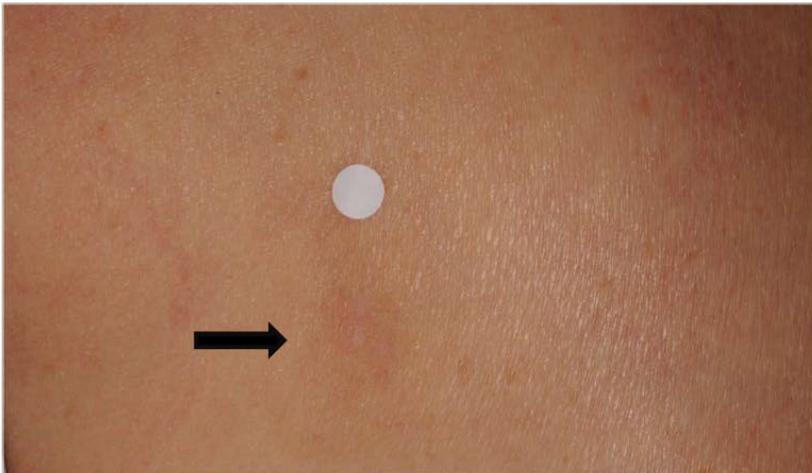
Photo guide

Grade "0" Clear: no visible seborrheic keratosis lesion

Photograph 1

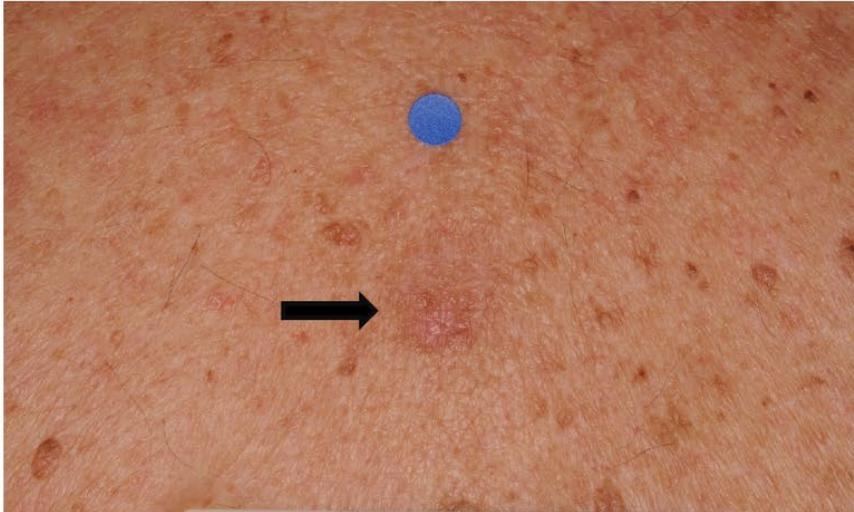


Photograph 2

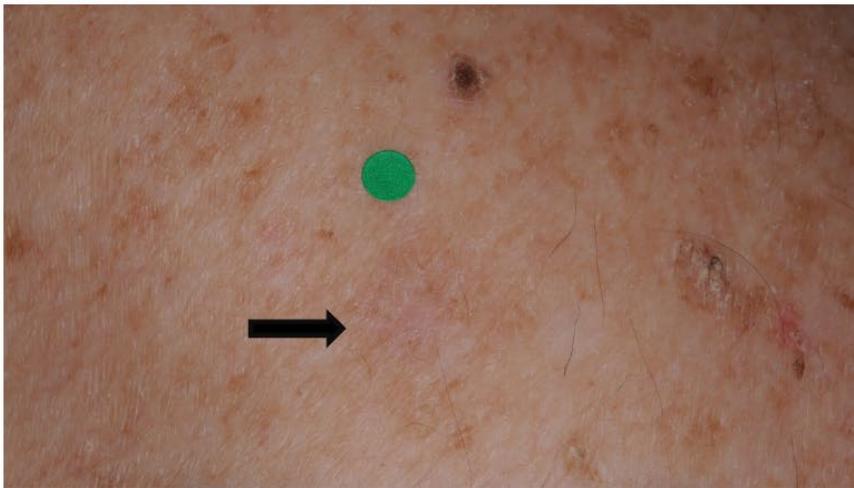


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Grade "0" Clear: no visible seborrheic keratosis lesion
Photograph 3



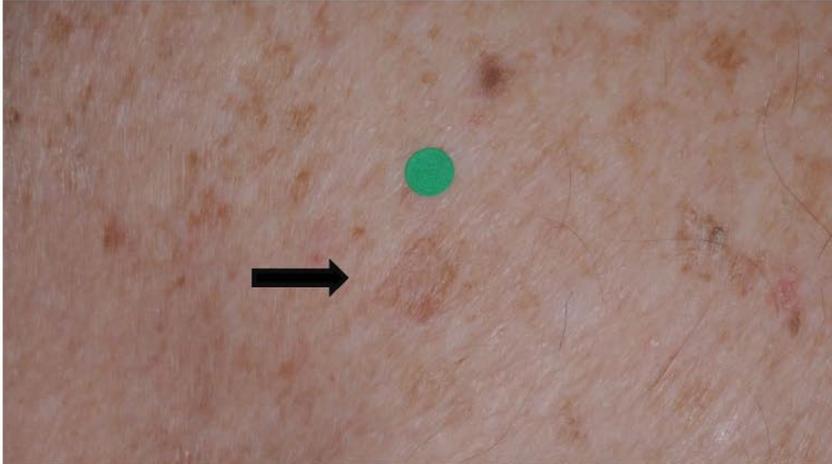
Photograph 4



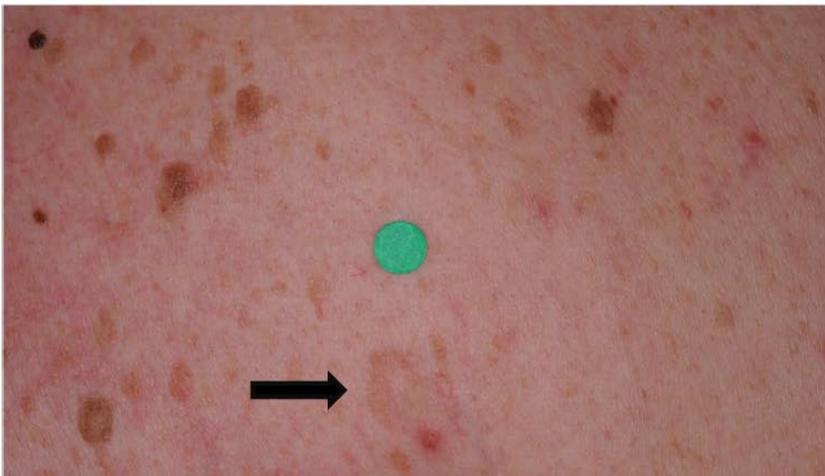
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Grade "1" Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)

Photograph 1



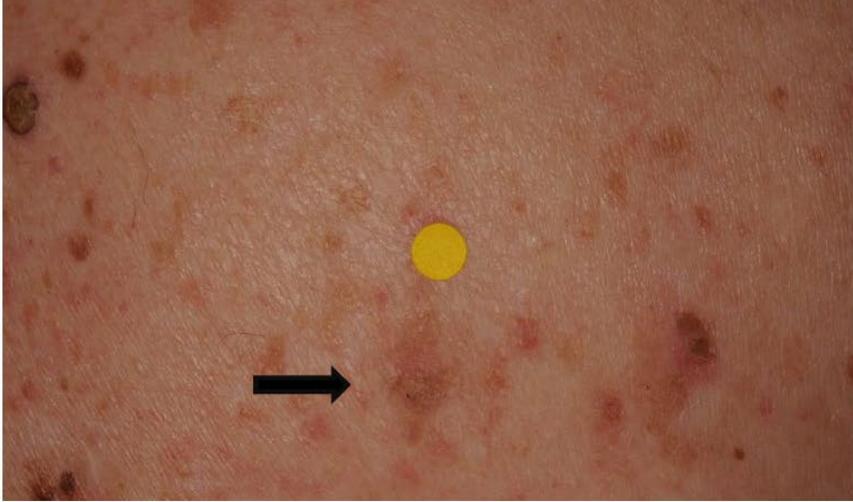
Photograph 2



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

Photograph 3



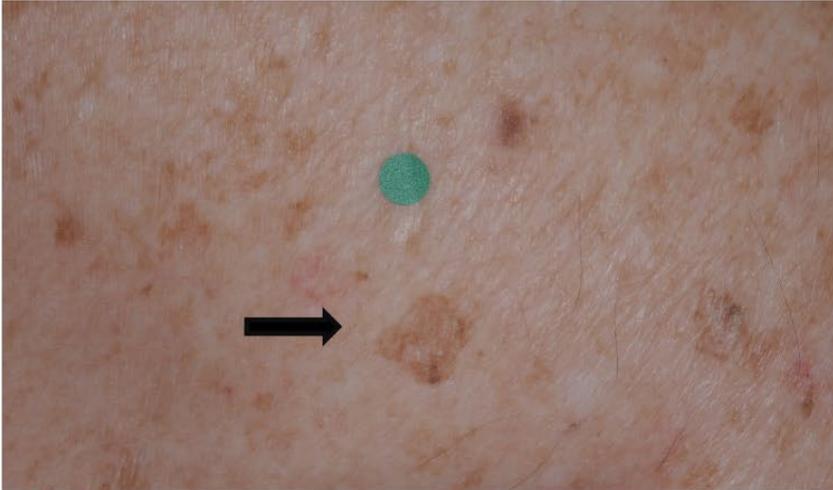
Photograph 4



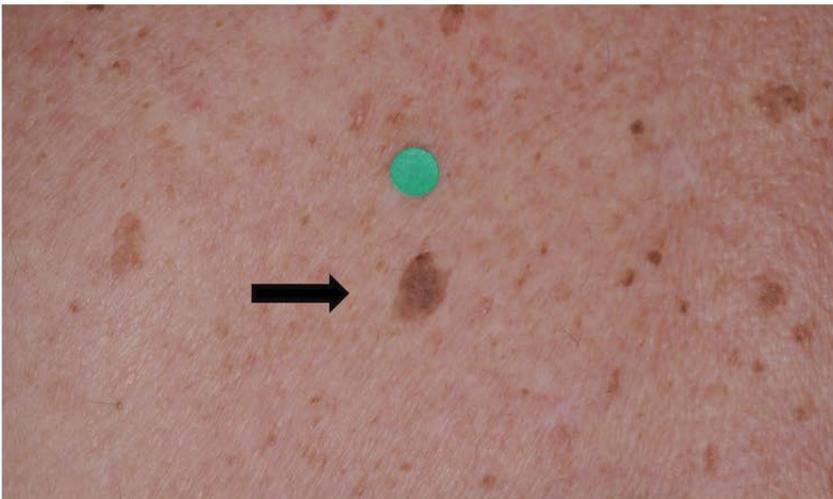
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Grade "2" Thin: a visible seborrheic keratosis lesion (thickness ≤ 1 mm)

Photograph 1



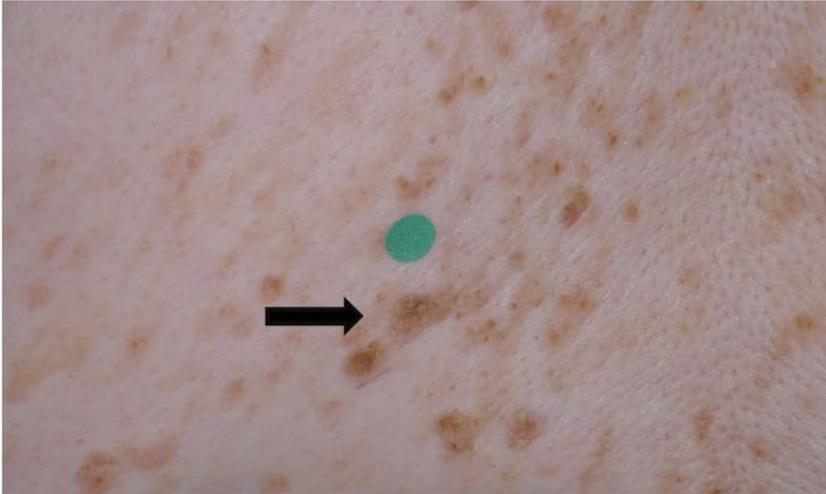
Photograph 2



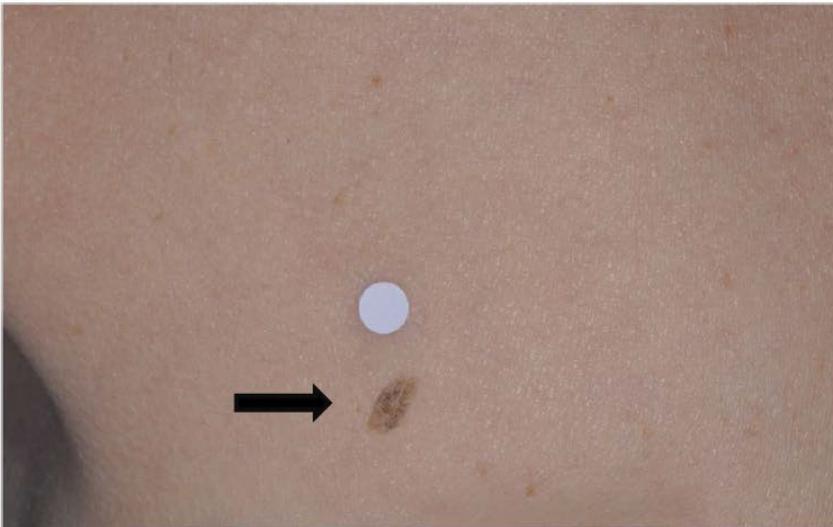
SK PLA Training Manual
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Grade "2" Thin: a visible seborrheic keratosis lesion (thickness \leq 1 mm)

Photograph 3



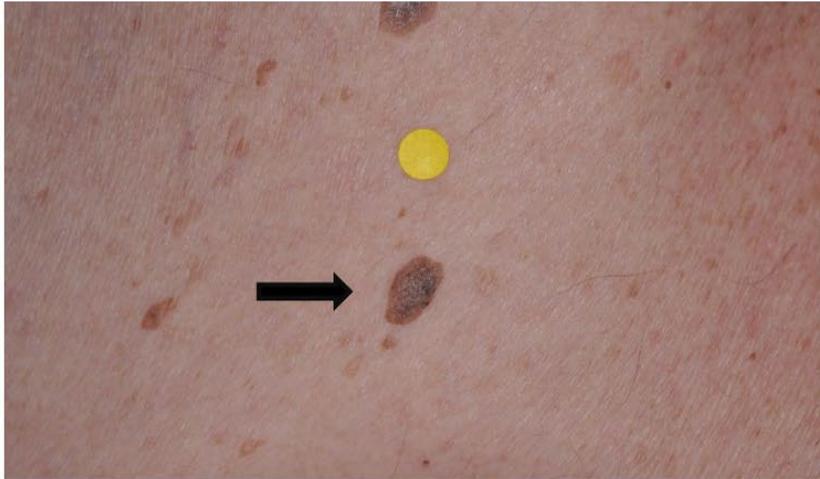
Photograph 4



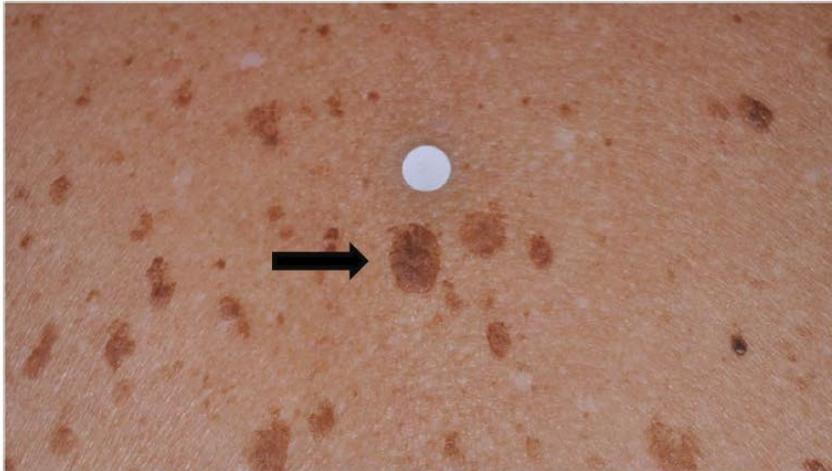
SK PLA Training Manual
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Grade "3" Thick: a visible seborrheic keratosis lesion (thickness > 1 mm)

Photograph 1



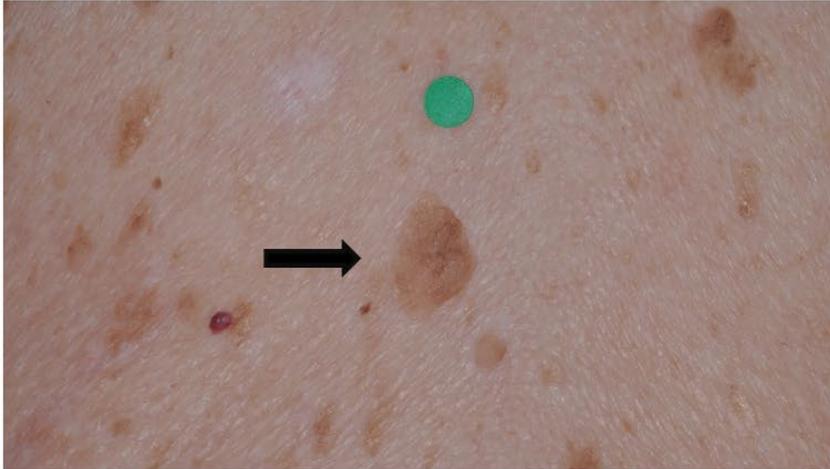
Photograph 2



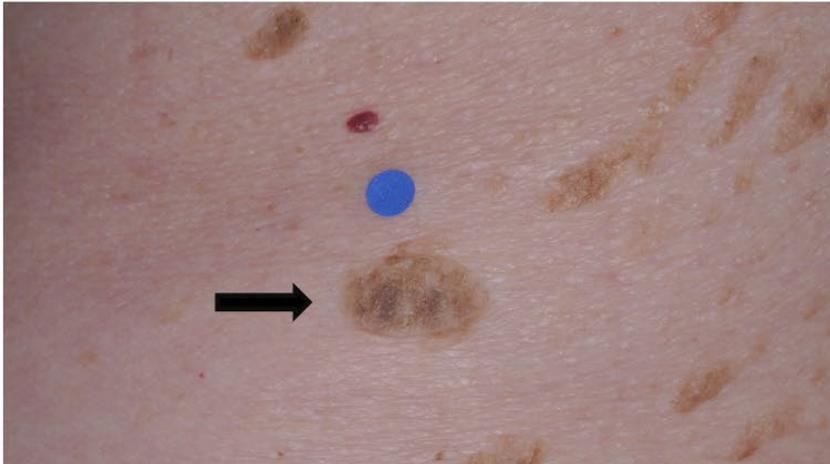
SK PLA Training Manual
January 12, 2016

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

Photograph 3



Photograph 4



16. References

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